Australian Government
Department of Health and Aged Care
Therapeutic Goods Administration

Australian Public Assessment Report for JARDIANCE

Active ingredient: Empagliflozin

Sponsor: Boehringer Ingelheim Pty Ltd

July 2024

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and Aged Care and is responsible for regulating therapeutic goods, including medicines, medical devices, and biologicals.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety, and efficacy.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to the Australian public outweigh any risks associated with the use of therapeutic goods.
- The TGA relies on the public, healthcare professionals and industry to report problems with therapeutic goods. The TGA investigates reports received to determine any necessary regulatory action.
- To report a problem with a therapeutic good, please see the information on the TGA website.

About AusPARs

- The Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission. Further information can be found in Australian Public Assessment Report (AusPAR) guidance.
- AusPARs are prepared and published by the TGA.
- AusPARs are static documents that provide information that relates to a submission at a particular point in time. The publication of an AusPAR is an important part of the transparency of the TGA's decision-making process.
- A new AusPAR may be provided to reflect changes to indications or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

List of abbreviations

Abbreviation	Meaning
ACM	Advisory Committee on Medicines
3P_MACE	3-point major adverse cardiovascular event
ACEi	Angiotensin converting enzyme inhibitor
AE	Adverse event
AESI	Adverse events of special interest
AKI	Acute kidney injury
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
ARB	Angiotensin receptor blocker
ASA	Australian Specific Annex
AST	Aspartate aminotransferase
BI	Boehringer Ingelheim
BIcMQ	BI customised MedDRA query
BP	Blood pressure
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CKD	Chronic kidney disease
CMI	Consumer Medicines Information
CSR	Clinical study report
CTSU	Clinical Trial Service Unit and Epidemiological Studies Unit, University of Oxford
CV	Cardiovascular
DB	Double-blind
DM	Diabetes mellitus
DMC	Data monitoring committee
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
EMPA-REG	Empagliflozin – Reducing Excess Glucose
ESKD	End stage kidney disease
EU	European Union
FDA	Food and Drug Administration
HF	Heart failure

Abbreviation	Meaning
HHF	Hospitalisation for heart failure
HR	Hazard ratio
KDIGO	Kidney Disease Improving Global Outcomes
LLA	Lower limb amputation
MI	Myocardial infarction
MMRM	Mixed model with repeated measurements
OC-AD	Observed case-all data
PI	Product Information
PT	Preferred term
RAS	Renin-angiotensin system
RMP	Risk management plan
RS	Randomised set
SAE	Serious adverse event
SCE	Summary of Clinical Efficacy
SCR	Screened set
SMQ	Standardised MedDRA query
SCS	Summary of Clinical Safety
SGLT	Sodium glucose cotransporter
SmPC	Summary of Product Characteristics
SOC	System organ class
SSAR	Suspected serious adverse reactions
T2DM	Type 2 diabetes mellitus
TS	Treated set
UACR	Urinary albumin to creatinine ratio
UK	United Kingdom
US	United States
UTI	Urinary tract infection

Product submission

Submission details

Type of submission:	Extension of indication
Product name:	JARDIANCE
Active ingredient:	empaglilflozin
Decision:	Approved
Date of decision:	6 February 2024
Date of entry onto ARTG:	8 February 2024
ARTG numbers:	208827, 208829
, *Black Triangle Scheme*	No
Sponsor's name and address:	Boehringer Ingelheim Pty Ltd, PO Box 1969, North Ryde, NSW, 2113
Dose form:	Film coated tablet
Strengths:	10 mg, 25 mg
Container:	Blister pack
Pack sizes:	10, 30
Approved therapeutic use for the current submission:	***Chronic kidney disease*** *JARDIANCE is indicated to reduce the risk of kidney disease progression in adults with chronic kidney disease (CKD Stages 2 and 3A with urine ACR ≥30 mg/g, or CKD Stages 3B, 4 and 5 irrespective of urine ACR).*
Routes of administration:	Oral
Dosage:	The recommended dose of JARDIANCE is 10 mg once daily. For further information regarding dosage, such as dosage modifications to manage adverse reactions, refer to the Product Information.
Pregnancy category:	D Drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Accompanying texts should be consulted for further details. The use of any medicine during pregnancy requires careful consideration of both risks and benefits by the treating health professional. The pregnancy database must not be used as the sole basis of decision making in the use of medicines during pregnancy. The TGA does not provide advice on the use of medicines in pregnancy for specific cases. More information is

available from obstetric drug information services in your state or territory.

Product background

This AusPAR describes the submission by Boehringer Ingelheim (the Sponsor) to register JARDIANCE (empagliflozin) for the following extension of indications proposed by the Sponsor:[1]

> *JARDIANCE is indicated in adult patients with chronic kidney disease to reduce the risk of:*
> *• Kidney disease progression (sustained decline in estimated glomerular filtration rate (eGFR), end-stage kidney disease or renal death) or cardiovascular death*
> *• All-cause hospitalisation.*

The disease/condition

Chronic kidney disease is a progressive disease characterised by kidney function decline. Of the variables associated with disease progression, albuminuria and reduced eGFR are the most important ones. Causes of chronic kidney disease are complex and include common chronic diseases, with diabetes being the leading cause, followed by arterial hypertension and glomerular diseases.

Chronic kidney disease affects over 10% of the population and represents a major public health burden with a high unmet medical need. The prevalence of chronic kidney disease is increasing as the population ages and type II diabetes mellitus becomes more prevalent. Worldwide, chronic kidney disease as a cause of years of life lost has risen and is projected to continue to rise. According to the 2017 Global Burden of Disease study, chronic kidney disease was associated with an age-standardised death rate of 16 per 100 000 people (2017: about 1.2 million deaths were due to chronic kidney disease). It is forecasted that by 2040, chronic kidney disease would be the 5th cause of death globally (3 million deaths due to chronic kidney disease).

As kidney function declines, patients with chronic kidney disease tend to develop a range of comorbidities and complications that have a major impact on patients' quality of life and prognosis as well as healthcare resource utilisation. All-cause hospitalisation rates are more than twice as high for chronic kidney disease patients as for people without chronic kidney disease, with the most common causes of hospitalisation being cardiovascular disease and infection. Patients with chronic kidney disease generally have lower survival probability following hospitalisations compared with patients without chronic kidney disease. cardiovascular disease is a major problem for patients with chronic kidney disease. The risk of cardiovascular events and cardiovascular death increases as chronic kidney disease progresses, and the highest risk is associated with kidney failure and chronic dialysis treatment. Patients with chronic kidney disease die primarily from cardiovascular disease, with HF being the most common cause of death. Thus, slowing kidney function decline is among the most important goals of treatment for patients with chronic kidney disease.

Current treatment options

Renin-angiotensin system (RAS) inhibitors (angiotensin-converting enzyme inhibitor [ACEis] or angiotensin receptor blockers [ARBs]) are recommended in patients with albuminuria by the Kidney Disease Improving Global Outcomes (KDIGO) clinical practice guidelines. Evidence on

[1] This is the original indication proposed by the Sponsor when the TGA commenced the evaluation of this submission. It may differ to the final indication approved by the TGA and registered in the Australian Register of Therapeutic Goods.

whether these compounds reduce the risk in patients with lower levels of albuminuria has not been generated in randomised clinical trials. There is limited evidence from large-scale randomised trials on the effects of ACEi/ARBs in non-diabetic patients with chronic kidney disease.

In practice, treatment with ACEi/ARBs requires up-titration to the highest approved dose that is tolerated. Combination therapies with ACEi and ARBs do not show kidney or cardiovascular benefits versus monotherapy and may cause hyperkalaemia or acute kidney injury (AKI) and are therefore not recommended for treatment of chronic kidney disease.

