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Name of company: Boehringer Ingelheim		Synopsis	 Boehringer Ingelheim
BI proprietary name: Jardiance®		EudraCT number: 2017-002971-24	
BI investigational product: Empagliflozin, BI 10773		Page: 1 of 11	
Report date: 28 Oct 2022	Trial no./Doc. no.: 1245-0137 / c37800399 / 206893_10628738_2.0	Dates of trial: 01 Feb 2019 – 05 Jul 2022	Date of revision: 30 Dec 2024
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Title of trial A multicentre international randomised parallel group double-blind placebo-controlled clinical trial of EMPagliflozin once daily to assess cardio-renal outcomes in patients with chronic KIDNEY disease Lay title EMPA-KIDNEY (The study of heart and kidney protection with empagliflozin) Chief investigator United Kingdom			
Trial sites with screened participants Multicentre trial in 241 sites (with screened participants) in Canada, China, Germany, Italy, Japan, Malaysia, United Kingdom, and the USA.			
Publications Herrington WG, Preiss D, Haynes R, Eynatten M, von Staplin N, Hauske SJ et al. The potential for improving cardio-renal outcomes by sodium-glucose co-transporter-2 inhibition in people with chronic kidney disease: a rationale for the EMPA-KIDNEY study. Clin Kidney J; 11(6), p. 746-761; 2018. EMPA-KIDNEY Collaborative Group. Design, recruitment and baseline characteristics of the EMPA-KIDNEY trial. Nephrol Dial Transplant; 37(7), p. 1317-1329; 2022. EMPA-KIDNEY Collaborative Group. Empagliflozin in Patients with Chronic Kidney Disease. N Engl J Med; 2023; 388(2); 117-127. Staplin N, Haynes R, Mayne KJ, Roddick AJ, Neuen BL, Hauske SJ et al. Impact of diabetes on the effects of sodium glucose cotransporter-2 (SGLT2) inhibitors on kidney outcomes: Collaborative meta-analysis of large placebo-controlled trials. Lancet; 2022; 400(10365); 1788-1801.			
Clinical phase: III			
Objectives The primary aim of this trial was to assess the effect of empagliflozin on time to kidney disease progression or cardiovascular (CV) death. Key secondary aims were to assess the effect of empagliflozin on time to hospitalisation for heart failure (HHF) or CV death, occurrences of hospitalisations from any cause, and time to death from any cause.			

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Methodology

This randomised, placebo-controlled, double-blind, parallel-group trial was to be continued until a minimum of 1070 primary outcome events had occurred. A formal, prespecified interim analysis was to be reviewed by the independent Data Monitoring Committee (DMC) when a minimum of 150 first end-stage kidney disease (ESKD) events had occurred (during trial design it was predicted that approximately 60% of the 1070 first primary outcomes would have occurred by that time). If the predefined stopping criteria were met, then the trial was to be stopped early for benefit.

The study design was streamlined: extra work for collaborating doctors and hospitals was kept to a minimum. The trial was focused on readily identifiable and important clinical outcomes. The main means of data collection were participant-reported information recorded directly into computer systems and centrally measured creatinine.

The study was initiated by Principal Investigators [redacted] at the University of Oxford and developed as an academic collaboration with Boehringer Ingelheim, the sponsor of the trial.

The CTR version 1.0, dated 28 October 2022, has been revised on XX December 2024 due to new data becoming available after unlocking the database for the non-interventional extension study called Post-Trial-Follow-Up (PTFU) data analysis. Two additional cases of death which occurred during the main trial period, three ESKD events, and one hospitalization event have been reported, triggering the re-run of the primary, secondary, and further endpoints analyses, including safety analyses. There are few changes and they do not affect the efficacy and safety conclusions, as well as the overall conclusions.

Number of participants

Planned:	Approximately 6000		
Actual:	Entered Run-in	Randomised (Treated)	Analysed (for primary endpoint)
	Overall	8266	6609
	Empagliflozin 10 mg	-	3304
	Placebo	-	3305

Diagnosis

Patients with evidence of chronic kidney disease (CKD) at risk of kidney disease progression, with or without diagnosed diabetes mellitus.

Main criteria for inclusion

Evidence of CKD at risk of progression was defined on the basis of local laboratory results recorded at least 3 months before and at the time of the Screening visit, and required that:

- (a) CKD-EPI eGFR ≥ 20 to <45 mL/min/ 1.73m²; or
- (b) CKD-EPI eGFR ≥ 45 to <90 mL/min/ 1.73m² with urinary albumin to creatinine ratio (UACR) ≥ 200 mg/g (or protein to creatinine ratio ≥ 300 mg/g)

CKD-EPI eGFR values were estimated using the 2009 Chronic Kidney Disease Epidemiology Collaboration creatinine formula [R12-1392].

CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate

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BI investigational product:	Empagliflozin, film-coated tablets
Dose:	10 mg once daily
Mode of administration:	Oral
Comparator product:	Placebo, film-coated tablets to match empagliflozin
Dose:	Not applicable
Mode of administration:	Oral

Duration of treatment

Prior to randomisation, potentially eligible participants entered a placebo run-in period for about 8-12 weeks. Thereafter, the participants were to receive treatment with empagliflozin or placebo until approximately 1070 first primary outcome events had occurred after randomisation (i.e. event-driven).

Interim analysis

A formal interim analysis to decide whether to stop the trial for benefit was planned to be made after 150 ESKD events had occurred (by which time it was expected that approximately 60% of all first primary outcomes had occurred). At the time the trigger for the interim analysis was achieved, 624 (58% of 1070) primary outcome events had occurred (interim database lock 22 Feb 2022). Based on the interim results which met the predefined stopping criteria (Section 9.7.1.3.5), the DMC recommended to stop the trial for benefit on 07 Mar 2022. The final decision to stop the trial was made on 09 Mar 2022 by the Executive Committee including BI representatives. As planned, further data were collected at final follow-up visits, including renal status and blood for central creatinine analysis. The first final follow-up was on 01 Apr 2022 and the last on 05 Jul 2022. The final database included these additional data.

Efficacy criteria for evaluation

The primary endpoint was a composite of time to the first occurrence of a composite of:

- Kidney disease progression (defined as ESKD, a sustained decline in eGFR to <10 mL/min/1.73m², renal death, or a sustained decline of $\geq 40\%$ in eGFR from randomisation), or
- CV death

ESKD was defined as the initiation of maintenance dialysis or receipt of a kidney transplant.

Key secondary endpoints:

- Time to the first occurrence of HHF or CV death
- Time to occurrences of all-cause hospitalisations (first and recurrent combined)
- Time to death from any cause

Other secondary endpoints:

- Time to the first occurrence of kidney disease progression
- Time to CV death
- Time to first occurrence of CV death or ESKD

Further endpoints included:

- Annual rate of change in eGFR

The subgroups of key interest were baseline diabetes status (yes, no), baseline eGFR (<30 , 30 to 45, ≥ 45 mL/min/1.73 m²), and baseline UACR (<30 , 30 to 300, >300 mg/g), which were analysed for the primary endpoint, the secondary endpoints, and several further endpoints, including the annual rate of change in eGFR. Other tertiary and further efficacy endpoints are described in the clinical trial report body.

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Safety criteria for evaluation

As the safety profile of empagliflozin has been well-studied in previous trials and in line with regulatory guidance, collection of safety data was streamlined. Only prespecified non-serious AEs were collected along

with all SAEs. The exception to this was for participants entered in Japanese sites, where all AEs (non-serious AEs and SAEs) were recorded. The prespecified non-serious AEs were AEs leading to study drug discontinuation, bone fracture, severe hypoglycaemia, gout, symptomatic dehydration, AEs of special interest (ketoacidosis, lower limb amputation, and liver injury), and AEs that could lead to amputation. Adjudicated AEs, specific AEs and a number of trial-specific safety endpoints were analysed. Biochemical assessments on blood were performed; changes in weight and blood pressure were also assessed.

Adjudication

Central, blinded adjudication was performed by trained clinicians [REDACTED] for death events and events initially reported as HHF, myocardial infarction, stroke, liver injury, ketoacidosis, lower limb amputation, acute kidney injury, and genital infections. Only events that have been confirmed or not refuted by adjudication were included in the relevant analyses.

Statistical methods

The analysis of the primary endpoint was performed at a 2-sided α of 0.0017. As the primary endpoint was statistically significant, the key secondary endpoints were analysed following the Hochberg procedure starting with a 2-sided α of 0.0290. The significance levels were predefined according to α -spending functions based on the number of primary outcome events observed at the time of the DMC interim analysis.

For the time-to-event analyses survival analytic methods were used to evaluate the time to the first event during the trial follow-up period. Cox proportional hazards regression, adjusted for treatment and for the prognostic variables used in the randomisation minimisation algorithm (age, sex, prior diabetes, eGFR, UACR, and region), was used to estimate the hazard ratio comparing empagliflozin with placebo. Estimates of the hazard ratio were shown with 95% confidence intervals and with adjusted confidence intervals for confirmatory analyses. Cumulative incidence function and/or Kaplan Meier plots were produced where appropriate. The analysis of the key secondary endpoint of all-cause hospitalisation (first and recurrent combined) was performed using a joint frailty model account for the dependence between recurrent hospitalisations and all-cause death. The analysis of the annual rate of change in eGFR was performed using a shared parameter model allowing for events of ESKD or death.

For analyses of continuous variables, such as blood pressure and analyses of biochemical effects, differences in means between the randomised groups were assessed (after appropriate transformation, where necessary).

Standard analyses of safety parameters were descriptive. For the evaluation of AESIs and specific AEs, a combination of adjudication results, investigator-defined events, standardised MedDRA query (SMQ), BI customised MedDRA query (BICMQ; when no SMQ was available), and/or additional definitions were prespecified. The focus of safety evaluation was based on the adjudication results if available, and these took precedence over investigator-reported results for all analyses.

SUMMARY – CONCLUSIONS

Trial participants and compliance with the clinical trial protocol

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Of the 6609 randomised participants, 6568 (99.4%) completed the trial, including 317 participants who died. Of the 6609 participants treated with study medication, 1603 prematurely discontinued treatment (24.3%, including participants who died). Participant characteristics for the overall population are shown in Table 1. Overall, the characteristics were balanced between the treatment groups.

The most common reasons for premature discontinuation of study medication were AEs (3.8% with fatal events and 3.6% of participants with non-fatal events) and unknown, i.e. largely consisting of participants who provided no early treatment discontinuation reason but attended the final follow-up with a treatment stop date >1 day prior to the visit date.

A total of 1.3% of the randomised participants had at least 1 important protocol deviation, with similar frequencies between the treatment groups. The most common category of protocol deviations was clustered/short visits, data were not entered in real-time (0.9% of participants).

Median observation time was 24.37 months (Q1, Q3 18.00, 29.80) in the empagliflozin group and 24.33 months (18.03, 29.70) in the placebo group. Median exposure to study medication was 21.92 months (16.87, 28.93) for empagliflozin and 21.57 months (16.73, 28.87) for placebo.

