NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Dapagliflozin for treating chronic kidney disease [ID6411]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Dapagliflozin for treating chronic kidney disease [ID6411]

Contents:

The following documents are made available to stakeholders:

Access the **final scope and final stakeholder list** on the NICE website.

1. **Company submission** from AstraZeneca:
   a. Full submission
   b. Submission addendum
   c. Summary of Information for Patients (SIP)

2. **Clarification questions and company responses**

3. **Patient group, professional group, and NHS organisation submission** from:
   a. Kidney Research UK
   b. UK Renal Pharmacy Group

4. **External Assessment Report** prepared by Centre for Reviews and Dissemination (CRD) and Centre for Health Economics (CHE) – York

5. **External Assessment Group response to factual accuracy check of EAR**

6. **Additional data** from AstraZeneca

7. **Clarification questions and company responses on additional data**

8. **External Assessment Report addendum** prepared by Centre for Reviews and Dissemination (CRD) and Centre for Health Economics (CHE) – York

9. **External Assessment Group response to factual accuracy check of EAG addendum**

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal: cost-comparison

Dapagliflozin for the treatment of adults with chronic kidney disease – Review of TA775 [ID6411]

Document B

Company evidence submission

June 2024

File name	Version	Contains confidential information	Date
ID6411_Dapagliflozin_CKD_TA775 review_document B [REDACTED]	**Final**	**Yes**	**19/06/2024**

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B.1 Decision problem, description of the technology and clinical care pathway

B.1.1 Decision problem

The aim of this submission is to review the current NICE recommendation for dapagliflozin in chronic kidney disease (CKD) and align it with the NICE recommendation for empagliflozin. Therefore, this targeted review includes the subgroups which are currently recommended in TA942 but not in TA775. These are:

1. Adults with CKD, without type 2 diabetes (T2D), and with:
    a. estimated glomerular filtration rate (eGFR) ≥20–45 mL/min/1.73m^2 and a urine albumin-to-creatinine ratio (uACR) <22.6 mg/mmol (200 mg/g); or
    b. eGFR ≥20–25 mL/min/1.73m^2 and a uACR ≥22.6 mg/mmol (≥200 mg/g); or
    c. eGFR >75–90 mL/min/1.73m^2 and a uACR ≥22.6 mg/mmol (≥200 mg/g).
2. Adults with CKD, with T2D, and with:
    a. eGFR ≥20–25 mL/min/1.73m^2; or
    b. eGFR >75–90 mL/min/1.73m^2.

These subgroups fall within the full marketing authorisation for dapagliflozin in adults with CKD,[1] and are subgroups of the population for which empagliflozin, the main comparator in this appraisal, is recommended in TA942, but are not currently covered in TA775.[2, 3] Incorporating these subgroups into the dapagliflozin recommendation will align the NICE recommendations between the two appraisals.

TA775 recommendation for dapagliflozin in CKD and CKD subgroup restrictions

Dapagliflozin is currently recommended by NICE for the treatment of adults with T2D (TA288),[4] with heart failure with reduced ejection fraction (HFrEF; TA679),[5] with heart failure with preserved or mildly reduced ejection fraction (HFpEF; TA902),[6] and with CKD (TA775).[2]

When dapagliflozin was evaluated by NICE for CKD in TA775, empagliflozin was not yet recommended for the treatment of CKD and, therefore, was not a relevant comparator in this population. The appraisal of dapagliflozin for CKD initiated in March 2021 and was conducted under the standard Single Technology Appraisal (STA) procedure. During the appraisal, the Appraisal Committee considered three subgroups of patients with eGFR of 25 mL/min/1.73 m^2 to 75 mL/min/1.73 m^2:

- Subgroup 1: uACR ≥22.6 mg/mmol, with or without T2D;
- Subgroup 2: uACR <22.6 mg/mmol, with T2D; and

- Subgroup 3: uACR <22.6 mg/mmol, without T2D.

The committee concluded that dapagliflozin should be recommended in both subgroups 1 and 2, but not in subgroup 3. Despite an incremental cost effectiveness ratio (ICER) of £17,000 in subgroup 3 which is below the NICE willingness to pay (WTP) threshold, the committee perceived there to be uncertainty in the plausibility of the cost-effectiveness estimates in this population. This was due to the lack of direct clinical evidence informing this subgroup and uncertainty around the real-world evidence (RWE) provided by the Clinical Practice Research Datalink (CPRD). As per the guidance issued for TA775, the committee considered there to be a potential consequence of overprescribing and, given the size of the population and uncertainty in the cost-effectiveness estimates, the committee considered the consequence of decision error to be too high to make a positive recommendation.[2] Therefore, the NICE recommendation for dapagliflozin in CKD is:[2]

- As an add-on to optimised standard of care (SoC) including the highest tolerated licensed dose of angiotensin-converting enzyme (ACE) inhibitors or angiotensin-receptor blockers (ARBs), unless these are contraindicated, and;
- In people who have an eGFR of 25 mL/min/1.73 m^2 to 75 mL/min/1.73 m^2 at the start of treatment and:
    - have T2D; or
    - have a uACR of 22.6 mg/mmol or more.