The effects of the non-steroidal mineralocorticoid receptor antagonist, finerenone, in patients with diabetic kidney disease were demonstrated in outcome trials, which supported approval of the Australian indication, "to delay progressive decline of kidney function in adults with chronic kidney disease associated with type 2 diabetes (with albuminuria), in addition to standard of care".

The benefits of sodium-glucose co-transporter-2 (SGLT-2) inhibitor therapies for patients with chronic kidney disease have also been demonstrated in the outcome trials:

- CREDENCE: canagliflozin reduced the risk of kidney disease progression or cardiovascular death in patients with eGFR ≥30 to <90 mL/min/1.73 m^2 and UACR >300 mg/g with T2DM [canagliflozin is not registered in Australia]
- DAPA-CKD: dapagliflozin reduced the risk of kidney disease progression or cardiovascular death in patients with eGFR ≥25 to ≤75 mL/min/1.73 m^2 and UACR ≥200 mg/g.

Clinical rationale

Empagliflozin works by blocking SGLT2 in the kidney which is the predominant transporter for re-absorption of glucose from the glomerular filtrate back into the circulation. Blocking SGLT2 reduces glucose re-absorption in the kidney leading to glucose excretion in the urine, thereby lowering levels of glucose in the blood of patients with type 2 diabetes.

Mechanisms behind the kidney effects of empagliflozin are likely multifactorial. Empagliflozin reduces sodium reabsorption and increases the delivery of sodium to the distal tubule. This may influence several physiological functions including, but not restricted to increasing tubule-glomerular feedback, reducing intraglomerular pressure, downregulating sympathetic activity, lowering both pre-and afterload of the heart and reducing left ventricular wall stress as evidenced by beneficial effects on filling pressures and diastolic function.

Regulatory status

Australian regulatory status

The product received initial registration in the Australian Register of Therapeutic Goods (ARTG) on 30 April 2014. It was approved for the following indications:

> *GLYCAEMIC CONTROL*
>
> *JARDIANCE is indicated in the treatment of type 2 diabetes mellitus to improve glycaemic control in adults as:*
>
> *Monotherapy*
>
> *When diet and exercise alone do not provide adequate glycaemic control in patients for whom use of metformin is considered inappropriate due to intolerance.*

Add-on combination therapy

In combination with other glucose–lowering medicinal products including insulin, when these, together with diet and exercise, do not provide adequate glycaemic control (see Clinical Trials).

On 18 January 2017, JARDIANCE was registered on the ARTG for the following extension of indications[2]:

PREVENTION OF CARDIOVASCULAR DEATH
JARDIANCE is indicated in patients with type 2 diabetes mellitus and established cardiovascular disease to reduce the risk of cardiovascular death (see Clinical Trials)

To prevent cardiovascular deaths, JARDIANCE should be used in conjunction with other measures to reduce cardiovascular risk in line with the current standard of care.

International regulatory status

At the time the TGA considered this submission, a similar submission had been considered by other regulatory agencies. Table 1 summarises these submissions and provides the indications where approved.

Table 1: International regulatory status at the time of product registration.

Region	Submission date	Status	Approved indications
European Union (centralised procedure)	21 November 2022	Approved on 27 July 2023	Type 2 diabetes mellitus JARDIANCE is indicated for the • treatment of adults with insufficiently controlled type 2 diabetes mellitus as an adjunct to diet and exercise. • as monotherapy when metformin is considered inappropriate due to intolerance • in addition to other medicinal products for the treatment of diabetes. **Heart failure** JARDIANCE is indicated in adults for the treatment of symptomatic chronic heart failure. **Chronic kidney disease** JARDIANCE is indicated in adults for the treatment of chronic kidney disease.

[2] AusPAR for extension of indication at: https://www.tga.gov.au/sites/default/files/auspar-empagliflozin-171026.pdf

Region	Submission date	Status	Approved indications
United States of America	21 November 2022	Approved 21 September 2023	JARDIANCE is indicated: • to reduce the risk of cardiovascular death and hospitalization for heart failure in adults with heart failure. • to reduce the risk of sustained decline in eGFR, end-stage kidney disease, renal death, cardiovascular death, and all-cause hospitalization in adults with chronic kidney disease. • to reduce the risk of cardiovascular death in adults with type 2 diabetes mellitus and established cardiovascular disease. • as an adjunct to diet and exercise to improve glycaemic control in adults and paediatric patients aged 10 years and older with type 2 diabetes mellitus.
Singapore	30 November 2022	Under consideration	Under consideration
Canada	14 December 2022	Under consideration	Under consideration
New Zealand	23 December 2022	Under consideration	Under consideration
Switzerland	23 December 2022	Under consideration	Under consideration

Registration timeline

This submission was evaluated under the standard prescription medicines registration process.

Table 2 captures the key steps and dates for this submission.

Table 2: JARDIANCE evaluation (submission PM-2022-05194-1-5) – key dates

Description	Date
Submission dossier accepted and first round evaluation commenced	31 January 2023
First round evaluation completed	14 August 2023
Sponsor provides responses on questions raised in first round evaluation	31 August 2023
Second round evaluation completed	9 October 2023

Description	Date
Sponsor's notification to the TGA of errors/omissions in evaluation reports	20 October 2023
Delegate's[3] Overall benefit-risk assessment and request for Advisory Committee advice	31 October 2023
Sponsor's pre-Advisory Committee response	14 November 2023
Advisory Committee meeting	1 December 2023
Registration decision (Outcome)	6 February 2024
Administrative activities and registration in the ARTG completed	8 February 2024
Number of working days from submission dossier acceptance to registration decision*	212

*Statutory timeframe for standard submissions is 255 working days

Submission overview and risk/benefit assessment

Quality evaluation summary

Quality evaluation is not required for this submission as there are no proposed changes to the quality of the currently approved product in Australia. The quality of the currently approved product is suitable for the proposed changes in this submission. A full quality evaluation was conducted at the time this product received initial registration.

Nonclinical (toxicology) evaluation summary

No new nonclinical data or further nonclinical evaluation were required for this submission. The TGA considers that previously submitted and evaluated data satisfactorily address nonclinical aspects of safety/efficacy relating to this submission.

Clinical evaluation summary

Efficacy

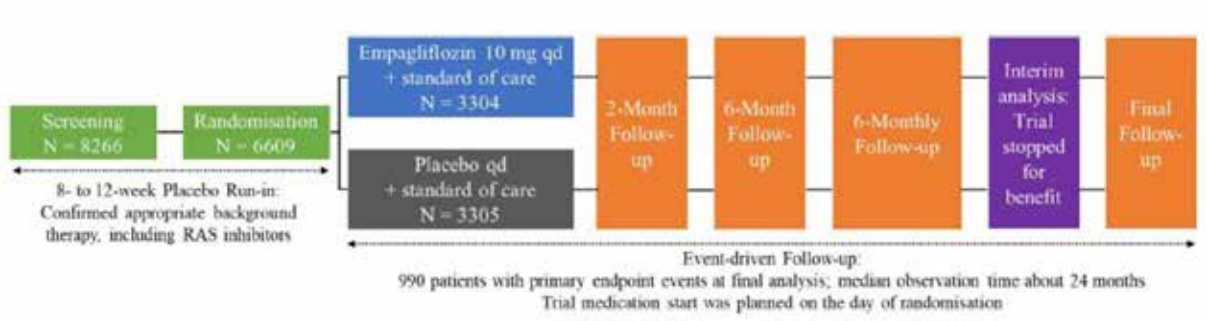
Study EMPA-KIDNEY (pivotal)

A Phase 3, multinational, placebo-controlled, randomised (1:1), double-blind (DB), parallel group study. It was designed to compare empagliflozin 10 mg once daily versus placebo, given on top of standard of care, in around 6000 participants with established CKD, with or without

[3] In this report the 'Delegate' is the Delegate of the Secretary of the Department of Health and Aged Care who decided the submission under section 25 of the Act.

diagnosed DM, who were being treated (where indicated and tolerated) with an appropriate dose of a single RAS inhibitor.