Table 1: Selected demographic and baseline data – randomised set

Characteristics at baseline	Total	Characteristics at baseline (cont.)	Total
Number of participants, N (%)	6609 (100.0)	BMI [kg/m ²], mean (SD)	29.7 (6.8)
Female, N (%)	2192 (33.2)	Age [years], mean (SD)	63.3 (13.9)
Race, N (%)		Baseline diabetes status, N (%)	
White	3859 (58.4)	No diabetes	3569 (54.0)
Asian	2393 (36.2)	Type 1 diabetes mellitus	68 (1.0)
Black/African American	262 (4.0)	Type 2 diabetes mellitus	2936 (44.4)
Ethnicity*, N (%)		Other/Unknown diabetes	36 (0.5)
Not Hispanic/Latino	1431 (21.7)	Primary cause of kidney disease, N (%)	
Hispanic/Latino	222 (3.4)	Diabetic	2057 (31.1)
Region, N (%)		Glomerular	1669 (25.3)
North America	1717 (26.0)	Hypertensive/renovascular	1445 (21.9)
Europe	2648 (40.1)	Other/unknown	1438 (21.8)
Japan	612 (9.3)	Prior CV disease, N (%)	1765 (26.7)
Other Asia (China, Malaysia)	1632 (24.7)	Myocardial infarction	702 (10.6)
SBP [mmHg], mean (SD)	136.5 (18.3)	Heart failure	657 (9.9)
≥145, N (%)	2022 (30.6)	Peripheral arterial disease	469 (7.1)
DBP [mmHg], mean (SD)	78.1 (11.8)	Stroke	404 (6.1)
≥85, N (%)	1977 (29.9)	Transient ischaemic attack	332 (5.0)
eGFR [mL/min/1.73 m ²], mean (SD)	37.32 (14.45)	KDIGO risk category, N (%)	
<30, N (%)	2282 (34.5)	Low risk	4 (0.1)
≥30 to <45, N (%)	2928 (44.3)	Moderately increased risk	255 (3.9)
≥45 to <60, N (%)	1399 (21.2)	High risk	1412 (21.4)
UACR [mg/g], median (Q1, Q3)	329.35 (48.53, 1068.93)	Very high risk	4938 (74.7)
Normal (<30), N (%)	1327 (20.1)	Use of RAS-inhibitors, N (%)	5628 (85.2)
Microalbuminuria (≥30 to ≤300), N (%)	1865 (28.2)	Use of diuretics, N (%)	4501 (68.1)
Macroalbuminuria (>300), N (%)	3417 (51.7)	Use of beta-blockers, N (%)	2761 (41.8)
		Use of lipid-lowering drugs, N (%)	2815 (42.6)

*Ethnicity was recorded only for sites in the US or Canada

BMI = body mass index, DBP = diastolic blood pressure, KDIGO = Kidney Disease Improving Global Outcomes, RAS-

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inhibitors defined according to the WHO-DD SDGs of ACEis, ARBs and renin inhibitors and BldDQ ARNIs., SBP = systolic blood pressure, SD = standard deviation

Efficacy results

Primary and key secondary endpoints

The risk of kidney disease progression or CV death was significantly reduced with empagliflozin treatment compared with placebo (Table 2). The separation of the estimated cumulative incidence of kidney disease progression or CV death between empagliflozin and placebo became evident approximately 1 year after randomisation and was maintained over time. An exploratory analysis by year since randomisation was performed to evaluate the treatment effect over time; the results were consistent, HR (95% CI) was 0.73 (0.57, 0.94) in the first year, 0.68 (0.57, 0.82) in the second year, and 0.78 (0.61, 0.98) afterwards (trend test interaction p-value = 0.7230). The results of the primary endpoint were consistent (interaction p-values >0.05) across the subgroups of key interest of baseline diabetes status and baseline eGFR, with the upper bound of the 95% CI for the HR for each subgroup <1. There was a trend towards increasing treatment effect in participants with higher levels of UACR at baseline (trend test interaction p-value = 0.0174).

The risk of all-cause hospitalisations was significantly reduced with empagliflozin treatment compared with placebo (Table 2). The separation of the estimated cumulative incidence of all-cause hospitalisations started shortly after randomisation and was maintained over time. The results were consistent (interaction p-values >0.05) across the 3 subgroups of key interest, with the upper bound of the 95% CI for the HR for each subgroup <1.

The risks of all-cause death and HHF or CV death were not significantly reduced with empagliflozin compared with placebo (Table 2).

Table 2: Confirmatory analyses for the primary and key secondary endpoints

	Placebo	Empa 10 mg
Primary endpoint: kidney disease progression or adjudicated CV death, Cox regression – randomised set		
Analysed participants, N (%)	3305 (100.0)	3304 (100.0)
Participants with event, N (%)	558 (16.9)	432 (13.1)
Kidney disease progression as the first event	504 (15.2)	384 (11.6)
CV death as the first event	54 (1.6)	48 (1.5)
Incidence rate per 100 years at risk (95% CI)	8.96 (8.23, 9.72)	6.85 (6.22, 7.51)
Hazard ratio vs. placebo (99.83% CI) ¹		0.72 (0.59, 0.89)
p-value		<0.0001
Key secondary endpoint: occurrence of all-cause hospitalisations (first and recurrent combined), joint frailty model – randomised set		
Analysed participants, N (%)	3305 (100.0)	3304 (100.0)
Total number of hospitalisations, N	1895	1612
Hazard ratio vs. placebo of all-cause hospitalisations (99.03% CI) ²		0.86 (0.76, 0.98)
p-value		0.0022
Key secondary endpoint: adjudicated HHF or adjudicated CV death, Cox regression – randomised set		
Analysed participants, N (%)	3305 (100.0)	3304 (100.0)
Participants with event, N (%)	153 (4.6)	131 (4.0)
Incidence rate per 100 years at risk (95% CI)	2.39 (2.03, 2.78)	2.04 (1.70, 2.40)
Hazard ratio vs. placebo (98.55% CI) ³		0.84 (0.63, 1.12)
p-value		0.1363
Key secondary endpoint: adjudicated death from any cause, Cox regression – randomised set		

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Analysed participants, N (%)	3305 (100.0)	3304 (100.0)	
Participants with event, N (%)	168 (5.1)	149 (4.5)	
Incidence rate per 100 years at risk (95% CI)	2.59 (2.21, 3.00)	2.29 (1.94, 2.68)	
Hazard ratio vs. placebo (97.10% CI) ⁴		0.87 (0.68, 1.11)	
p-value		0.2122	
^{1, 2, 3, 4} The CI corresponding to a 2-sided significance level of ¹ <0.0097, ² <0.0017, ³ <0.0145, ⁴ <0.0290 required to claim superiority.			
Other secondary endpoints			
Kidney disease progression occurred in a lower proportion of participants in the empagliflozin group (384 participants, 11.6%) than in the placebo group (504 participants, 15.2%). The risk of kidney disease progression was reduced with empagliflozin treatment vs. placebo (HR 0.71; 95% CI 0.62, 0.81). The separation of the cumulative incidence of kidney disease progression became evident approximately 1 year after randomisation and continued over time.			
CV death or ESKD occurred in a lower proportion of participants in the empagliflozin group (164 participants, 5.0%) than in the placebo group (220 participants, 6.7%). The risk of CV death or ESKD was reduced with empagliflozin treatment vs. placebo (HR 0.72; 95% CI 0.59, 0.89). The separation of the estimated cumulative incidence of CV death or ESKD between empagliflozin and placebo became evident approximately 1 year after randomisation and continued over time.			
Adjudicated CV death occurred in a low proportion of participants in both the empagliflozin group (59 participants, 1.8%) and the placebo group (70 participants, 2.1%); HR 0.83 (95% CI 0.59, 1.17; p = 0.2932).			
Further endpoints			
The exploratory analyses of the annual rate of change in eGFR (chronic slope) showed that the eGFR decline was lower for empagliflozin compared with placebo, with a between-group difference of			
1.38 mL/min/1.73 m ² per year and a relative difference of -50%. Subgroup analyses indicated that empagliflozin slowed the rate of eGFR decline with an estimated difference of 0.79 mL/min/1.73 m ² per year vs. placebo in participants with normal UACR, 1.19 and 1.76 mL/min/1.73 m ² per year vs. placebo in participants with micro- and macroalbuminuria, respectively.			
Safety results			
Unless specified otherwise, safety was analysed based on the treated set (all participants who were dispensed study treatment) and included AEs up to 7 days after study treatment termination. For trial-specific safety endpoints (time to first occurrence of events), safety analyses were based on the randomised set (all randomised participants) and included data through trial completion.			
Adverse events			
Empagliflozin and placebo groups had similar frequencies of participants with reported SAEs and prespecified non-serious AEs (Table 3). The frequency of participants reported with AEs leading to discontinuation of study medication was also similar between treatment groups. The frequency of participants with investigator-defined drug-related AEs was low. The frequency of participants with SAEs overall was comparable between both groups. The frequency of participants with fatal AEs was similar in both groups.			
Table 3: Overall summary of serious and prespecified non-serious adverse events – treated set			

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Category of AEs	Placebo N (%)	Empa 10 mg N (%)
Number of participants	3305 (100.0)	3304 (100.0)
Participants with serious and prespecified non-serious AEs	1520 (46.0)	1448 (43.8)
Investigator-defined drug-related AEs	60 (1.8)	79 (2.4)
AEs leading to discontinuation of study medication	242 (7.3)	233 (7.1)
Participants with SAEs	1167 (35.3)	1089 (33.0)
Results in death ¹	96 (2.9)	91 (2.8)

SAEs and protocol prespecified non-serious AEs included.

¹ Only one reason for meeting the seriousness criterion could be selected. Not all fatal events had the "results in death" seriousness criterion selected. The total number of participants with fatal outcome was 130 for empagliflozin and 137 for placebo.

The frequencies of SAEs in each SOC were similar in the empagliflozin and placebo groups. SAEs and prespecified non-serious AEs were most frequently reported in the SOC metabolism and nutrition disorders, followed by infections and infestations, investigations, and renal and urinary disorders. On the PT level, the most frequently reported SAEs and prespecified non-serious AEs were gout (empagliflozin: 231 participants, 7.0%; placebo: 266 participants, 8.0%); acute kidney injury (empagliflozin: 93 participants, 2.8%; placebo: 117 participants, 3.5%); and coronavirus infection (empagliflozin: 98 participants, 3.0%; placebo: 107 participants, 3.2%).

SAEs were most frequently reported in the SOC renal and urinary disorders, and in infections and infestations. For SAEs, the most common PTs were acute kidney injury and coronavirus infection (values were the same as above).

AESIs and specific AEs

The overall frequencies for liver injury, serious urinary tract infection, serious genital infection, severe hypoglycaemia, and urinary tract malignancy were comparable in the empagliflozin and placebo groups (Table 4). Within the individual categories of AESIs and specific AEs, generally similar proportions of participants in both treatment groups had serious AEs. Few AEs in any category of AESIs or specific AEs led to treatment discontinuation.

Table 4: Summary of AESIs and specific AEs – treated set

Category of AESIs and specific AEs	Placebo		Empa 10 mg	
	N (%)	Rate/100 pt-yrs	N (%)	Rate/100 pt-yrs
Number of participants	3305 (100.0)		3304 (100.0)	
Liver injury (adjudicated, AESI)	12 (0.4)	0.20	13 (0.4)	0.22
Serious	7 (0.2)	0.12	5 (0.2)	0.08
Up to 30 days after treatment discontinuation	12 (0.4)	0.20	13 (0.4)	0.22
Ketoacidosis (adjudicated, AESI)	1 (<0.1)	0.02	6 (0.2)	0.10
Serious	1 (<0.1)	0.02	6 (0.2)	0.10
Leading to discontinuation	0	0	0	0
Lower limb amputation (adjudicated, AESI)	14 (0.4)	0.23	26 (0.8)	0.43
Leading to discontinuation	1 (<0.1)	0.02	1 (<0.1)	0.02
Up to final follow up visit	19 (0.6)	0.29	28 (0.8)	0.43
Gout (user-defined)	303 (9.2)	5.35	270 (8.2)	4.75

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Serious	7 (0.2)	0.12	8 (0.2)	0.13
Leading to discontinuation	0	0	1 (<0.1)	0.02
Serious hyperkalaemia (user-defined)	96 (2.9)	1.62	85 (2.6)	1.42
Leading to discontinuation	2 (0.1)	0.03	2 (0.1)	0.03
Serious urinary tract infection (narrow-sub BICMQ)	47 (1.4)	0.78	42 (1.3)	0.70
Leading to discontinuation	5 (0.2)	0.08	3 (0.1)	0.05
Serious genital infection (adjudicated)	0	0	1 (<0.1)	0.02
Volume depletion (narrow sub-BICMQ)	90 (2.7)	1.51	98 (3.0)	1.64
Hypotension (narrow sub-BICMQ, subset of volume depletion)	22 (0.7)	0.36	22 (0.7)	0.36
Serious	41 (1.2)	0.68	46 (1.4)	0.76
Leading to discontinuation	1 (<0.1)	0.02	2 (0.1)	0.03
Symptomatic dehydration (user-defined)	70 (2.1)	1.17	80 (2.4)	1.34
Severe hypoglycaemic events (narrow SMQ)	72 (2.2)	1.21	74 (2.2)	1.24
Serious	14 (0.4)	0.23	13 (0.4)	0.21
Leading to discontinuation	2 (0.1)	0.03	1 (<0.1)	0.02
Bone fracture events (user-defined)	106 (3.2)	1.78	121 (3.7)	2.04
Serious	49 (1.5)	0.82	53 (1.6)	0.88
Leading to discontinuation	2 (0.1)	0.03	1 (<0.1)	0.02
Bone fracture events (narrow BICMQ) up to trial completion	123 (3.7)	1.86	136 (4.1)	2.06
Urinary tract malignancy up to trial completion (broad sub-BICMQ)	15 (0.5)	0.22	19 (0.6)	0.28

SMQ, standardised MedDRA query; BICMQ, Boehringer Ingelheim customised MedDRA query

Adjudication of events stopped at final follow-up period; any residual effect period afterwards was not considered for these events.

Lower limb amputation

The frequency of participants with lower limb amputation (LLA) (adjudicated) in the empagliflozin group and in the placebo group is provided in Table 4. In both groups, the most commonly reported PT was toe amputation. The majority of events were reported in participants with diabetes.