Figure 1 EMPA-KIDNEY trial: Study design



Eligible subjects were randomised to receive either empagliflozin 10 mg or matching placebo once daily. Following randomisation, subjects were scheduled to attend follow-up visits at 2 and 6 months, then 6-monthly until the end of the trial.

A formal interim analysis to decide whether to stop the trial for benefit was planned to be made after 150 end-stage kidney disease (ESKD) events had occurred, by which time it was expected that approximately 60% of all first primary outcomes would have 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).

Inclusion and exclusion criteria

Key inclusion criteria:

- Age was ≥18 years at time of screening.
- Evidence of progressive CKD at risk of kidney disease progression. This was based on local laboratory results recorded at least 3 months before and at the time of the Screening visit, and required that: CKD-EPI eGFR ≥20- 45 mL/min/1.73m^2 or CKD-EPI eGFR ≥45 - <90 mL/min/1.73m^2 with urinary albumin:creatinine ratio ≥200 mg/g (or protein:creatinine ratio ≥300 mg/g).

Key exclusion criteria:

- Currently receiving SGLT-2 or SGLT-1/2 inhibitor
- Diabetes mellitus type 2 and prior atherosclerotic cardiovascular disease with an eGFR >60 mL/min/1.73m^2 at time of Screening
- Receiving combined ACEi and ARB treatment
- Maintenance dialysis, functioning kidney transplant, or scheduled living donor transplant.
- Polycystic kidney disease
- Symptomatic hypotension, or systolic blood pressure 180 mmHg at time of Screening
- Any immunosuppression therapy in the last 3 months (except prednisolone ≤10 mg or equivalent); or anyone currently on >10 mg prednisolone (or equivalent)

Objectives

The primary objective was to assess the effect of empagliflozin on time to kidney disease progression or CV death.

The **key secondary objectives** were to assess the effect of empagliflozin on time to HHF or CV death, occurrences of hospitalisations from any cause, and time to death from any cause.

Other assessments, including analyses of safety, were also planned.

Endpoints

The following endpoints were defined for the EMPA-KIDNEY trial:

Primary endpoint:

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

- Kidney disease progression (defined as ESKD, a sustained decline in eGFR[4] to <10 mL/min/1.73 m^2, 'as adjudicated' renal death, or a sustained decline of ≥40% in eGFR from randomisation), or
- Cardiovascular death ('as adjudicated')

Secondary endpoints: Key secondary endpoints (confirmatory):

Key secondary endpoints (confirmatory) were:

- Time to the first occurrence of hospitalisation for heart failure (HHF, 'as adjudicated') or CV death ('as adjudicated')
- Time to occurrences of all-cause hospitalisations (first and recurrent combined)
- Time to death from any cause ('as adjudicated')

Other secondary endpoints (exploratory):

- time to the first occurrence of kidney disease progression
- time to cardiovascular death ('as adjudicated')
- time to first occurrence of CV death ('as adjudicated') or ESKD*

Sample size

The trial was planned to randomise approximately 6000 participants from about 200-250 sites and to continue until a minimum of 1070 primary outcome events has occurred. Such an event-driven trial would provide an overall power of 90% at p = 0.05 (2-sided) to detect an 18% relative reduction in the primary outcome (time to kidney disease progression or CV death).

Participant flow

Of the 8266 screened participants, 1657 were not randomised, most commonly due to ineligible screening lab results. Of the 6609 randomised participants, 6568 (99.4%) completed the trial, including 315 participants who died. Of the 6609 participants treated with study medication, 1603 prematurely discontinued treatment (24.3%, including participants who died) (Table 3).

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).

[4] To meet the requirement for a 'sustained' decline in eGFR, this was defined as either: • Measured at 2 consecutive scheduled trial follow-up visits (at least 30 days apart); or • Measured at the last scheduled trial follow-up visit or the last scheduled visit before death, withdrawal of consent or loss to follow-up.

Table 3 Disposition of participants

	Placebo N (%)	Empa 10 mg N (%)	Total N (%)
Screened			8266
Randomised	3305 (100.0)	3304 (100.0)	6609 (100.0)
Completed trial or died[1]	3287 (99.5)	3281 (99.3)	6568 (99.4)
Died	167 (5.1)	148 (4.5)	315 (4.8)
Prematurely discontinued trial	18 (0.5)	23 (0.7)	41 (0.6)
Lost to follow-up[2]	9 (0.3)	9 (0.3)	18 (0.3)
Consent withdrawn	9 (0.3)	14 (0.4)	23 (0.3)
Treated	3305 (100.0)	3304 (100.0)	6609 (100.0)
Completed treatment	2457 (74.3)	2549 (77.1)	5006 (75.7)
Prematurely discontinued study medication	848 (25.7)	755 (22.9)	1603 (24.3)
Study drug stopped, reason missing[3]	337 (10.2)	295 (8.9)	632 (9.6)
Adverse event	248 (7.5)	236 (7.1)	484 (7.3)
Serious fatal events	129 (3.9)	120 (3.6)	249 (3.8)
Non-fatal events	119 (3.6)	116 (3.5)	235 (3.6)
Other reason	263 (8.0)	224 (6.8)	487 (7.4)
Participant wishes	89 (2.7)	68 (2.1)	157 (2.4)
Doctor advice	38 (1.1)	40 (1.2)	78 (1.2)
Participant concerned about study treatment	23 (0.7)	28 (0.8)	51 (0.8)
Contraindicated drug started	32 (1.0)	18 (0.5)	50 (0.8)
Cannot attend clinic because moving out of the area	15 (0.5)	9 (0.3)	24 (0.4)
Cannot attend clinic because of personal problems	8 (0.2)	16 (0.5)	24 (0.4)
Other[4]	58 (1.8)	45 (1.4)	103 (1.6)

[1] Defined as all participants with a primary event or follow-up for the primary endpoint until study end/death.
[2] Other participants with incomplete follow-up for the primary endpoint.
[3] Participants who recorded a treatment stop date >1 day prior to the final follow-up visit were considered as early treatment discontinuations.
[4] Other reasons included any category with a frequency <20 participants in total.

Results

Baseline data

Demographics, baseline characteristics, medical history, and concomitant medications were well balanced across the treatment groups (Table 4).

Table 4. Baseline data

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	1413 (21.4)
UACR [mg/g], median (Q1, Q3)	329.35 (48.53, 1068.93)	Very high risk	4937 (74.7)
		Use of RAS-inhibitors, N (%)	5628 (85.2)
Normal (<30), N (%)	1328 (20.1)	Use of diuretics, N (%)	4501 (68.1)
Microalbuminuria (≥30 to ≤300), N (%)	1864 (28.2)	Use of beta-blockers, N (%)	2761 (41.8)
Macroalbuminuria (>300), N (%)	3417 (51.7)	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-inhibitors defined according to the WHO-DD SDGs of ACEis, ARBs and renin inhibitors and BIcDQ ARNIs., SBP = systolic blood pressure, SD = standard deviation

Primary efficacy outcome

Treatment with empagliflozin (10 mg) reduced the risk of kidney disease progression or CV death by 28% when compared with placebo, which was statistically significant (HR 0.72; 99.83% CI 0.59, 0.89; p<0.0001) (Table 5).