The hazard ratio based on Cox regression for empagliflozin vs. placebo for time to first occurrence of an adjudicated LLA was 1.43 (95% CI 0.80, 2.57) (randomised set, data through trial completion).

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Volume depletion

The frequency of participants with volume depletion (narrow sub-BIcMQ) for the empagliflozin group compared with placebo is provided in Table 4. In both treatment groups the most frequently reported PT was dehydration. The treatment groups were similar in the frequencies of participants with serious volume depletion and few participants in either group discontinued study treatment due to volume depletion. The frequency of participants with hypotension (narrow sub-BIcMQ) was similar between groups. The treatment groups were similar in the frequencies of participants with serious hypotension and one participant in each group discontinued study treatment due to hypotension.

The hazard ratio based on Cox regression for empagliflozin participants vs. placebo for time to first occurrence of a (user-defined) dehydration SAE was 1.25 (95% CI 0.73, 2.14) (randomised set, data through trial completion).

Symptomatic dehydration

The frequency of symptomatic dehydration between groups (symptomatic dehydration, user-defined) is provided in Table 4. One participant in the empagliflozin group and no patients in the placebo group discontinued study treatment due to symptomatic dehydration.

The hazard ratio based on Cox regression for empagliflozin participants vs. placebo for time to first occurrence of a symptomatic dehydration (user-defined) was 1.10 (95% CI 0.81, 1.51) (randomised set, data through trial completion).

Bone fracture

The overall frequency of bone fracture AEs in participants in the empagliflozin group and the placebo group is provided in Table 4.

The hazard ratio based on Cox regression for empagliflozin vs. placebo for time to first occurrence of an AE of bone fracture was 1.08 (95% CI 0.84, 1.38) (randomised set, data through trial completion).

Ketoacidosis

The rate of ketoacidosis was low. It occurred in 6 participants in the empagliflozin group vs. 1 participant in the placebo group (0.10 vs. 0.02 per 100 patient-years, respectively) (Table 4).

Laboratory and other observations

Haemoglobin and haematocrit levels at Month 18 were higher in the empagliflozin group than the placebo group in UK participants, with an increase compared with baseline observed in the empagliflozin group and a decrease in the placebo group. No relevant changes in the other safety laboratory parameters were observed.

Participants in both treatment groups had decreases in weight over time. Average change from baseline in the empagliflozin group was -1.55 kg and was -0.68 kg in the placebo group (MMRM analysis; RS, OC-AD).

Participants in both treatment groups had decreases in SBP and DBP over time. Average change from baseline in SBP was -3.9 mm Hg in the empagliflozin group and -1.3 mm Hg in the placebo group (MMRM analysis; RS, OC-AD). Average change from baseline in DBP was -1.6 mm Hg in the empagliflozin group and -1.2 mm Hg in the placebo group (MMRM analysis; RS, OC-AD).

Conclusions

Treatment with empagliflozin demonstrated a clinically meaningful cardio-renal benefit in a broad range of CKD patients. A statistically significant 28% risk reduction in kidney disease progression or CV death

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(primary endpoint) was observed with empagliflozin as compared to placebo. Of note, the kidney protective effects of empagliflozin were evident in patients irrespective of diabetes status and eGFR category at baseline. There was a trend towards an increasing treatment effect in participants with higher levels of UACR at baseline. However, exploratory analyses on accepted surrogate endpoints for kidney disease progression, e.g. chronic eGFR slopes support that empagliflozin is also likely to be effective in patients with less pronounced albuminuria. Empagliflozin was also superior to placebo in reducing the risk of			
hospitalisations for any cause by 14% and the treatment effects were consistent regardless of diabetes status, eGFR or albuminuria levels. The results from the adverse events and safety laboratory analyses were generally consistent with the known safety profile of empagliflozin. The overall benefit and risk assessment was positive for empagliflozin in a broad spectrum of patients with CKD.			

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Name of company: Boehringer Ingelheim		Synopsis		 Boehringer Ingelheim																									
BI proprietary name: Jardiance®		EudraCT number(s): 2017-002971-24																											
BI investigational product: Empagliflozin, BI 10773		Page: 1 of 11																											
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Title of substudy A post-trial observational substudy of EMPA-KIDNEY participants followed for mortality and kidney disease progression Lay title of the main trial EMPA-KIDNEY (The study of heart and kidney protection with empagliflozin) Coordinating investigator [REDACTED] [REDACTED] UK Trial sites with screened participants Multicentre trial in 185 sites (with screened participants) in Canada, China, Germany, Italy, Malaysia, United Kingdom, and the USA Publications Herrington WG, Staplin N, Agrawal N, et al. Long-term effects of empagliflozin in patients with chronic kidney disease. NEJM 2025;392(8):777-787 Clinical phase(s): III + Post trial Objectives The objective of this post-trial follow-up (PTFU) study was to continue FU of a subset of surviving EMPA-KIDNEY patients for at least 2 years after the end of the within-trial period in order to provide valuable information on the longer-term effects of empagliflozin 10 mg daily versus matching placebo on mortality and kidney disease progression in people with chronic kidney disease (CKD) Methodology Randomised, parallel group, double-blind, placebo-controlled within-trial period followed by an observational PTFU study Number of participants <table border="1"><tr><td>Planned:</td><td>Entered into main study: 6609</td><td colspan="3"></td></tr><tr><td>Actual:</td><td>Entered into substudy: 4891</td><td colspan="3"></td></tr><tr><td></td><td></td><td>Entered</td><td>Completed</td><td>Analysed</td></tr><tr><td></td><td></td><td>2472</td><td>2472</td><td>2472</td></tr><tr><td></td><td></td><td>2419</td><td>2371</td><td>2419</td></tr></table>					Planned:	Entered into main study: 6609				Actual:	Entered into substudy: 4891						Entered	Completed	Analysed			2472	2472	2472			2419	2371	2419
Planned:	Entered into main study: 6609																												
Actual:	Entered into substudy: 4891																												
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Diagnosis

Patients with evidence of CKD at risk of kidney disease progression, with or without diagnosed diabetes mellitus.

Main criteria for inclusion

For the main trial:

Adults with a race-adjusted estimated glomerular filtration rate (eGFR, calculated with the use of the 2009 Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] formula) of

- CKD-EPI eGFR ≥ 20 to < 45 mL/min/1.73 m²; or
- CKD-EPI eGFR ≥ 45 to < 90 mL/min/1.73 m² with urinary albumin to creatinine ratio (UACR) ≥ 200 mg/g (or protein to creatinine ratio ≥ 300 mg/g)

For the PTFU: Any randomised EMPA-KIDNEY participant from a contributing region/site who consented to be contacted to provide updated information about their health after the scheduled FU period and was known to be alive at Final Follow-up (FU).

BI investigational product: Empagliflozin, film-coated tablets

Dose: Not applicable, no study treatment was issued

Mode of administration: Not applicable

Comparator product: Placebo

Dose: Not applicable, no study treatment was issued

Mode of administration: Not applicable

Observational period

≥ 2 years

Efficacy

All assessments were for the entire FU period, i.e. the within-trial plus the PTFU periods combined and were as follows:

The **primary outcome** was the time to the first occurrence of composite kidney disease progression (defined as ESKD [end stage kidney disease; defined as the initiation of maintenance dialysis or receipt of a kidney transplant], a sustained decline in eGFR to < 10 mL/min/1.73m², renal death, or a sustained decline of $\geq 40\%$ in eGFR from randomisation); or cardiovascular death

The **secondary outcomes** were time to first occurrence of:

- kidney disease progression alone; and
- death from any cause or ESKD
- ESKD.

The **tertiary outcomes** were

- mortality-based outcomes: time to death from any cause and, death from cardiovascular and non-cardiovascular causes (cardiovascular causes included coronary death, other cardiac [including heart failure and sudden cardiac death not known to be coronary], stroke, other cardiovascular and presumed cardiovascular causes. Non-cardiovascular included renal, infection, cancer, other medical, and non-medical causes).

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- b) subgroup analyses of the primary PTFU assessment based on data recorded at baseline:
- 1) diabetes status (present, absent)
 - 2) eGFR (<30, 30 to <45, ≥45)
 - 3) UACR (<30, 30 to <300, ≥300)
 - 4) primary renal disease (diabetic kidney, hypertensive/renovascular, glomerular, other/unknown)

Exploratory eGFR-based assessments included analyses of the effects of empagliflozin on annual rate of change in eGFR calculated for the whole within- and post-trial FU period (combined) for the overall population and among the key subgroups.

Safety criteria for evaluation

As no study treatment was issued during the post-trial FU phase there were no pre-specified assessments of Serious Adverse Events (SAEs) or other biochemical data from the post-trial observational FU period (other than those specified above).

Statistical methods

Cox proportional hazards regression adjusted for the variables specified in the protocol for the minimisation algorithm (age, sex, prior diabetes, eGFR, urinary albumin-to-creatinine ratio, and region) were used to estimate the hazard ratio associated with allocation to empagliflozin versus placebo (with the Wald chi-square statistic used to both test significance and generate an asymptotic 95% confidence interval). Any ties were handled using Breslow's method. If any regression models failed to converge, the approaches set out in the main data analysis plan (DAP) were followed. Kaplan-Meier estimates for the time to each of the primary and secondary assessments were also calculated. Plots included indicators of median within-trial and entire FU durations. To explore whether the effect of allocation to empagliflozin versus placebo on the primary outcome differed over time, FU time was split into categories by year since randomisation and the significance of the time by treatment allocation interaction was assessed. In addition to the pre-specified comparisons, other post-hoc analyses could be performed with due allowance for their exploratory and, perhaps, data-dependent nature. Methods for handling missing and incomplete data followed the approaches from the main DAP, with the exception of when local eGFR measurements were used in preference to central samples in the relevant analyses. eGFR was estimated using the same CKD-EPI formula as per the main DAP analyses and used the DAP defined FU windows and the principles of the algorithm to define sustained. No interim analyses was conducted.

SUMMARY - CONCLUSIONS:

Trial participants and compliance with the clinical trial protocol

The substudy was conducted in 4891 participants (empagliflozin: 2472 participants, placebo: 2419 participants). The PTFU was completed by 2427 participants in the empagliflozin group, and 2371 in the placebo group. For 45 participants in the empagliflozin group and 48 participants in the placebo group follow-up was incomplete (in the empagliflozin group 4 participants withdrew consent during PTFU, for 41 participants the mortality status was unknown after 01 Apr 2024; in the placebo group 3 participants withdrew consent and for 45 participants the mortality status was unknown after 01 Apr 2024). In the empagliflozin group 148 participants and in the placebo group 167 participants died during the active trial period and 1 participant each from both groups died during the PTFU. The demographic and baseline characteristics of the participants entering the PTFU are presented in Table 1; Table 2 summarises the use of SGLT2 inhibitors by time.

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Table 1 Demographic and baseline characteristics by treatment allocation

	Empagliflozin 10 mg	Placebo
Number of participants, N	2472	2419
Age at randomisation in years (SD)	63 (14)	63 (14)
Female, N (%)	840 (34%)	824 (34%)
Male, N (%)	1632 (66%)	1595 (66%)
Race, N (%)		
White	1552 (63%)	1503 (62%)
Black	91 (4%)	87 (4%)
Asian	791 (32%)	791 (33%)
Mixed	14 (1%)	6 (<1%)
Other	24 (1%)	32 (1%)
Prior disease		
Prior diabetes ¹	1087 (44%)	1020 (42%)
Prior cardiovascular disease ²	639 (26%)	641 (26%)
Clinical measurements		
Systolic blood pressure (mmHg)	136.9 (18.3)	136.9 (18.3)
Diastolic blood pressure (mmHg)	78.6 (11.6)	78.6 (11.8)
Body mass index (kg/m ²) ³	29.9 (6.6)	30.0 (6.7)
Laboratory measurements		
eGFR (mL/min/1.73m²)⁴		
Mean (SD)	36.9 (14.1)	36.9 (14.1)
<30	854 (35%)	857 (35%)
≥30 to <45	1128 (46%)	1082 (45%)
≥45	490 (20%)	480 (20%)
uACR (mg/g)⁴		
Geometric mean (approx. SE)	212 (9)	214 (9)
Median (Q1-Q3)	324 (44-1045)	313 (45-1079)
<30	515 (21%)	515 (21%)
≥30 to ≤300	686 (28%)	677 (28%)
>300	1271 (51%)	1227 (51%)
Concomitant medication use		
RAS inhibitor ⁵	2142 (87%)	2066 (85%)
Any diuretic	1028 (42%)	1052 (43%)
Any lipid-lowering medication	1638 (66%)	1582 (65%)
Cause of kidney disease		
Diabetic kidney disease	727 (29%)	677 (28%)
Hypertensive/renovascular disease	553 (22%)	572 (24%)
Glomerular disease	670 (27%)	636 (26%)
Other/unknown	522 (21%)	534 (22%)
5 year predicted kidney failure risk (%)		
Median (Q1-Q3)	10 (3-29)	10 (3-30)

N=total number of participants included in the analysis; Q = quartile; RAS = renin-angiotensin system; SD = standard deviation; SE = standard error of the mean; Data are n (%), mean (SD), geometric mean (approx. SE), or median (Q1-Q3); eGFR=estimated glomerular filtration rate, uACR=urinary albumin-to-creatinine ratio, RAS=renin-angiotensin system.

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- 1) Prior diabetes mellitus at randomisation was defined as participant-reported history of diabetes of any type, use of glucose-lowering medication, or baseline HbA1c ≥ 48 mmol/mol at randomisation visit. Prior cardiovascular disease defined as self-reported history of myocardial infarction, heart failure, stroke, transient ischemic attack, or peripheral arterial disease.
- 2) Those with missing data for BMI (n=12) are not presented in relevant rows.
- 3) Used central measurement taken at the randomisation visit, or most recent local laboratory result before randomisation.
- 4) Participants were required to be taking a clinically appropriate dose of a single-agent renin-angiotensin system (RAS) inhibitor, unless the investigator had determined that such medication either was not indicated or had an unacceptable side-effect profile (see Section 3.3.4 of the CTP of main study).

The participants who were included in the PTFU were broadly representative of the population of participants with chronic kidney disease who are at risk for disease progression, and baseline characteristics at randomisation were similar in the empagliflozin and placebo groups (Table 1).

Table 2 Use of SGLT2 inhibitors by time.

	Empagliflozin 10 mg	Placebo
All patients	N=3304	N=3305
Active trial period		
12 months	2920/3164 (92%)	21/3159 (1%)
24 months	1661/1884 (88%)	41/1875 (2%)
36 months	270/326 (83%)	12/323 (4%)
Participants entering PTFU	N=2472	N=2419
Active trial period		
12 months	2264/2423 (93%)	13/2363 (1%)
24 months	1319/1483 (89%)	30/1417 (2%)
36 months	254/297 (86%)	10/289 (3%)
Post-trial period		
12 months	885/2186 (40%)	804/2147 (37%)
24 months	1078/2376 (45%)	972/2312 (42%)
All Participants entering PTFU excluding participants on kidney replacement therapy		
12 months	880/2032 (43%)	797/1960 (41%)
24 months	1069/2129 (50%)	961/2015 (48%)

Active trial periods defined using 12-, 24-, and 36-months FU visit windows. Use in the active trial defined as a participant reporting taking $\geq 80\%$ of allocated study drug or open-label SGLT2 inhibitor (denominators are those known to be alive in each period). Post-trial periods were defined using information nearest to 12 and 24 months since completion of active trial follow-up. Post-trial open-label SGLT2 inhibitor use was ascertained from review of participant's medical records, or where necessary, direct contact with participants (denominators are those who joined post-trial FU, had a FU in the period and were known to be alive in the relevant period).

Empagliflozin (or an open-label SGLT2 inhibitor) was used during the active-trial period at 12, 24 and 36 months by 93%, 89%, and 86%, respectively, of the participants entering the PTFU from the empagliflozin group, and 1%, 2%, and 3%, respectively, of those from the placebo group. During the post-trial period, the use of open-label SGLT2 inhibitors was similar in the two groups (40% and 45% at 12 and 24 months, and 37% and 42%, respectively) (Table 2).

Efficacy

Figure 1 presents the results of the primary endpoint, Table 3 presents the primary, secondary, tertiary and exploratory outcomes over the entirety of FU (i.e. the within-trial plus PTFU).

During the combined active- and post-trial periods, the progression of kidney disease or death from cardiovascular causes (the primary outcome) occurred in 865 of 3304 participants (26.2%) in the

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empagliflozin group and in 1001 participants of 3305 (30.3%) in the placebo group (hazard ratio, 0.79; 95% confidence interval [CI] 0.72, 0.87). This hazard ratio is a combination of the hazard ratio for the active trial period (0.72; 95% CI 0.64, 0.82, with 990 outcomes) and the hazard ratio for the post-trial period (0.87; 95% CI 0.76, 0.99, with 876 additional first primary-outcome events) (Figure 1, upper panel and Table 3). Much of the post-trial benefit regarding the primary outcome event occurred early, with a hazard ratio for the first 6 months of the post-trial period of 0.60 (95% CI, 0.38, 0.93), a hazard ratio for the first year of 0.76 (95% CI 0.60, 0.96), and a hazard ratio for the second year of 0.90 (95% CI 0.7, 1.07) (Figure 1, lower panel). The effect on the primary outcome during the combined periods included a risk of kidney disease progression (a secondary outcome) that was 21% lower in the empagliflozin group than in the placebo group (23.5% and 27.1%, respectively), with a hazard ratio of 0.79 (95% CI 0.72, 0.87). The risk of end-stage kidney disease was 9.0% in the empagliflozin group and 11.3% in the placebo group (hazard ratio, 0.74; 95% CI 0.64, 0.87). During the combined active- and post-trial periods, the risk of death from a cardiovascular cause was 3.8% in the empagliflozin group and 4.9% in the placebo group (hazard ratio, 0.75; 95% CI 0.59, 0.95); no material effect on the risk of death from non-cardiovascular causes was observed, with 5.3% in both groups (hazard ratio, 0.97; 95% CI 0.79, 1.20). There were 301 deaths (9.1%) and 336 deaths (10.2%) in the empagliflozin and placebo group, respectively, from any cause (hazard ratio, 0.86; 95% CI 0.74, 1.01) (Table 3 and Figure 2).

Table 3 Effect of allocation to empagliflozin on primary, secondary, tertiary and exploratory (estimated glomerular filtration rate-based) outcomes over the entirety of follow-up (i.e. combining active trial and post-trial follow-up periods)

	Empagliflozin (N=3304)		Placebo (N=3305)		
	Participants with event	No. of events per 100 py	Participants with event	No. of events per 100 py	Hazard ratio (95% CI)
Primary outcome					
Progression of kidney disease or death from cardiovascular causes	865 (26.2%)	8.4	1001 (30.3%)	10.0	0.79 (0.72 to 0.87)
Secondary outcomes					
Kidney disease progression	778 (23.5%)	7.5	897 (27.1%)	9.0	0.79 (0.72 to 0.87)
Death from any cause or ESKD	559 (16.9%)	5.1	648 (19.6%)	6.1	0.81 (0.72 to 0.90)
ESKD	296 (9.0%)	2.7	372 (11.3%)	3.5	0.74 (0.64 to 0.87)
Tertiary outcomes:					
Death from any cause	301 (9.1%)	2.7	336 (10.2%)	3.0	0.86 (0.74 to 1.01)
Death from cardiovascular cause	126 (3.8%)	1.1	162 (4.9%)	1.5	0.75 (0.59 to 0.95)
Death from non-cardiovascular cause	175 (5.3%)	1.5	174 (5.3%)	1.6	0.97 (0.79 to 1.20)
Exploratory outcomes					
	Participants with measurement	Mean eGFR	Participants with measurement	Mean eGFR	Absolute difference ² (95% CI)
eGFR at last local measurement, [mL/min/1.73m ²] ¹	3295 (>99%)	31.4 (0.2)	3295 (>99%)	30.6 (0.2)	0.8 (0.1,1.4)

ESKD = end-stage kidney disease; eGFR = estimated glomerular filtration rate; py = patient year.

All analyses included all patients for the active trial period preserving the active trial results.

- 1) Last local measurement defined as the last local creatinine value recorded prior to death, ESKD (i.e. date of commencement of maintenance dialysis or receipt of a kidney transplant), withdrawal of consent, or end of FU.
- 2) Absolute difference estimated using ANCOVA.

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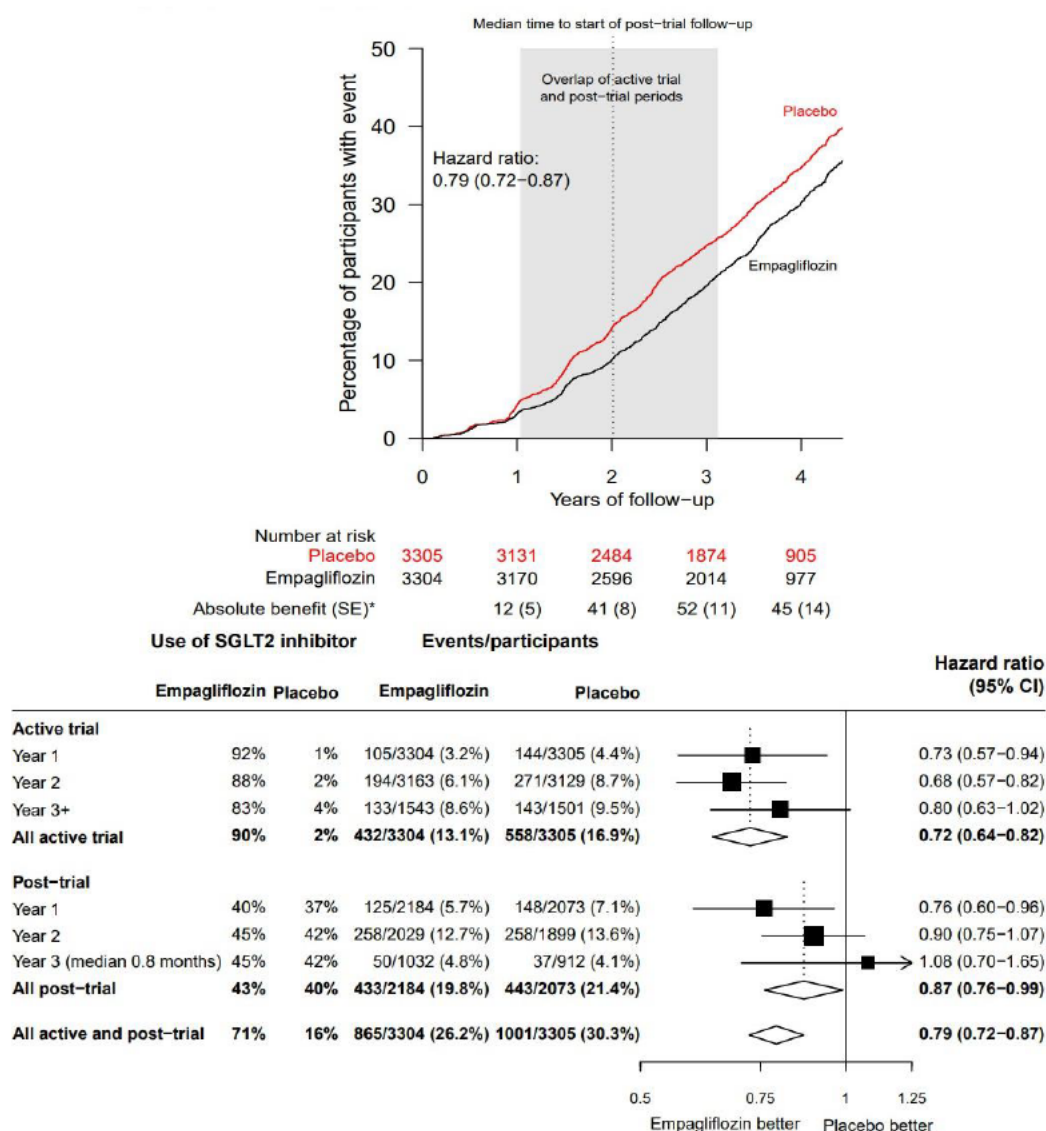


Figure 1 Effect of allocation to empagliflozin on progression of kidney disease or death from cardiovascular causes (upper panel: for the entirety of FU, i.e. active and PTFU combined, lower panel: by year during active trial and PTFU)

* Absolute difference in number of events per 1000 patients allocated to receive empagliflozin during the active trial period as calculated from the between-group difference in Kaplan-Meier curves