Table 5. Time to the first event of kidney disease progression or adjudicated CV death, Cox regression – Randomised set

	Placebo	Empa 10 mg
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[1]	504 (15.2)	384 (11.6)
ESKD only	63 (1.9)	47 (1.4)
eGFR reduction <10 mL/min/1.73 m² and ≥40%	67 (2.0)	43 (1.3)
eGFR reduction to <10 mL/min/1.73 m² only	1 (<0.1)	1 (<0.1)
eGFR reduction ≥40% only	373 (11.3)	293 (8.9)
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 (95% CI)		0.72 (0.64, 0.82)
(99.83% CI)[2]		(0.59, 0.89)
p-value		<0.0001

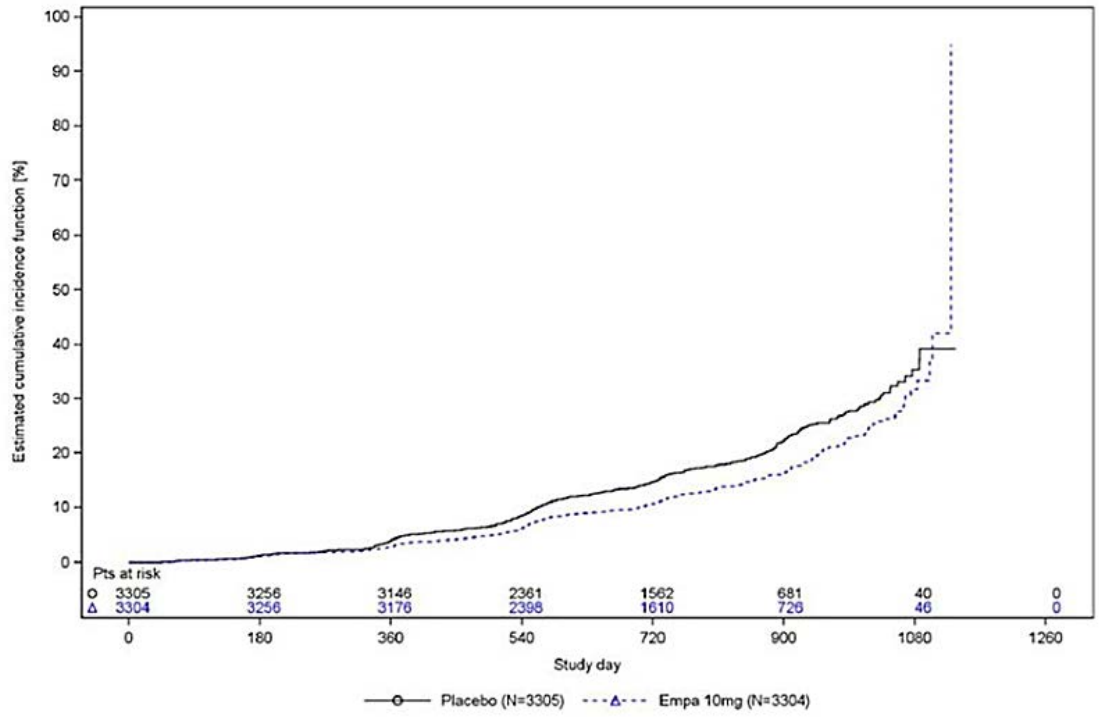
Cox regression model included factors age, sex, baseline diabetes status, local screening eGFR, local screening UACR, region and treatment.

[1] Where there were multiple components contributing to the endpoint these occurred on the same day.

[2] 99.83% CI, corresponding to a 2-sided significance level of <0.0017 required to claim superiority.

Approximately 1 year after randomisation, separation of the estimated cumulative incidence of kidney disease progression or CV death between empagliflozin and placebo became evident and continued over time until the number of participants at risk became too low to provide stable estimates (Figure 2).

Figure 2. Time to the first event of kidney disease progression or adjudicated CV death, estimated cumulative incidence function (considering non-CV/renal death as a competing risk) – Randomised set



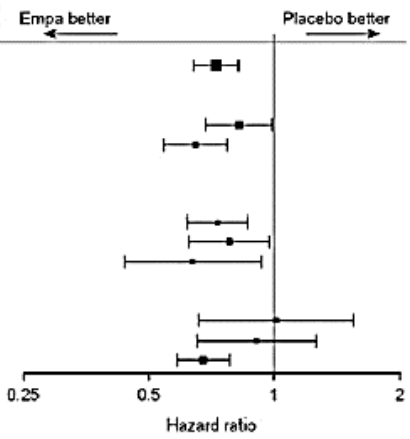
An exploratory analysis by year since randomisation was performed to evaluate the treatment effect over time. The results were consistent with the overall results, with HRs (95% CIs) of 0.73 (0.57, 0.94) in the first year, 0.68 (0.57, 0.82) in the second year, and 0.77 (0.61, 0.98) afterwards (trend test interaction p-value = 0.7241).

Subgroup analyses

The results of the primary endpoint were consistent (interaction p-values >0.05) across the subgroups of baseline diabetes status and baseline eGFR, with the upper bound of the 95% CI for the HR for each subgroup <1 (Table 6). 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 subgroup analyses were not adjusted for multiple testing.

Table 6. Key interest subgroup analyses of time to the first event of kidney disease progression or adjudicated CV death, Cox regression – Randomised set

Subgroup Category	N with event / Empa 10mg vs	N analysed Placebo	Hazard ratio (95% CI)	Interaction p-value
Overall	432/3304	558/3305	0.72 (0.64,0.82)	
Baseline Diabetes Status				0.0598
No	214/1779	252/1790	0.82 (0.68,0.99)	
Yes	218/1525	306/1515	0.64 (0.54,0.77)	
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]				0.7800*
<30	247/1131	317/1151	0.73 (0.62,0.86)	
30 to <45	140/1467	175/1481	0.78 (0.62,0.97)	
≥45	45/ 706	66/ 693	0.64 (0.44,0.93)	
Baseline UACR [mg/g]				0.0174*
Normal (<30)	42/ 665	42/ 663	1.01 (0.66,1.55)	
Microalbuminuria (30 to ≤300)	67/ 927	78/ 937	0.91 (0.65,1.26)	
Macroalbuminuria (>300)	323/1712	438/1705	0.67 (0.58,0.78)	



*Trend test

Results for other efficacy outcomes

Time to first occurrence of kidney disease progression

Kidney disease progression occurred in a lower proportion of participants in the empagliflozin group than in the placebo group. The risk of kidney disease progression was reduced with empagliflozin treatment vs. placebo.

Time to adjudicated CV death

Adjudicated CV death occurred in a low proportion of participants in both treatment groups. There was no strong evidence of a treatment difference between empagliflozin and placebo.

Time to first occurrence of adjudicated CV death or ESKD

CV death or ESKD occurred in a lower proportion of participants in the empagliflozin group than in the placebo group. The risk of CV death or ESKD was reduced with empagliflozin treatment vs. placebo.

Exploratory endpoints

Time-to-event renal endpoints

The risk of all further time-to-event endpoints with renal components was reduced with empagliflozin treatment compared with placebo, with all upper 95% CIs below 1.

eGFR changes over time (MMRM analyses)

In the empagliflozin group, there was an initial drop in eGFR. The adjusted mean change from baseline, (mixed model for repeated measures (MMRM) results) in eGFR [mL/min/1.73 m^2] at 2 months in the empagliflozin group was -2.76 (95% CI -2.95, -2.58) and -0.64 (95% CI -0.82, -0.45) in the placebo group. After the initial drop, a slower decrease was observed for empagliflozin compared with placebo. This resulted in adjusted mean change from baseline at 36 months of -6.25 (95% CI -6.87, -5.63) in the empagliflozin group compared with -7.42 (95%

CI -8.05, -6.79) in the placebo group. The treatment group difference in adjusted means for the average change from baseline over time was -0.31 (95% CI -0.60, -0.01).

Annual rate of change in eGFR

The annual rate of change in eGFR (allowing for the competing events of ESKD or death) was evaluated using a shared parameter model. The main analysis was based on central laboratory evaluations and included all samples collected prior to ESKD.