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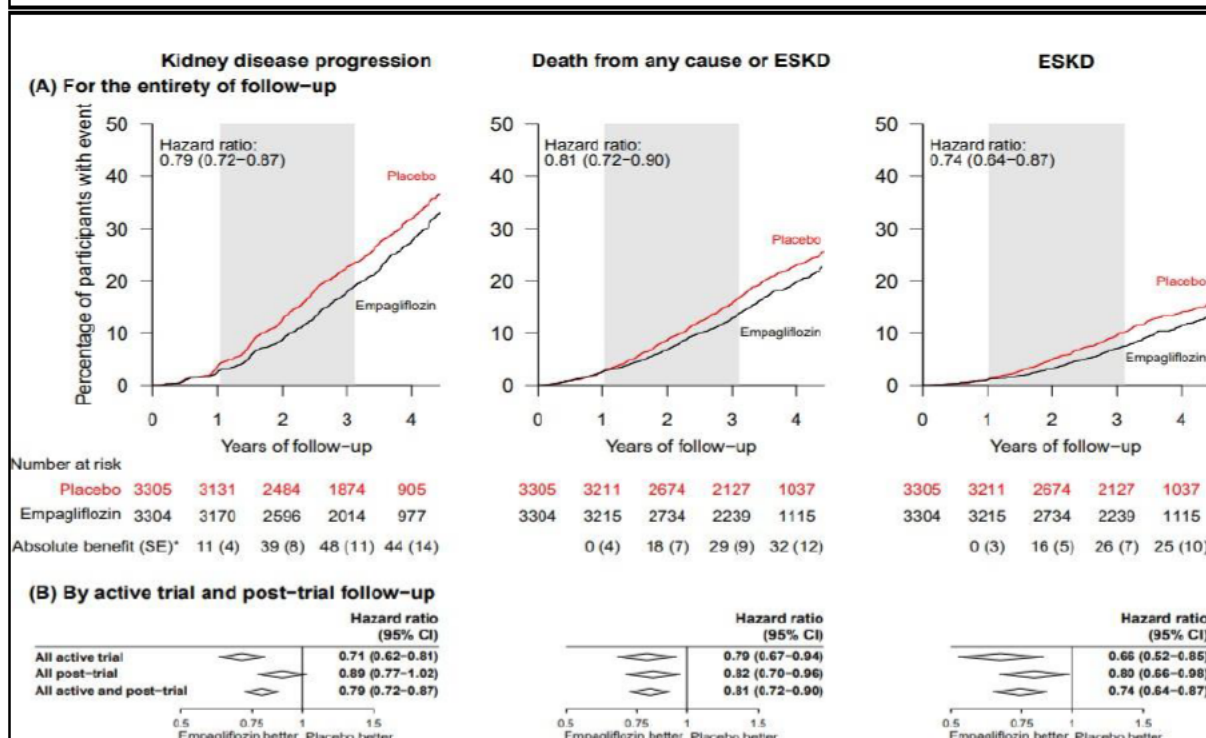


Figure 2 Effect of allocation to empagliflozin on secondary outcomes over the entirety of FU

* Absolute difference in number of events per 1000 patients allocated to receive empagliflozin during the active trial period as calculated from the between-group difference in Kaplan-Meier curves

Table 4 presents the absolute between-group difference ($\pm$ SE) in Kaplan-Meier curves. A primary-outcome event had occurred in 57 ± 14 fewer patients per 1000 population in the empagliflozin group than in the placebo group at the end of the active-trial period and in 45 ± 14 fewer patients per 1000 population at the end of the combined active- and post-trial periods; ESKD had occurred in 26 ± 8 fewer patients per 1000 population in the empagliflozin group at the end of the active-trial period and in 25 ± 10 fewer patients per 1000 population at the end of the combined period; and death or ESKD had occurred in 25 ± 11 and 32 ± 12 fewer patients per 1000 population, respectively, at the end of the two periods.

Table 4 Absolute benefits of allocation to empagliflozin on primary and secondary outcomes over the entirety of follow-up

Absolute difference in number of events per 1000 patients allocated to empagliflozin				
	Kidney disease progression or CV death	Kidney disease progression	Death from any cause or ESKD	ESKD
Active trial period only				
End of year 1	12 (5)	11 (4)	0 (4)	0 (3)
End of year 2	43 (10)	42 (9)	19 (8)	17 (6)
End of active trial period (2.5 y)	57 (14)	56 (14)	25 (11)	26 (8)
Post-trial period only				

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Table 4 (continued) Absolute benefits of allocation to empagliflozin on primary and secondary outcomes over the entirety of follow-up

Absolute difference in number of events per 1000 patients allocated to empagliflozin				
	Kidney disease progression or CV death	Kidney disease progression	Death from any cause or ESKD	ESKD
End of year 1	15 (8)	14 (7)	10 (7)	8 (6)
End of year 2	25 (13)	19 (13)	19 (10)	12 (9)
Active trial and post-trial periods combined				
End of year 1	12 (5)	11 (4)	0 (4)	0 (3)
End of year 2	41 (8)	39 (8)	18 (7)	16 (5)
End of year 3	52 (11)	48 (11)	29 (9)	26 (7)
End of year 4	45 (14)	44 (14)	32 (12)	25 (10)

CV = cardiovascular; ESKD = end-stage kidney disease (i.e. date of commencement of maintenance dialysis or receipt of a kidney transplant).

Subgroup analyses

Figure 3 presents the results of the primary outcome among subgroups.

The relative effects on the primary outcome were similar in subgroup analyses according to baseline diabetes status, eGFR, UACR, and primary cause of kidney disease.

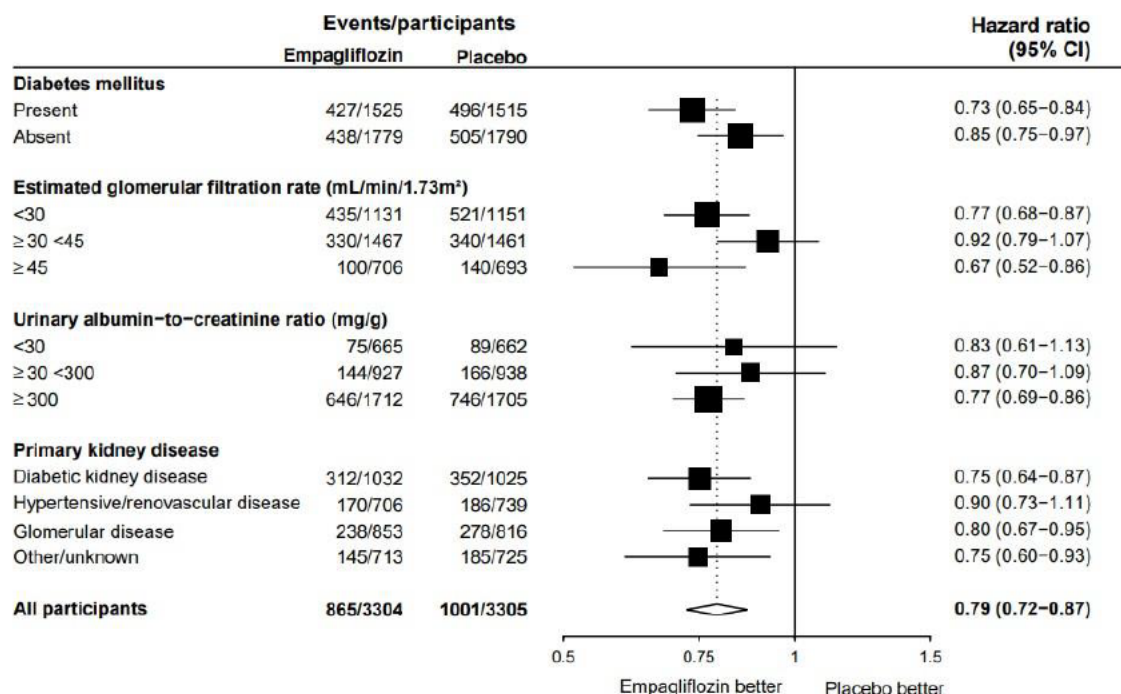
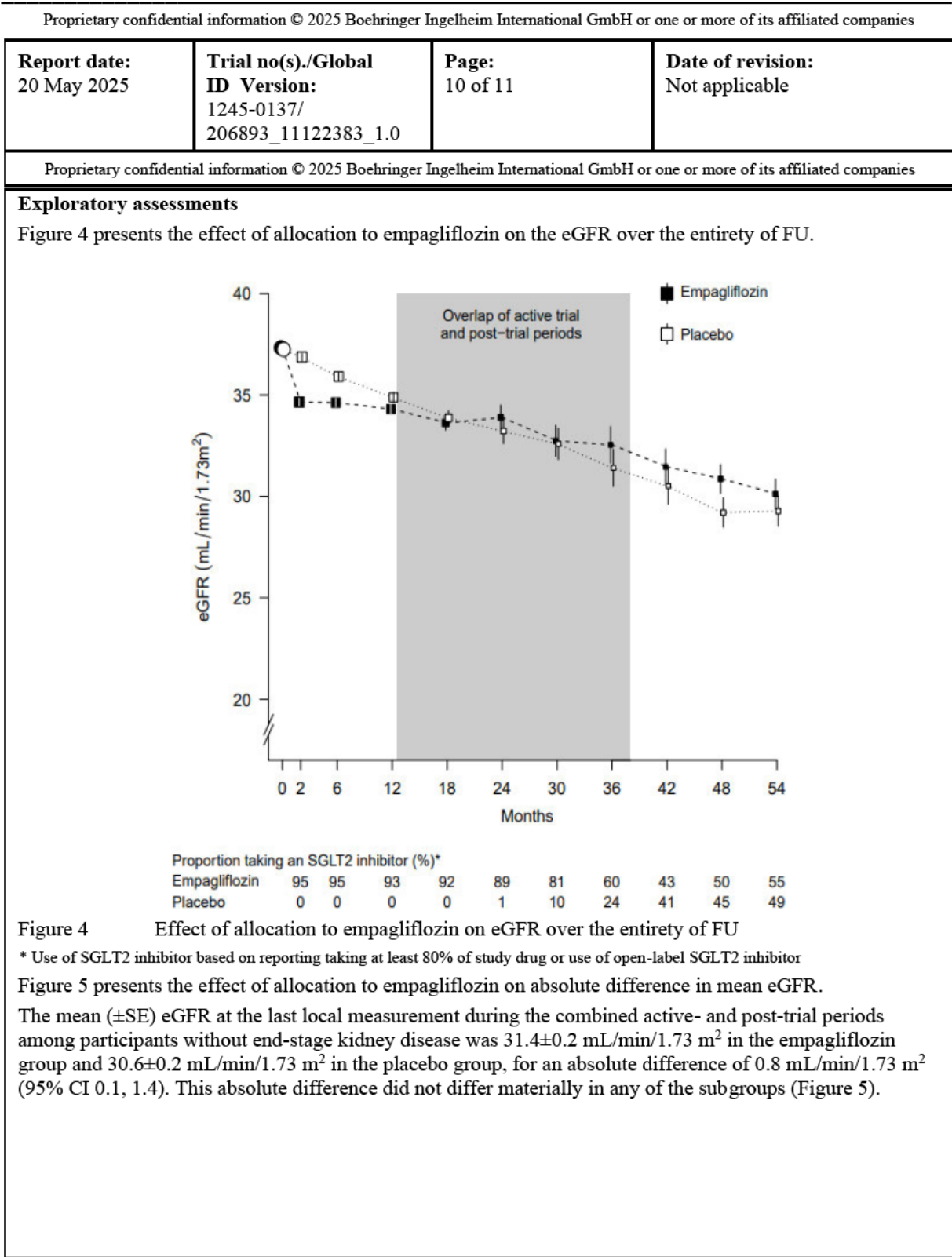


Figure 3 Effect of allocation to empagliflozin on progression of kidney disease or death from cardiovascular causes over the entirety of follow-up by key pre-specified subgroups



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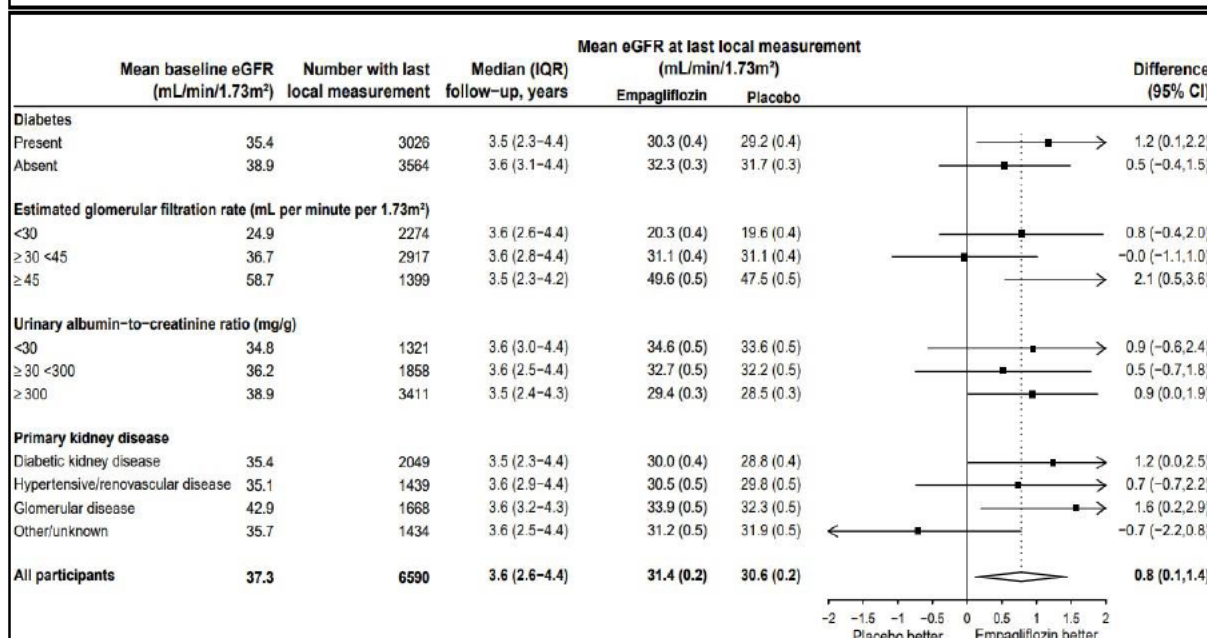


Figure 5 Effect of allocation to empagliflozin on absolute difference in mean estimated glomerular filtration rate in key pre-specified subgroups

* Last measurement was defined at the last creatinine value recorded prior to death, ESKD (i.e. date of commencement of maintenance dialysis or receipt of a kidney transplant), withdrawal of consent or end of FU. All analyses are based on local creatinine values.

Safety results

Not applicable

Conclusions

In a broad range of participants with chronic kidney disease at risk for progression, empagliflozin continued to have additional cardiorenal benefits for up to 12 months after it was discontinued.

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Name of company: Boehringer Ingelheim		Synopsis	 Boehringer Ingelheim
Boehringer Ingelheim proprietary name: Jardiance®		EudraCT number: 2017-002971-24	
Boehringer Ingelheim investigational product: Empagliflozin, BI 10773		Page: 1 of 8	
Report date: 22 May 2025	Trial no./ Global ID_Version: 1245-0137/ 206893_11122607_1.0	Dates of substudy: 04 Feb 2020 – 05 Dec 2022	Date of revision: Not applicable
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Title of substudy EMPA-KIDNEY Magnetic Resonance Imaging Substudy EMPA-KIDNEY: A multicentre international randomized parallel group double-blind placebo-controlled clinical trial of EMPagliflozin once daily to assess cardio-renal outcomes in patients with chronic KIDNEY disease Lay title of main trial EMPA-KIDNEY (The study of heart and kidney protection with empagliflozin) Chief investigator [REDACTED] [REDACTED] UK Co-Principal investigator [REDACTED] [REDACTED] UK Trial sites with screened participants Eight sites with screened participants in the UK (7 sites) and Germany (1 site) contributed to the substudy. Publications Judge P. Effects of empagliflozin on kidney and cardiac MRI measures in patients with chronic kidney disease. Nephrology Dialysis Transplantation, Volume 38, Issue Supplement_1, June 2023. Judge P. Effects of empagliflozin on renal and cardiac MRI measures in patients with chronic kidney disease. Presented at: 60 th European Renal Association Congress, 15-18 Jun 2023, Milan and Virtual. Clinical phase: Not applicable Objectives The objective of this substudy was to image participant's kidneys and hearts using multiparametric Magnetic Resonance Imaging (MRI) to assess the effects of empagliflozin 10 mg versus matching placebo on the structure and function of the kidneys and hearts of participants with chronic kidney disease (CKD) at around 18 months after randomisation. Methodology It was planned to include approximately 172 EMPA-KIDNEY participants from the UK and Germany.			

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Methodology (continued)

Images were taken of the participants' kidneys and hearts using MRI during Follow-up (at about 18 months after randomisation). An MRI was also taken at baseline, if possible. The substudy did not alter the main protocol of the EMPA-KIDNEY trial in any respect.

Number of subjects

Planned:	Entered: Approximately 172			
Actual:		Consented to join substudy	Included in substudy	Analysed (for primary outcome)
	Overall	172	172	172
	Empagliflozin 10 mg	93	93	93
	Placebo	79	79	79

Diagnosis

Participants with CKD at risk of kidney disease progression.

Main criteria for inclusion

EMPA-KIDNEY participants without an obvious contraindication for an MRI scan were invited to join the optional substudy at participating sites in the UK and Germany.

The main criteria for inclusion in the EMPA-KIDNEY trial and therefore in the substudy were evidence of progressive CKD at risk of kidney disease progression defined on the basis of local laboratory results recorded at least 3 months before and at the time of the Screening visit, and required that:

- CKD-EPI eGFR ≥ 20 to < 45 mL/min/1.73 m²; or
- CKD-EPI eGFR ≥ 45 to < 90 mL/min/1.73 m² with uACR ≥ 200 mg/g (or protein to creatinine ratio ≥ 300 mg/g)

CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration; eGFR = estimated Glomerular Filtration Rate; uACR = urinary Albumin:Creatinine Ratio

Participants were to be ≥ 18 years at Screening and a local investigator had to judge that the participant neither required empagliflozin (or any other sodium-glucose co-transporter [SGLT]-2 or SGLT-1/2 inhibitor), nor that such treatment was inappropriate.

BI investigational product:	Empagliflozin, film-coated tablets
Dose:	10 mg once daily
Mode of administration:	Oral
Comparator product:	Placebo, film-coated tablets to match empagliflozin
Dose:	Not applicable
Mode of administration:	Oral

Duration of treatment

Around 18 months after randomisation in the main trial.

Other criteria for evaluation

The primary outcome was the effect of allocation to empagliflozin versus matching placebo on kidney cortical T1 mapping as measured by Modified Look-Locker Inversion Recovery (MOLLI) at about 18 months after randomisation, measured using MRI.

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Other criteria for evaluation (continued)

Secondary outcomes used multiparametric MRI to assess the effects of empagliflozin 10 mg versus matching placebo at 18 months on:

- Kidney measures: kidney size (measured by total kidney volume), kidney arterial flow (measured using the mean of left and right renal arterial flow), kidney global perfusion (measured by phase contrast MRI corrected for total kidney volume), kidney diffusion (measured by apparent diffusion coefficient), kidney oxygenation (measured by blood oxygen level dependent [BOLD] T2), and kidney fat content mapping (measured by modified DIXON [mDIXON])
- Cardiac measures: Left ventricular mass index (i.e., normalised to body surface area), left ventricular ejection fraction, cardiac fibrosis measured by T1 MOLLI (mean of measurements at apex, wall, and base of left ventricle), and diastolic dysfunction (measured by left ventricular strain, left ventricular global longitudinal strain, left ventricular diastolic strain rate, and left ventricular volume)

Tertiary outcomes included:

- Subgroup analyses of the effects of empagliflozin 10 mg versus matching placebo on T1 mapping by baseline feature (age, sex, diabetes status, eGFR, and uACR)
- Amongst the proportion of participants with a baseline MRI scan, assessments of the effects of empagliflozin 10 mg versus matching placebo on follow-up MRI measurements adjusted for baseline

Safety criteria for evaluation

None

Statistical methods

All analyses involved an intention-to-treat comparison among all randomised participants with a valid MRI scan. All MRI measurements were analysed as continuous variables. Differences in MRI measurements between treatment groups were assessed using a linear regression approach adjusted for the elements included in the minimisation algorithm which determined treatment allocation (age, sex, prior diabetes, eGFR, and uACR). If outcomes were not normally distributed, then appropriate transformations (e.g. log transformation) were made.

Subgroup analyses were conducted by fitting relevant interaction terms for subgroups in linear regression models with the aim of assessing whether the effects in specific subgroups were statistically different from the overall effect. Among those with both a baseline and follow-up MRI scan, sensitivity analyses were additionally adjusted for the baseline MRI estimates by fitting a linear regression model.

Participants with a particular missing MRI measurement were still included in analyses and these values were imputed using multiple imputation, using 20 imputed data sets, with results across imputations combined. The imputation procedure took into consideration each participant's key baseline characteristics, treatment allocation, and other available MRI measurement parameters. Results from the imputed analyses were compared with those from equivalent "complete-case" analyses, but primary emphasis was placed on the results after multiple imputation.

No interim analyses were planned or performed.

SUMMARY - CONCLUSIONS:

Trial participants

The substudy was conducted in 172 participants (empagliflozin: 93 participants; placebo: 79 participants). The demographic and baseline characteristics of the participants are presented in Table 1.

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Trial participants (continued)

Table 1 Baseline characteristics by treatment allocation

Characteristics	Empagliflozin (N=93)	Placebo (N=79)	Total (N=172)
Age [years], mean±SD	59.7±15.5	61.0±15.2	60.3±15.3
Sex			
Male, N (%)	67 (72%)	60 (76%)	127 (74%)
Female, N (%)	26 (28%)	19 (24%)	45 (26%)
Race			
White, N (%)	86 (92%)	74 (94%)	160 (93%)
Black/African American, N (%)	1 (1%)	1 (1%)	2 (1%)
Asian, N (%)	5 (5%)	2 (3%)	7 (4%)
Other (e.g. Mixed race), N (%)	1 (1%)	2 (3%)	3 (2%)
Country			
United Kingdom, N (%)	61 (66%)	47 (59%)	108 (63%)
Germany, N (%)	32 (34%)	32 (41%)	64 (37%)
Prior diabetes ¹ , N (%)	22 (24%)	18 (23%)	40 (23%)
History of cardiovascular disease ² , N (%)	13 (14%)	20 (25%)	33 (19%)
History of patient-reported heart failure, N (%)	5 (5%)	8 (10%)	13 (8%)
Clinical measurements			
Systolic blood pressure [mmHg], mean±SD	139±18	138±19	138±19
Diastolic blood pressure [mmHg], mean±SD	80±11	82±12	81±12
Body mass index [kg/m ²], mean±SD	29.4±5.7	28.4±5.3	28.9±5.5
Estimated Glomerular Filtration Rate ³ (mL/min/1.73m ²), mean±SD	36.1±14.2	37.3±10.9	36.6±12.8
<30, N (%)	32 (34%)	20 (25%)	52 (30%)
≥30 to <45, N (%)	45 (48%)	43 (54%)	88 (51%)
≥45, N (%)	16 (17%)	16 (20%)	32 (19%)
Urinary Albumin:Creatinine Ratio ³ [mg/g], median (Q1-Q3)	555 (81-1253)	409 (54-746)	442 (63-1030)
<30, N (%)	17 (18%)	15 (19%)	32 (19%)
≥30 to <300, N (%)	20 (22%)	21 (27%)	41 (24%)
≥300, N (%)	56 (60%)	43 (54%)	99 (58%)
NT-proBNP [ng/L], median (Q1-Q3)	134 (59-248)	128 (71-314)	132 (67-267)
Concomitant medication use			
RAS inhibitor, N (%)	84 (90%)	69 (87%)	153 (89%)
Any diuretic, N (%)	29 (31%)	31 (39%)	60 (35%)
Any lipid-lowering medication, N (%)	58 (62%)	44 (56%)	102 (59%)
Any mineralocorticoid receptor antagonist, N (%)	4 (4%)	3 (4%)	7 (4%)
Any glucagon like peptide-1 receptor agonist, N (%)	1 (1%)	2 (3%)	3 (2%)
Cause of kidney disease			
Diabetic kidney disease, N (%)	14 (15%)	7 (9%)	21 (12%)
Hypertensive/renovascular disease, N (%)	15 (16%)	15 (19%)	30 (17%)
Glomerular disease, N (%)	38 (41%)	35 (44%)	73 (42%)
Other/Unknown, N (%)	26 (28%)	22 (28%)	48 (28%)

N = total number of participants included in the analysis; NT-proBNP = N-terminal prohormone of Brain Natriuretic Peptide; Q = quartile; RAS = renin-angiotensin system; SD = standard deviation

1 Prior diabetes was defined as a patient-reported history of diabetes of any type, use of glucose-lowering medication, or a glycated haemoglobin level of at least 48 mmol per mole (6.5%) at the randomisation visit.

2 History of cardiovascular disease was defined as a patient-reported history of myocardial infarction, heart failure, stroke, transient ischemic attack, or peripheral arterial disease.

3 Values represent measurement recorded at randomisation visit or most recent local laboratory result before randomisation.

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Substudy results

Primary outcome

The primary outcome was to assess the effect of empagliflozin 10 mg versus matching placebo on kidney cortex fibrosis and inflammation of the kidney by measuring kidney cortical T1 at 18 months after randomisation. Table 2 presents the effect of allocation to empagliflozin versus placebo on the primary outcome at about 18 months. Adjusted mean (standard error [SE]) cortical T1 mapping by MOLLI was 1622 ms (10) in participants treated with empagliflozin and 1634 ms (11) in participants treated with placebo, with a difference in means (95% Confidence Interval [CI]) of -12 (-42, 17), $p = 0.41$. As medullary T1 MOLLI scores were similar between treatment groups, empagliflozin was considered to have no detectable effect on the kidney T1 MOLLI measure when compared to placebo.