The total slope analysis was based on the time from baseline to final follow-up, and the intercept reflects the modelled mean eGFR value per treatment group at baseline. The total slope results for the empagliflozin group were considered to be biased, as the analysis assumed a single linear relationship, and non-linearity was introduced by the acute drop in eGFR.

The chronic slope analysis was performed based on the time from 2 months to final follow-up. The intercept reflected the mean change from baseline to the 2-month visit per group; this acute slope was more pronounced in the empagliflozin group (-2.32 mL/min/1.73 m^2) compared with the placebo group (-0.24 mL/min/1.73 m^2). The annual rate of change from the 2-month visit onwards (i.e., the chronic slope) models the approximately linear decline in the chronic phase.

From the 2-month visit onwards, there was a greater eGFR decline in the placebo group compared with the empagliflozin group, with a between group difference of 1.37 mL/min/1.73 m^2 per year (95% CI 1.16, 1.59) and relative difference to placebo of -50% (95% CI -56%, -44%).

UACR changes over time

The urinary albumin-to-creatinine ratio (UACR) initially decreased after 2 months in the empagliflozin group and later fluctuated below baseline, while UACR in the placebo group increased over the course of the trial (MMRM results). UACR remained lower in the empagliflozin group compared with the placebo group throughout the trial. The difference in the average relative change from baseline over time (MMRM results, geometric mean ratio) was 0.81 (95% CI 0.77, 0.85) for empagliflozin compared with placebo.

Time to new onset of diabetes

The number of participants without diabetes at baseline who had new onset of diabetes during the trial was low in both treatment groups, and there was no difference in the time to new onset of diabetes in participants without diabetes at baseline between the empagliflozin and placebo groups.

HbA1c changes over time

The initial timepoints assessed for the majority of participants showed a greater reduction of hemoglobin A1C (HbA1c) in the empagliflozin group compared with the placebo group, while the later timepoints considering fewer participants showed large variability. The average change from baseline over time (MMRM results) was -0.4 (95% CI -0.8, 0.0) for empagliflozin compared with placebo.

Safety

The EMPA-KIDNEY study provided evaluable safety data.

In the EMPA-KIDNEY trial, the collection of safety data was streamlined; only pre-specified non-serious adverse events (AEs) and serious adverse events (SAEs) were collected.

Study EMPA-KIDNEY

Exposure

Safety population included 3304 patients treated with empagliflozin and 3305 with placebo, respectively, with a median exposure of 22 months and 91% treated for at least 1 year and 44% at least 2 years.

Overall safety profile

Empagliflozin and placebo groups had similar frequencies of participants with reported SAEs and prespecified non-serious AEs. The frequency of participants reported with AEs leading to discontinuation of study medication was also similar between the treatment groups. The frequency of participants with investigator-defined drug-related AEs was low. The frequency of participants with SAEs overall was comparable between groups. The frequency of participants with fatal AEs was similar in both groups (Table 7).

Table 7. Overall summary of serious and prespecified non-serious adverse events – Treated set

Category of AEs	Placebo N (%)	Empa 10 mg N (%)
Number of participants	3305 (100.0)	3304 (100.0)
Participants with any prespecified non-serious AEs	1520 (46.0)	1447 (43.8)
Investigator-defined drug-related AEs	60 (1.8)	79 (2.4)
AEs leading to discontinuation of study medication	241 (7.3)	232 (7.0)
Participants with SAEs[1]	1167 (35.3)	1088 (32.9)
Results in death	93 (2.8)	88 (2.7)
Is life threatening	33 (1.0)	36 (1.1)
Persistent or significant disability/incapacity	17 (0.5)	14 (0.4)
Requires or prolongs hospitalisation	937 (28.4)	852 (25.8)
Congenital anomaly or birth defect	1 (<0.1)	0
Other medically important serious event[2]	315 (9.5)	308 (9.3)

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 is 126 for empagliflozin and 135 for placebo.

Most frequently reported AEs

The frequencies of SAEs in each SOC were similar in the empagliflozin and placebo groups. The most frequently reported AEs were in the SOC metabolism and nutrition disorders, followed by infections and infestations, investigations, and renal and urinary disorders. The most frequently reported PTs were gout, acute kidney injury, and coronavirus infection. Additional serious and prespecified non-serious AEs with PTs reported in >2% of participants in either treatment group included blood potassium increased, dehydration, and hypoglycaemia (Table 8).

Table 8. Participants with serious and prespecified non-serious adverse events (frequency >2% in either treatment group at the PT level) – Treated set

MedDRA SOC	Placebo		Empa 10 mg	
MedDRA PT	N (%)	Rate/100 pt-yrs	N (%)	Rate/100 pt-yrs
Number of participants	3305 (100.0)		3304 (100.0)	
Total with serious and prespecified non-serious AEs	1520 (46.0)	34.44	1447 (43.8)	32.28
Metabolism and nutrition disorders	445 (13.5)	8.06	416 (12.6)	7.51
Gout	266 (8.0)	4.66	231 (7.0)	4.02
Dehydration	65 (2.0)	1.09	72 (2.2)	1.20
Hypoglycaemia	67 (2.0)	1.12	68 (2.1)	1.13
Infections and infestations	324 (9.8)	5.60	355 (10.7)	6.17
Coronavirus infection	107 (3.2)	1.79	98 (3.0)	1.63
Investigations	199 (6.0)	3.39	177 (5.4)	3.00
Blood potassium increased	87 (2.6)	1.46	76 (2.3)	1.27
Renal and urinary disorders	182 (5.5)	3.06	158 (4.8)	2.65
Acute kidney injury	117 (3.5)	1.96	93 (2.8)	1.55

SAEs and protocol prespecified non-serious AEs included.
If adjudicated, the resulting preferred terms are presented.

Adverse events of special interest and specific adverse events

AESIs (adverse events of special interest) and specific AEs that represent medical concepts were analysed (Table 9). To capture all events related to a specific medical concept, a combination of applicable adjudication results, investigator-defined events, standardised Medical Dictionary for Regulatory Activities (MedDRA) query (SMQ), BI-customised MedDRA query (BIcMQ; when no SMQ was available), and/or additional definitions were used to analyse 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. Ketoacidosis occurred in 6 participants in the empagliflozin group and 1 in the placebo group (0.10 and 0.02 per 100 participants-years, respectively). Lower limb amputations occurred in 26 participants in the empagliflozin group and 14 in the placebo group (0.43 and 0.23 per 100 participant-years, respectively). 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 9. 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
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.

Liver injury

Serious liver injury and liver injury up to 30 days after treatment discontinuation frequencies were similar between groups and in the subgroups by diabetes status (Table 10).

Table 10 Participants with Liver Injury (AESI, Adjudicated)- Treated set

MedDRA PT Cause of liver injury	Placebo N (%)	 Rate/100 pt-yrs	Empa 10 mg N (%)	 Rate/100 pt-yrs
Number of participants	3305 (100.0)		3304 (100.0)	
Liver injury (adjudicated)	12 (0.4)	0.20	13 (0.4)	0.22
Hepatitis	1 (<0.1)	0.02	6 (0.2)	0.10
Hepatitis toxic	4 (0.1)	0.07	1 (<0.1)	0.02
Hepatitis cholestatic	2 (0.1)	0.03	1 (<0.1)	0.02
Adenocarcinoma pancreas	0	0	1 (<0.1)	0.02
Alcohol abuse	0	0	1 (<0.1)	0.02
Coronavirus infection	1 (<0.1)	0.02	1 (<0.1)	0.02
Non−alcoholic fatty liver	1 (<0.1)	0.02	1 (<0.1)	0.02
Sepsis	0	0	1 (<0.1)	0.02
Biliary neoplasm	1 (<0.1)	0.02	0	0
Cardiac failure	1 (<0.1)	0.02	0	0
Influenza	1 (<0.1)	0.02	0	0
Liver injury (adjudicated), up to 30 days after treatment discontinuation	12 (0.4)	0.20	13 (0.4)	0.22
Liver injury (adjudicated), serious	7 (0.2)	0.12	5 (0.2)	0.08
Liver injury (adjudicated), serious, up to 30 days after treatment discontinuation	7 (0.2)	0.12	5 (0.2)	0.08
Fatal hepatobiliary disorder	2 (0.1)	0.03	5 (0.2)	0.08
With diabetes	7/1515 (0.5)	0.25	8/1525 (0.5)	0.29
Without diabetes	5/1790 (0.3)	0.16	5/1779 (0.3)	0.16

The hazard ratio based on Cox regression for empagliflozin vs. placebo for time to first occurrence of an adjudicated liver injury was 1.09 (95% CI 0.50, 2.38) (RS, OC-AD). The frequency of participants with elevated liver enzyme values was similar between treatment groups through the follow-up period including post-treatment events.