Table 2 Effect of allocation to empagliflozin versus placebo on the primary outcome at about 18 months

Outcome	No. with measured values	No. with imputed values ¹	Adjusted mean (SE) values of MRI parameter ²		Difference in means (95% CI) ³	p-value
			Empagliflozin (n=93)	Placebo (n=79)		
Primary outcome at about 18 months						
Kidney cortical T1 mapping using MOLLI [ms]	167	5	1622 (10)	1634 (11)	-12 (-42, 17)	0.41

No. = number

1 Missing MRI parameter values at 18 months were imputed with the use of multiple imputation.

2 Arithmetic mean values presented.

3 Values were absolute differences in arithmetic means (95% CI). The estimates and p values were derived from linear regression with adjustment for factors included in the minimisation algorithm which determined treatment allocation (age, sex, prior diabetes, eGFR, and uACR [but not region as the MRI substudy was only conducted in Europe]).

Secondary outcomes – kidney structure and function

The secondary outcomes included the assessment of the effect of empagliflozin 10 mg versus matching placebo on different aspects of kidney structure and function at 18 months after randomisation. Empagliflozin had no significant effect on the secondary outcomes of kidney structure and function when compared to placebo (Table 3).

Table 3 Effect of allocation to empagliflozin versus placebo on the secondary outcomes in the kidney at about 18 months

Outcome	No. with measured values	No. with imputed values ¹	Adjusted mean (SE) values of MRI parameter ²		Difference in means (95% CI) ³	p-value
			Empagliflozin (N=93)	Placebo (N=79)		
Secondary outcomes at about 18 months						
Kidney size (mL)	167	5	192 (7)	204 (8)	-12 (-33, 9)	0.27
Kidney arterial flow (mL/s)	96	76	4.5 (0.4)	3.5 (0.4)	1.0 (-0.2, 2.1)	0.10
Kidney global perfusion (mL/100g/min)	89	83	295 (46)	246 (38)	20% (-22%, 84%)	0.42
Kidney diffusion (x10 ⁻³ mm ² /s)	134	38	2.10 (0.03)	2.05 (0.03)	0.05 (-0.04, 0.14)	0.28

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Substudy results (continued)

Table 3 (cont) Effect of allocation to empagliflozin versus placebo on the secondary outcomes in the kidney at about 18 months

Outcome	No. with measured values	No. with imputed values ¹	Adjusted mean (SE) values of MRI parameter ²		Difference in means (95% CI) ³	p-value
			Empagliflozin (N=93)	Placebo (N=79)		
Kidney oxygenation (ms)	166	6	49.1 (1.3)	48.6 (1.4)	0.6 (-3.3, 4.4)	0.77
Kidney fat content mapping (%)	172	0	3.7 (0.1)	3.6 (0.1)	0.1 (-0.1, 0.3)	0.32

1 Missing MRI parameter values at 18 months were imputed with the use of multiple imputation.

2 Arithmetic mean values presented, with the exception of kidney global perfusion for which geometric means were presented (due to use of log transformed values).

3 Values are absolute differences in arithmetic means (95% CIs), with the exception of kidney global perfusion for which a relative difference is presented due to use of log-transformed values in the analyses. The estimates and p values were derived from linear regression with adjustment for factors included in the minimisation algorithm which determined treatment allocation (age, sex, prior diabetes, eGFR, and uACR [but not region as the MRI substudy was only conducted in Europe]).

Secondary outcomes – cardiac structure, function, and fibrosis

The secondary outcomes included the assessment of the effect of empagliflozin 10 mg versus matching placebo on different aspects of cardiac structure, function, and fibrosis at 18 months after randomisation. Empagliflozin had no significant effect on the secondary outcomes of cardiac structure, function, and fibrosis when compared to placebo (Table 4).

Table 4 Effect of allocation to empagliflozin versus placebo on the secondary outcomes in the heart at about 18 months

Outcome	No. with measured values	No. with imputed values ¹	Adjusted mean (SE) values of MRI parameter ²		Difference in means (95% CI) ³	p-value
			Empagliflozin (N=93)	Placebo (N=79)		
Secondary outcomes at about 18 months						
Left ventricular mass index (g/m ²)	166	6	45 (1)	47 (1)	-3 (-5, 0)	0.05
Left ventricular ejection fraction (%)	166	6	52 (1)	50 (1)	2 (-1, 4)	0.20
Cardiac fibrosis (ms)	166	6	1275 (5)	1278 (5)	-4 (-17, 10)	0.60
Left ventricular global circumferential strain (%)	166	6	-17.6 (0.3)	-17.4 (0.3)	-0.2 (-1.0, 0.6)	0.63
Left ventricular global longitudinal strain (%)	166	6	-16.8 (0.3)	-16.6 (0.3)	-0.1 (-1.0, 0.7)	0.78
Left ventricular diastolic strain rate (1/s)	153	19	0.76 (0.03)	0.73 (0.03)	0.04 (-0.04, 0.11)	0.33
Left ventricular stroke volume (mL)	166	6	65 (2)	68 (2)	-3 (-9, 2)	0.24

1 Missing MRI parameter values at 18 months were imputed with the use of multiple imputation.

2 Arithmetic mean values presented.

3 Values were absolute differences in arithmetic means (95% CI). The estimates and p values were derived from linear regression with adjustment for factors included in the minimisation algorithm which determined treatment allocation (age, sex, prior diabetes, eGFR, and uACR [but not region as the MRI substudy was only conducted in Europe]).

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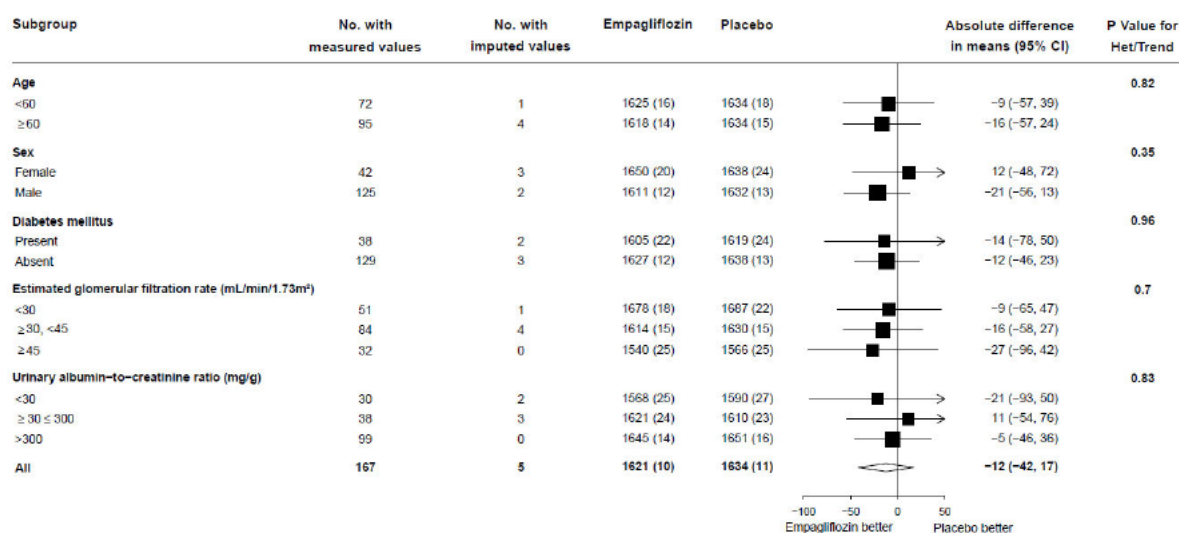
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Substudy results (continued)

Tertiary outcomes – Kidney fibrosis modification by baseline characteristic

The subgroup analyses examined whether any effects of empagliflozin 10 mg versus matching placebo on T1 mapping differed by baseline subgroups of age, sex, diabetes status, eGFR, and uACR. The subgroup analyses were consistent with the main analysis results, indicating no evidence of any treatment effect or heterogeneity (Figure 1).

Figure 1 Effect of allocation to empagliflozin versus placebo on renal cortical T1 MOLLI at about 18 months by key prespecified subgroups



CI = confidence interval; Het = heterogeneity; N = total number of participants included in the analysis; No. = number. The unit for the 'Empagliflozin/Placebo better scale' was ms.

Tertiary outcomes – Sensitivity analysis for estimated baseline MRI measurements

Amongst participants with a baseline MRI scan, the effects of empagliflozin 10 mg versus matching placebo on follow-up MRI measurements adjusted for baseline were assessed. In total, there were 21 participants with baseline scan measurements. Sensitivity analyses of the primary and secondary MRI outcomes restricted to those with a baseline MRI scan and adjusted for baseline MRI measures yielded broadly similar results to the main analyses, albeit with wider CIs (Table 5).

Table 5 Prespecified sensitivity analysis of the effect of allocation to empagliflozin versus placebo on MRI parameters at about 18 months, with adjustment for baseline values of parameters (in subset of participants with a baseline scan)

Outcome	No. with measured values	No. with imputed values ¹	Mean (SE) values of MRI parameter ²		Difference in means (95% CI) ³
			Empagliflozin (n=12)	Placebo (n=9)	
Primary outcome at about 18 months					
Kidney cortical T1 mapping using MOLLI [ms]	21	0	1609 (29)	1621 (36)	-12 (-103, 78)

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Substudy results (continued)

Table 5 (cont) Prespecified sensitivity analysis of the effect of allocation to empagliflozin versus placebo on MRI parameters at about 18 months, with adjustment for baseline values of parameters (in subset of participants with a baseline scan)

Outcome	No. with measured values	No. with imputed values ¹	Mean (SE) values of MRI parameter ²		Difference in means (95% CI) ³
			Empagliflozin (n=12)	Placebo (n=9)	
Secondary outcomes at about 18 months					
Kidney					
Kidney size (mL)	20	1	244 (22)	194 (24)	51 (-14, 115)
Kidney arterial flow (mL/s)	10	11	5.4 (1.3)	2.5 (1.5)	2.9 (-1.1, 6.9)
Kidney global perfusion (mL/100g/min)	10	11	270 (142)	148 (93)	82% (-64%, 813%)
Kidney diffusion (x10 ⁻³ mm ² /s)	11	10	2.06 (0.12)	2.08 (0.13)	-0.01 (-0.35, 0.33)
Kidney oxygenation (ms)	21	0	50 (2)	46 (2)	4 (-2, 10)
Kidney fat content mapping (%)	21	0	4.2 (0.1)	3.9 (0.2)	0.2 (-0.2, 0.7)
Cardiac					
Left ventricular mass index (g/m ²)	21	0	41 (2)	43 (2)	-2 (-9, 4)
Left ventricular ejection fraction (%)	21	0	47 (3)	47 (4)	1 (-10, 11)
Cardiac fibrosis (ms)	21	0	1283 (11)	1263 (13)	20 (-14, 54)
Left ventricular global circumferential strain (%)	21	0	-16.7 (0.6)	-17.4 (0.7)	0.7 (-1.2, 2.5)
Left ventricular global longitudinal strain (%)	21	0	-16.6 (0.8)	-17.5 (1.0)	0.9 (-1.6, 3.3)
Left ventricular stroke volume (mL)	21	0	54 (5)	59 (6)	-5 (-19, 10)

n =total number of participants included in the analysis

1 Missing MRI parameter values at 18 months were imputed with the use of multiple imputation and left ventricular diastolic strain rate is excluded due to the absence of baseline scan measurements.

2 Arithmetic mean values are presented, with the exception of kidney global perfusion for which geometric means are presented (due to use of log transformed values).

3 Values are absolute differences in arithmetic means (95% CIs), with the exception of kidney global perfusion for which a relative difference is presented due to use of log transformed values in the analyses. The estimates and p-values were derived from linear regression with adjustment for factors included in the minimisation algorithm which determined treatment allocation (age, sex, prior diabetes, eGFR, and uACR [but not region as the MRI substudy was only conducted in Europe]).

Safety results

Not applicable.

Conclusions

Empagliflozin had no significant effect on the kidney T1 MOLLI measure of inflammation and fibrosis when compared to placebo and no significant effect on the secondary measures of kidney structure and function or cardiac structure, function, and fibrosis when compared to placebo. Results were consistent regardless of baseline age, sex, diabetes status, eGFR, and uACR.