Ketoacidosis

The rate of ketoacidosis (adjudicated) was low. The empagliflozin group had 6 participants with adjudicated events of ketoacidosis (narrow BIcMQ) overall, and by PTs including diabetic ketoacidosis and ketoacidosis, compared with one participant in the placebo group (0.10 vs. 0.02 per 100 patient-years, respectively).

Lower limb amputation

Lower limb amputation (LLA) is summarised for EMPA-KIDNEY 1245-0137, and for a post-hoc meta-analysis of 4 large randomised, double-blind, placebo-controlled clinical outcome trials (EMPA-KIDNEY (1245-0137), EMPA-REG OUTCOME (1245-0025), EMPEROR-Preserved (1245-0110) and EMPEROR-Reduced (1245-0121),) (pooled dataset SAF-M3).

The frequency of participants with LLA (adjudicated) in the empagliflozin group and in the placebo group is provided in the table below. In both groups, the most reported PT was toe amputation. Most events were reported in participants with diabetes (Table 11).

The meta-analysis which included 4 large outcome trials did not indicate an increase in the risk of LLA in participants treated with empagliflozin compared to placebo.

Table 11. Participants with an AE of lower limb amputation (AESI, adjudicated) – Treated set, 1245-0137

MedDRA PT	Placebo		Empa 10 mg	
Level of amputation	N (%)	Rate/100 pt-yrs	N (%)	Rate/100 pt-yrs
Number of participants	3305 (100.0)		3304 (100.0)	
LLA (adjudicated), up to 7 days after study treatment discontinuation	14 (0.4)	0.23	26 (0.8)	0.43
Toe amputation, toe or toes	13 (0.4)	0.22	18 (0.5)	0.30
Foot amputation, transmetatarsal	1 (<0.1)	0.02	5 (0.2)	0.08
Leg amputation	1 (<0.1)	0.02	7 (0.2)	0.12
Below knee	1 (<0.1)	0.02	5 (0.2)	0.08
Above knee	0	0	2 (0.1)	0.03
LLA (adjudicated), up to final follow-up visit	19 (0.6)	0.29	28 (0.8)	0.43
Toe amputation, toe or toes	14 (0.4)	0.22	20 (0.6)	0.31
Foot amputation, transmetatarsal	1 (<0.1)	0.02	7 (0.2)	0.11
Leg amputation	5 (0.2)	0.08	7 (0.2)	0.11
Below knee	4 (0.1)	0.06	5 (0.2)	0.08
Above knee	1 (<0.1)	0.02	2 (0.1)	0.03
LLA (adjudicated), among subgroups up to final follow-up visit				
Baseline eGFR <30 mL/min/1.73m²	10/1151 (0.9)	0.44	11/1131 (1.0)	0.49
Baseline eGFR 30 to <45 mL/min/1.73m²	6/1461 (0.4)	0.21	14/1467 (1.0)	0.49
Baseline eGFR ≥45 mL/min/1.73m²	3/693 (0.4)	0.23	3/706 (0.4)	0.22
Baseline UACR <30 mg/g	4/663 (0.6)	0.30	4/665 (0.6)	0.30
Baseline UACR 30 to ≤300 mg/g	6/937 (0.6)	0.33	10/927 (1.1)	0.55
Baseline UACR >300 mg/g	9/1705 (0.5)	0.27	14/1712 (0.8)	0.42
With diabetes	17/1515 (1.1)	0.56	23/1525 (1.5)	0.76
Without diabetes	2/1790 (0.1)	0.06	5/1779 (0.3)	0.15

In EMPA-KIDNEY, 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) (RS, OC-AD). The estimated cumulative incidence of time to first occurrence of LLA (adjudicated) in the empagliflozin and placebo groups started to diverge shortly after randomisation and remained separated throughout the trial.

Severe hypoglycaemia

Similar frequencies of participants in both treatment groups were observed for SAEs of severe hypoglycaemia, and few participants in either group had severe hypoglycaemic events leading to treatment discontinuation (Table 12).

Four non-diabetic participants in the empagliflozin group had severe hypoglycaemic events; 1 of the events was considered serious but not related to study treatment. In 2 cases, participants were taking concomitant traditional herbal mixes containing cinnamon, and in 1 case the participant was concomitantly taking valproic acid; all are known to cause hypoglycaemia. In the fourth case, the participant had concomitant gastric irritability and poor nutrition due to underlying H. pylori infection.

Table 12 Nondiabetic participants in the empagliflozin group with severe hypoglycaemic events (user-specified and/or narrow SMQ AEs) – Randomised set

Age/sex	AE duration (days)	Relatedness per Investigator	Outcome	Serious
78/M	21	yes	recovered	no
55/M	1	yes	recovered	no
45/M	1	no	recovered	no
59/M	11	no	recovered	yes

User-defined severe hypoglycaemic events are from a predefined list of preferred terms. All events shown were classified as both user-specified and narrow SMQ AEs.

The HR based on Cox regression for empagliflozin versus placebo for time to first occurrence of severe hypoglycaemia was 1.00 (95% CI 0.73, 1.37) (RS, OC-AD). The estimated cumulative incidence of time to first occurrence of severe hypoglycaemia was the same between groups throughout the trial.

Urinary tract infection /Genital infection /Urinary tract malignancy

No meaningful imbalances in the frequency of participants with an SAE of urinary tract infection /genital infection /urinary tract malignancy were observed between the treatment groups.

Acute kidney injury (AKI)

In both treatment groups, the most common cause of serious AKI was pre-renal haemodynamic. The stages of serious AKI were similar between the treatment groups. The frequency of subjects with serious AKI was generally lower for participants in the empagliflozin group across subgroups.

Results were the same for the analyses of participants with serious AKI (specific AE).

The HR based on Cox regression for empagliflozin versus placebo for time to first occurrence of an SAE of AKI (adjudicated) was 0.78 (95% CI 0.60, 1.00) (RS, OC-AD). The estimated cumulative incidence of time to first occurrence of an SAE of kidney injury (adjudicated) in the empagliflozin and placebo groups started to diverge shortly before 1 year after randomisation and remained separated throughout the trial.

Bone fracture

Findings in both groups were similar when analysed as frequency of participants with bone fracture events.

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) (RS, OC-AD). The estimated cumulative incidence of time to first occurrence of an AE of bone fracture was similar between groups throughout the trial.

Serious adverse event/deaths/other significant events

The overall frequency of participants with SAEs was comparable between treatment groups. SAEs were most frequently reported in the SOCs renal and urinary disorders, and in infections and infestations (Table 13). The most common PTs were acute kidney injury and coronavirus infection. The most reported SAEs (PTs reported in >1% of participants in either group) are summarised in the table below. No relevant difference between treatment groups was observed in the frequency of participants with SAEs assessed by the investigator as drug related.

Table 13. Participants with SAEs (frequency >1% in either treatment group at the PT level) – Treated set

MedDRA SOC	Placebo		Empa 10 mg	
MedDRA PT	N (%)	Rate/100 pt-yrs	N (%)	Rate/100 pt-yrs
Number of participants	3305 (100.0)		3304 (100.0)	
Total with SAEs	1167 (35.3)	23.51	1088 (32.9)	21.68
Renal and urinary disorders	177 (5.4)	2.98	157 (4.8)	2.63
Acute kidney injury	117 (3.5)	1.96	93 (2.8)	1.55
End stage renal disease	27 (0.8)	0.45	35 (1.1)	0.58
Infections and infestations	297 (9.0)	5.11	296 (9.0)	5.09
Coronavirus infection	107 (3.2)	1.79	98 (3.0)	1.63
Pneumonia	42 (1.3)	0.70	39 (1.2)	0.65
Investigations	190 (5.7)	3.23	168 (5.1)	2.85
Blood potassium increased	87 (2.6)	1.46	76 (2.3)	1.27
Blood creatinine increased	56 (1.7)	0.93	43 (1.3)	0.71
Cardiac disorders	203 (6.1)	3.45	179 (5.4)	3.02
Ischaemic cardiomyopathy	45 (1.4)	0.75	33 (1.0)	0.55
Cardiac failure	44 (1.3)	0.73	41 (1.2)	0.68
Myocardial infarction	31 (0.9)	0.51	39 (1.2)	0.65
Atrial fibrillation	32 (1.0)	0.53	18 (0.5)	0.30
Nervous system disorders	108 (3.3)	1.81	101 (3.1)	1.69
Ischaemic stroke	34 (1.0)	0.56	30 (0.9)	0.50
With investigator-defined drug-related SAEs	11 (0.3)	0.18	16 (0.5)	0.26

If adjudicated, the resulting preferred terms are presented.

Deaths

Fatal AEs on treatment were reported for 3.8% of participants in the empagliflozin group (event rate 2.09 per 100 participant years) and 4.1% of participants in the placebo group (event rate 2.25 per 100 participant years) (Table 14). Fatal AEs up to the final follow-up visit were reported for 4.5% of participants in the empagliflozin group (event rate 2.28 per 100 participant years) and 5.1% of participants in the placebo group (event rate 2.61 per 100 participant years).

Table 14. Participants with fatal AEs by protocol-specified categorisation – Treated set

Main death category	Placebo	Empa 10 mg
Sub-category	N (%)	N (%)
Number of participants	3305 (100.0)	3304 (100.0)
Participants with fatal AEs (adjudicated)	135 (4.1)	126 (3.8)
Cardiovascular cause	60 (1.8)	52 (1.6)
Coronary heart disease	10 (0.3)	11 (0.3)
Other cardiac disease	30 (0.9)	20 (0.6)
Stroke	6 (0.2)	9 (0.3)
Other cardiovascular	5 (0.2)	2 (0.1)
Presumed cardiovascular	9 (0.3)	10 (0.3)
Non-cardiovascular cause	75 (2.3)	74 (2.2)
Renal	3 (0.1)	3 (0.1)
Infection	39 (1.2)	35 (1.1)
Cancer	18 (0.5)	21 (0.6)
Other medical	11 (0.3)	12 (0.4)
Non-medical	4 (0.1)	3 (0.1)
Participants with fatal AEs (adjudicated), up to final follow-up visit	169 (5.1)	148 (4.5)

Laboratory findings-Haematology and haematological toxicity (in UK participants)

Haemoglobin and haematocrit levels at Month 18 were higher in the empagliflozin group than in the placebo group in UK participants. Both parameters showed an increase compared with baseline in the empagliflozin group and a decrease in the placebo group (Table 15) .

Table 15 ANCOVA results for haemoglobin and haematocrit, locally assessed (UK participants only) – Randomised set (Observed case-all data)

	Placebo	Empa 10 mg
Haemoglobin [g/dL]		
Analysed participants, N	374	437
Baseline, mean (SE)	12.95 (0.09)	12.90 (0.08)
Value at Month 18, adjusted[1] mean (95% CI)	12.79 (12.67, 12.90)	13.53 (13.42, 13.64)
Change from baseline	-0.14 (-0.26, -0.02)	0.60 (0.49, 0.71)
Comparison vs. placebo		0.74 (0.58, 0.90)
Haematocrit [%]		
Analysed participants, N	300	347
Baseline, mean (SE)	38.92 (0.29)	38.74 (0.26)
Value at Month 18, adjusted[1] mean (95% CI)	38.24 (37.82, 38.66)	40.62 (40.23, 41.01)
Change from baseline	-0.58 (-1.00, -0.16)	1.80 (1.41, 2.19)
Comparison vs. placebo		2.38 (1.81, 2.95)

[1] Model for 18 months includes baseline value as linear covariates and treatment as fixed effects.

Risk management plan evaluation summary

The TGA decided a RMP was not required. The Sponsor has provided a 'Submission of an updated RMP form' with their submission. Considering the updated version of the RMP submitted has changed significantly since the last version submitted to the TGA, the updated RMP documents will be reviewed and approved via a separate RMP update process.

The TGA may request an updated RMP at any stage of a product's life-cycle, during both the pre-approval and post-approval phases. Further information regarding the TGA's risk management approach can be found in risk management plans for medicines and biologicals and the TGA's risk management approach. Information on the Australia-specific annex (ASA) can be found on the TGA website.

Risk-benefit analysis

Delegate's considerations

Clinical efficacy and comments

The study population (N=6609) in EMPA-KIDNEY study was at high risk of disease progression, with a baseline eGFR of 37 mL/min/1.73 m2, and macro-albuminuria occurring in 52%. The study included both diabetic (46%) and non-diabetic (54%) subjects. Baseline RAS inhibitor use occurred in 85% of subjects, in line with standard of care treatment.

Empagliflozin 10 mg, in addition to standard of care therapy, in patients with CKD at risk of kidney disease progression, statistically significantly reduced:

- The risk of kidney disease progression or adjudicated CV death by 28% (HR 0.72; 99.83% CI 0.59, 0.89; p<0.0001) (primary endpoint).

- The risk of all-cause hospitalisations by 14% (HR 0.86; 95% CI 0.78, 0.95; p=0.0025) (key secondary endpoint)

The primary results did appear to be consistent across the key subgroups of baseline eGFR and diabetes status. However, for the normal and micro-albuminuria groups, the treatment benefits were less evident.

Consistency in all sensitivity analyses showed the robustness of the primary finding. Also, secondary, and exploratory renal (composite) endpoints supported the major finding, including endpoints of time to first occurrence of kidney disease progression, time to different renal outcome definitions, a slower rate in eGFR change (slope), and slower annual rate for total slope and chronic slope. Time to adjudicated death from any cause and time to first occurrence of HHF or CV death, the results were numerically in favour of empagliflozin compared to placebo.

Even though patients with eGFR <20 mL/min/1.73 m^2 were not eligible, few subjects (N=254) with eGFR <20 mL/min/1.73 m^2 at baseline were included in the study. In a post-hoc analysis regarding the primary efficacy outcome, the results in this subgroup were consistent with the overall population [HR 0.73; 95% CI 0.50, 1.06]. However, given the post-hoc nature of the analysis and the relatively low number of subjects, empagliflozin should not be initiated in those with an eGFR <20 mL/min/1.73 m^2.

Clinical safety

The results from 3304 patients with CKD (median exposure of ~22 months) showed that the AEs and safety laboratory analyses in the EMPA-KIDNEY trial were generally consistent with the known safety profile of empagliflozin.

The empagliflozin and placebo groups had similar frequencies of subjects with reported SAEs, fatal AEs, prespecified non-serious AEs, and AEs leading to discontinuation of study medication, and the frequency of participants with investigator-defined drug-related AEs was low.