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Name of company: Boehringer Ingelheim		Synopsis	 Boehringer Ingelheim
BI proprietary name: Jardiance®		EudraCT number: 2017-002971-24	
BI investigational product: Empagliflozin, BI 10773		Page: 1 of 7	
Report date: 24 Apr 2025	Substudy no./Doc. no.: 1245.0137/ c42621649-01, 206893_11076960_1.0	Dates of substudy: 22 May 2019 – 14 Apr 2021	Date of revision: Not applicable
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Title of substudy EMPA-KIDNEY Body Composition Measurement Substudy EMPA-KIDNEY: A multicentre international randomised parallel group double-blind placebo controlled clinical trial of EMPagliflozin once daily to assess cardio-renal outcomes in patients with chronic KIDNEY disease Chief investigator UK Trial sites with screened participants 21 sites with screened participants in the UK (13 sites) and Germany (8 sites) contributed to the substudy. Publications Mayne K. Effects of empagliflozin on fluid overload in chronic kidney disease: an EMPA-KIDNEY bioimpedance substudy, Nephrology Dialysis Transplantation, Volume 38, Issue Supplement_1, June 2023. Clinical phase: not applicable Objectives The primary aim of the substudy was to use bioimpedance spectroscopy on a body composition monitor (BCM) to assess, in a subset of EMPA-KIDNEY participants, the effect of empagliflozin 10 mg vs matching placebo on Fluid Overload at the 2 months and 18 months follow-up visits. Methodology It was planned to include approximately 650 EMPA-KIDNEY participants from the UK and Germany. Participants' body composition was measured using bioimpedance spectroscopy on a BCM. The substudy did not alter the main protocol of the EMPA-KIDNEY trial in any respect.			

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Number of subjects

Planned:	Approximately 650			
Actual:		Consented to join substudy	Included in substudy	Analysed (for primary assessment)
	Overall	668	660	620
	Empagliflozin 10 mg		332	311
	Placebo		328	309

Diagnosis

Patients with evidence of chronic kidney disease (CKD) at risk of kidney disease progression, with or without diagnosed diabetes mellitus.

Main criteria for inclusion

In UK and Germany, EMPA-KIDNEY Local Clinical Centres (LCCs) with a Fresenius Medical Care Body Composition Monitor machine were invited to join the substudy. All participants at these LCCs who had yet to attend the relevant scheduled trial visit were eligible for invitation.

The main criteria for inclusion in the EMPA-KIDNEY trial and thus in the substudy were evidence of CKD at risk of progression was defined on the basis of local laboratory results recorded at least 3 months before and at the time of the Screening visit, and required that:

- CKD-EPI eGFR ≥ 20 to < 45 mL/min/1.73 m²; or
- CKD-EPI eGFR ≥ 45 to < 90 mL/min/1.73 m² with urinary albumin to creatinine ratio (UACR) ≥ 200 mg/g (or protein to creatinine ratio ≥ 300 mg/g)

CKD-EPI eGFR values were estimated using the 2009 Chronic Kidney Disease Epidemiology Collaboration creatinine formula.

CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate

BI investigational product: Empagliflozin, film-coated tablets

Dose: 10 mg once daily

Mode of administration: Oral

Comparator product: Placebo, film-coated tablets to match empagliflozin

Dose: Not applicable

Mode of administration: Oral

Observational period

18 months for the substudy

Efficacy criteria for evaluation

The primary assessment was the effect of empagliflozin 10 mg on mean absolute Fluid Overload (also referred to as overhydration) in litres. Effects on relative Fluid Overload (overhydration indexed to extracellular water [ECW], expressed as a percentage) was presented alongside. Effects were averaged over the two follow-up time points (with weights proportional to the amount of time between visits), adjusted for randomisation Fluid Overload values.

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Absolute Fluid Overload (overhydration) in litres, computed as the difference between expected (based upon weight and body composition) vs measured extracellular water (ECW) volume, with positive values representing excess fluid. Absolute Fluid Overload = $ECW_{\text{measured}} - ECW_{\text{expected}}$. Relative Fluid Overload (overhydration index) was defined as overhydration indexed to measured ECW volume, expressed as a percentage. relative Fluid Overload = $\text{absolute Fluid Overload} \div ECW_{\text{measured}}$.			

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The key secondary assessment was time-to-first development or worsening of Clinically Significant Fluid Overload, defined as:

- Death from Heart Failure;
- Hospitalisation for Heart Failure; or
- Development of moderate Clinically Significant Fluid Overload (defined as $>7\%$ to $\leq 15\%$ relative Fluid Overload) among those without any Clinically Significant Fluid Overload at baseline; or
- Development of severe Clinically Significant Fluid Overload (defined as $>15\%$ relative Fluid Overload) among those without this outcome at baseline.

The other secondary assessment was to test whether the effects of empagliflozin 10 mg vs matching placebo on absolute and relative Fluid Overload vary with time. In addition to the primary randomised assessment, analyses were presented for the separate early (2 months) vs late (18 months) time points.

The further assessments were: subgroup analyses (sex, diabetes status, NT-proBNP, and eGFR) of absolute Fluid Overload; the effects of empagliflozin 10 mg vs placebo overall, and early vs later during follow-up on ECW, intracellular water, lean tissue index, fat tissue index, body weight, BMI, waist circumference, hip circumference, and waist-to-hip ratio; the effects of empagliflozin 10 mg vs placebo on the four separate components of the key secondary outcome; the effects of empagliflozin 10 mg vs placebo on regression of Clinically Significant Fluid Overload from severe ($>15\%$) to moderate ($>7\%$); severe to normal ($\leq 7\%$); or moderate to normal.

Safety criteria for evaluation

None

Statistical methods

For the primary assessment, differences in Fluid Overload between treatment groups were assessed using a mixed model repeated measures (MMRM) approach adjusted for the elements included in the minimization algorithm which determined treatment allocation (age, sex, prior diabetes, eGFR, and UACR [but not region as the BCM substudy was only conducted in two European countries]). The model included fixed, categorical effects of treatment allocation, treatment-by-time interaction, and the prognostic variables used in the minimization algorithm (in the same categories used in the minimization process) along with continuous effects of baseline (randomisation) measurements and baseline-by-time interaction. The within-person error correlations were assumed to be unstructured.

Time-to-first event analyses of the key secondary assessment used adjusted Cox regression.

Analyses of the other secondary assessment followed the same approach as for the primary assessment.

SUMMARY - CONCLUSIONS:

Trial subjects and compliance with the protocol

The substudy was conducted in 660 participants (empagliflozin: 332 participants, placebo: 328 participants). The demographic and baseline characteristics of the participants are presented in Table 1.

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Table 1: Demographic and baseline characteristics

	Placebo	Empa 10 mg
Number of participants, N (%)	328 (100.0)	332 (100.0)
Age [years], mean (SD)	64.1 (14.9)	65.2 (14.2)
Female, N (%)	103 (31.4)	102 (30.7)
White race, N (%)	315 (96.0)	321 (96.7)
Absolute Fluid Overload [L], mean (SD)	0.32 (1.68)	0.45 (1.68)
Relative Fluid Overload [%], mean (SD)	1.3 (8.3)	1.9 (8.7)
Moderate Fluid Overload, N (%)	56 (17.1)	70 (21.1)
Severe Fluid Overload, N (%)	16 (4.9)	14 (4.2)
Extracellular water [L], mean (SD)	18.4 (3.7)	19.0 (3.8)
Intracellular water [L], mean (SD)	20.1 (4.6)	20.7 (4.5)
Lean tissue index [kg/m ²], mean (SD)	12.9 (3.0)	13.3 (3.1)
Fat tissue index [kg/m ²], mean (SD)	12.5 (5.1)	12.6 (5.4)
With diabetes at baseline, N (%)	121 (36.9)	135 (40.7)
With heart failure at baseline, N (%)	74 (22.6)	62 (18.7)
Weight [kg], mean (SD)	87.9 (19.3)	89.8 (20.2)
Body mass index [kg/m ²], mean (SD)	30.1 (6.3)	30.5 (6.2)
Systolic blood pressure [mmHg], mean (SD)	137.5 (18.9)	137.0 (18.8)
Diastolic blood pressure [mmHg], mean (SD)	78.6 (11.9)	77.8 (12.2)
eGFR [mL/min/1.73 m ²], mean (SD)	35.8 (11.4)	36.1 (13.4)
<30, N (%)	118 (36.0)	123 (37.0)
≥30 <45, N (%)	154 (47.0)	148 (44.6)
≥45, N (%)	56 (17.1)	61 (18.4)
UACR [mg/g], median (Q1, Q3)	205 (29, 865)	203 (26, 958)
NTpro-BNP [ng/L], median (Q1, Q3)	225 (95, 550)	197 (90, 596)
Use of RAS-inhibitors, N (%)	288 (87.8)	304 (91.6)
Use of diuretics, N (%)	173 (52.7)	180 (54.2)

eGFR, estimated glomerular filtration rate; NTpro-BNP, N-terminal pro-brain-type natriuretic peptide; RAS, renin-angiotensin system; UACR, urinary albumin-to-creatinine ratio.

The MMRM analyses included 620 participants; 40 participants (empagliflozin: 21 participants, placebo: 19 participants) were excluded due to death (3 participants), no follow-up measurements (28 participants), or low data quality (9 participants).

Compliance to the trial medication in the substudy was similar to that in the main EMPA-KIDNEY trial. At the 12 months follow-up, of substudy participants who remained alive, 282 of 318 participants in the empagliflozin group (88.7%) and 292 of 320 participants in the placebo group (91.3%) reported taking at least 80% of their trial medication.

Efficacy results

The substudy-average in absolute Fluid Overload was -0.24 L (95% CI -0.38, -0.11) lower in the empagliflozin group than in the placebo group. Similar differences at the 2 months and 18 months follow-up were obtained from the secondary assessments (Table 2). The effect of empagliflozin on the primary outcome was similar in the subgroup analyses by sex, diabetes status, and across the spectrum of NT-proBNP and

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eGFR (all p-values for heterogeneity or trend >0.3). There was no significant differences between treatment groups in the composite key secondary outcome or its components. The number of events was low (Table 2).

Table 2: Results of the primary, key secondary, and other secondary assessments

	Placebo	Empa 10 mg
Primary assessment		
N analysed	309	311
Absolute Fluid Overload [L], substudy-average, adjusted mean (SE)	0.34 (0.05)	0.10 (0.05)
Absolute difference vs placebo (95% CI)		-0.24 (-0.38, -0.11)
p-value		<0.001
Relative Fluid Overload [%], substudy-average, adjusted mean (SE)	1.33 (0.25)	0.14 (0.25)
Absolute difference vs placebo		-1.19 (-1.90, -0.48)
p-value		0.001
Key secondary assessment		
Death from heart failure, hospitalisation for heart failure, development of new moderate or severe Fluid Overload ¹ , n/N (%)	38/328 (11.6)	35/332 (10.5)
Hazard ratio vs placebo (95% CI)		0.91 (0.57, 1.45)
p-value		0.69
Death from heart failure, n/N (%)	0	0
Hospitalisation for heart failure, n/N (%)	16/328 (4.9)	11/332 (3.3)
Hazard ratio vs placebo (95% CI)		0.67 (0.31, 1.46)
Development of new moderate Fluid Overload ² , n/N (%)	25/247 (10.1)	18/232 (7.8)
Hazard ratio vs placebo (95% CI)		0.68 (0.37, 1.26)
Development of new severe Fluid Overload ³ , n/N (%)	4/303 (1.3)	8/302 (2.7)
Hazard ratio vs placebo (95% CI)		1.96 (0.57, 6.71)
Secondary assessments		
N analysed	309	311
Absolute Fluid Overload		
Randomisation [L], mean (SE)	0.35 (0.09)	0.50 (0.09)
2 months follow-up [L], adjusted mean (SE)	0.40 (0.05)	0.18 (0.05)
Absolute difference vs placebo (95% CI)		-0.23 (-0.37, -0.08)
18 months follow-up [L], adjusted mean (SE)	0.27 (0.07)	0.01 (0.07)
Absolute difference vs placebo (95% CI)		-0.26 (-0.46, -0.06)
p-value for interaction with time		0.11
Relative Fluid Overload		
Randomisation [L], mean (SE)	1.39 (0.45)	2.24 (0.47)
2 months follow-up [L], adjusted mean (SE)	1.65 (0.27)	0.52 (0.27)
Absolute difference vs placebo (95% CI)		-1.12 (-1.88, -0.37)
18 months follow-up [L], adjusted mean (SE)	0.92 (0.37)	-0.36 (0.38)
Absolute difference vs placebo (95% CI)		-1.28 (-2.32, -0.23)
p-value for interaction with time		0.39

¹Requires randomisation value of relative Fluid Overload ≤7% and follow-up value >7%.

²Requires randomisation value of relative Fluid Overload ≤7% and follow-up value >7% to ≤15%.

³Requires randomisation value of relative Fluid Overload ≤15% and follow-up value >15%.

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Safety results

Not applicable

Conclusions

Treatment with empagliflozin led to a lower average Fluid Overload over the follow-up period compared to placebo, a difference of -0.24 L (95% CI -0.38, -0.11). Results were consistent regardless of sex, diabetes status, NT-proBNP or eGFR categories.