The overall frequencies for liver injury, serious UTI, serious genital infection, gout, severe hypoglycaemia, and urinary tract malignancy were comparable in the empagliflozin and placebo groups. Within individual categories of AESIs and specific AEs, generally similar proportions of participants in both treatment groups had serious AEs, and few AEs in any category of AESIs or specific AEs led to treatment discontinuation. Fatal AEs by main category and sub-category were comparable between the groups.

Four cases of severe hypoglycaemic events were seen in non-diabetic subjects treated with empagliflozin versus none for placebo, but there were alternative explanations provided for the events in these cases.

Ketoacidosis occurred in a small number of patients, most of whom had diabetes, but occurred more frequently in those treated with empagliflozin versus placebo (0.10 versus 0.02 per 100-patient years, respectively).

In the EMPA-KIDNEY study, the incidence of lower limb amputation (LLA) was numerically higher in patients treated with empagliflozin compared with placebo (0.8% versus 0.4%), and mainly concerned toe amputation. Most events occurred in subjects with DM. Meta-analysis including 4 large outcome trials which included 23,340 randomised and treated participants did not show a significant increase in the risk of LLA in subjects treated with empagliflozin compared to placebo (HR 1.16 [95% CI 0.86, 1.57]). Based on the current data, no stronger conclusions can be drawn and the current statement in the PI is appropriate.

There was a numerical increase in the incidence rate of bone fractures in the empagliflozin group as compared to the placebo group, although the Cox-regression analysis did not reveal a higher incidence for empagliflozin (HR 1.08 [95% CI 0.84, 1.38]).

Overall, empagliflozin appears to have reassuring safety profile and usually well tolerated, including in a population with reduced renal function. The safety profile was generally on expected lines, except the one case of ketoacidosis in a non-diabetic patient, which had not previously been noted for empagliflozin.

Data limitation

- Lower than expected number of cardiovascular events, reducing the statistical power for the assessment of the secondary and tertiary cardiovascular outcomes.
- Only 10 mg daily dose was studied. A dose of 25 mg daily was not evaluated, which might have offered better efficacy. In the EMPA-REG OUTCOME trial, risk reductions observed with 10 mg and 25 mg were virtually identical with a similar safety profile, hence only 10mg dose was studied. However, EMPA-REG OUTCOME trial did not include moderate/severe CKD patients.
- No data to support used of Empagliflozin in patients with mild chronic kidney disease. Patients only with eGFR < 60 were included[5].

Proposed action

Overall, the submitted data and subsequent responses by the Sponsor support following extension of indication:

> *JARDIANCE is indicated in adult patients with chronic kidney disease to reduce the risk of kidney disease progression (see Section 5.1 Pharmacodynamic properties – Clinical trials).*

Advisory committee on medicines considerations

Specific advice to the Delegate

The Advisory Committee on Medicines (ACM), having considered the evaluations and the Delegate's overview, as well as the Sponsor's response to these documents, advised the following.

1. ***Does the ACM agree with the proposed extension of the therapeutic indication to the broad range of CKD patients? Especially in view that the submitted data does not provide information on benefit in less advanced CKD patients (that is, those at lower risk of disease progression)***

   The ACM discussed the additional information added by the pivotal trial (EMPA-KIDNEY) compared to other landmark trials of SGLT2 inhibitors in CKD. The pivotal trial included a broader population of participants, captured a substantial population of participants without diabetes mellitus, and a greater range of eGFR and albuminuria levels. The ACM noted the greater population of participants without diabetes mellitus was important as empagliflozin is already indicated for use in diabetic patients.

   Empagliflozin was shown to benefit CKD patients both with and without diabetes mellitus. There was an 8-fold difference in chronic eGFR slopes and patients at the lower end of albuminuria were stabilised. The ACM noted patients with polycystic kidney disease, kidney transplant recipients and patients on dialysis were not included in the trial.

   The ACM was of the view that there is sufficient evidence to support the efficacy of empagliflozin in the CKD categories studied.

[5] Patients with eGFR <90 mL/min/1.73m^2 were included in the EMPA-KIDNEY trial (refer to page 13 of this AusPAR for key inclusion criteria)

The ACM discussed the potential to include additional specificity regarding CKD stage and ACR levels within the indication noting that the submitted data does not provide information on benefit in less advanced CKD patients. The ACM proposed the following be considered for inclusion in the indication:

CKD Stages 2 and 3A with urine ACR ≥ 30mg/g, or CKD Stages 3B, 4 and 5 irrespective of urine ACR

The ACM noted similar indication wording for other SGLT2 inhibitors.

2. ***Does the ACM agree with safety profile for proposed use of empagliflozin in the patients with chronic kidney disease to reduce the progression?***

   The ACM agreed there are no new or major safety signals in CKD. Diabetic ketoacidosis (DKA) and lower limb amputation (LLA) remain relevant considerations, particularly in diabetes.

3. ***The committee is also requested to provide advice on any other issues that it thinks may be relevant to this application?***

   The ACM noted consideration should be given to how to most appropriately highlight the groups not studied in clinical trials (i.e., patients with polycystic kidney disease, patients with kidney transplant and patients on dialysis) within the PI.

   The ACM was of the view the CMI should include advice about use of empagliflozin before surgery as this information is provided in the PI. The ACM indicated the CMI could state 'JARDIANCE may need to be suspended before a medical procedure such as surgery. Contact your doctor to obtain advice'.

Conclusion

The ACM considered this product to have an overall positive benefit-risk profile for the indication:

JARDIANCE is indicated to reduce the risk of kidney disease progression in adult patients with chronic kidney disease (CKD Stages 2 and 3A with urine ACR ≥ 30mg/g, or CKD Stages 3B, 4 and 5 irrespective of urine ACR).

Outcome

Based on a review of quality, safety, and efficacy, the TGA decided to register JARDIANCE for the following extension of indications

> ***Chronic kidney disease***
> *JARDIANCE is indicated to reduce the risk of kidney disease progression in adults with chronic kidney disease (CKD Stages 2 and 3A with urine ACR ≥30 mg/g, or CKD Stages 3B, 4 and 5 irrespective of urine ACR).*

As such, the full indications at this time were:

> ***Type 2 diabetes mellitus***
>
> ***Glycaemic control***
>
> *JARDIANCE is indicated in the treatment of type 2 diabetes mellitus to improve glycaemic control in adults as:*
>
> *Monotherapy*

When diet and exercise alone do not provide adequate glycaemic control in patients for whom use of metformin is considered inappropriate due to intolerance.

Add-on combination therapy

In combination with other glucose–lowering medicinal products including insulin, when these, together with diet and exercise, do not provide adequate glycaemic control (see Section 5.1 Pharmacodynamic properties - Clinical trials).

Prevention of cardiovascular death

JARDIANCE is indicated in patients with type 2 diabetes mellitus and established cardiovascular disease to reduce the risk of cardiovascular death (see Section 5.1 Pharmacodynamic properties - Clinical trials). To prevent cardiovascular deaths, JARDIANCE should be used in conjunction with other measures to reduce cardiovascular risk in line with the current standard of care.

Heart failure

JARDIANCE is indicated in adults for the treatment of symptomatic heart failure independent of left ventricular ejection fraction, as an adjunct to standard of care therapy (see Section 5.1 Pharmacodynamic properties - Clinical trials).

Chronic kidney disease

JARDIANCE is indicated to reduce the risk of kidney disease progression in adults with chronic kidney disease (CKD Stages 2 and 3A with urine ACR ≥30 mg/g, or CKD Stages 3B, 4 and 5 irrespective of urine ACR).

The above extension of indications is inclusive of the previous approved indications.

Product Information

The Product Information (PI) approved with the submission for Jardiance which is described in this AusPAR (and can be accessed on this AusPAR's webpage) may have been superseded. For the most recent PI and Consumer Medicines Information (CMI), please refer to the TGA PI/CMI search facility.

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