Restrictions in TA775 irrespective of T2D status

TA775 also restricted the use of dapagliflozin within patients with CKD, irrespective of T2D status, to those with an eGFR of 25 mL/min/1.73 m^2 to 75 mL/min/1.73 m^2. This was driven predominately by the DAPA-CKD trial inclusion criteria and the CPRD analysis likely underestimating the CKD population size.[7] Therefore, TA775 does not contain a recommendation for dapagliflozin in patients with CKD without T2D, with an eGFR between 25 and 45 mL/min/1.73m^2 and a uACR less than 22.6 mg/mmol (200 mg/g), or in those with CKD with or without T2D with an eGFR >75–90 mL/min/1.73m^2. However, recent RWE evidence (detailed in section B.3.3.2 OPTIMISE-CKDB.3.3.3 Nakhleh *et al.,* 2024) and subgroup analyses from dapagliflozin trials (detailed in section B.3.3.4 DECLARE-TIMI 58B.3.3.5 DAPA-HF) further demonstrate the efficacy of dapagliflozin in patients with an eGFR ≥20 mL/min/1.73 m^2 as per the Medicines and Healthcare products Regulatory Agency (MHRA) label and, therefore, warrant a reconsideration of this restriction by NICE to align to the population in the empagliflozin recommendation.

Since the publication of TA775, there have been three major factors for consideration in this review:

1. Recent RWE from OPTIMISE-CKD and Nakhleh et al., 2024 has demonstrated the consistent effect of dapagliflozin in CKD irrespective of T2D status or uACR levels at baseline, thereby

addressing uncertainties raised in TA775. This is further supported by post-hoc analyses from dapagliflozin RCTs, namely DAPA-CKD and DAPA-HF;

2. Subgroup analyses from DECLARE-TIMI 58 and DAPA-HF also demonstrate clinical efficacy in line with the MHRA label for dapagliflozin (specifically eGFR ≥20 mL/min/1.73 m^2 and ≥75 mL/min/1.73 m^2, and ≥75 mL/min/1.73 m^2, respectively), therefore, eliminating the need to restrict the population in TA775;
3. NICE has made a broader recommendation for empagliflozin in CKD than that for dapagliflozin, supported by an indirect treatment comparison (ITC) demonstrating similar effectiveness to dapagliflozin. Despite some uncertainties, the original concerns surrounding a perceived risk of decision error in patients with non-T2D CKD with uACR <22.6 mg/mmol seem to have reduced, so much so that a streamlined decision-making process was applied to the appraisal;

Evidence addressing uncertainties raised in TA775 regarding patients with non-T2D CKD and uACR <22.6 mg/mmol

Since dapagliflozin was appraised in TA775, additional evidence is available in the form of the abovementioned ITC and meta-analyses considered in TA942, a post-hoc analysis of the DAPA-CKD trial and global RWE, including OPTIMISE-CKD and a retrospective study by Nakhleh *et al.,* 2024, which all inform the efficacy of dapagliflozin in patients who currently are not recommended for use by NICE.

OPTIMISE-CKD (presented in section B.3.3.2 OPTIMISE-CKDB.3.6.2 OPTIMISE-CKD) was an observational study which included 28,795 patients newly treated with dapagliflozin for CKD with or without T2D in the United States (US), and claims data from 20,407 patients with CKD in the US and Japan. The study demonstrated the consistent treatment effect of dapagliflozin in patients with an eGFR of 15–60 mL/min/1.73 m^2, irrespective of T2D status and uACR level, and a clinically meaningful attenuation of eGFR slope compared with patients who did not initiate dapagliflozin, supporting that the effectiveness of dapagliflozin observed in clinical trials extends to real-world patients. This evidence highlights dapagliflozin's broad applicability in the management of CKD, particularly in patients with normal to moderately increased uACR levels, reinforcing its potential to protect against CKD progression without the constraint of albuminuria severity.[8, 9] Additionally, the retrospective study by Nakhleh *et al.,* 2024 (presented in section B.3.3.3 Nakhleh *et al.,* 2024B.3.6.3 Nakhleh *et al.,* 2024) was conducted in Israel to evaluate the effect of sodium-glucose co-transporter-2 (SGLT2) inhibitors on the progression of CKD in patients without diabetes, with and without albuminuria.[10] Patient interaction data was assessed from the Maccabi Healthcare Service (MHS) central database in patients who started on an SGLT2 inhibitor (75.4% on dapagliflozin and 24.6% on empagliflozin) between 2020 and 2022, with a median follow up of 527 days. The study demonstrated that SGLT2 inhibitors significantly slowed the annual decline in eGFR from -5.6 mL/min/1.73 m² to -1.7 mL/min/1.73 m² across the albuminuria range in those without T2D

and an eGFR between 25–60 mL/min/1.73m^2, 41.2% of whom had normal to mildly increased albuminuria (uACR <3 mg/mmol) at baseline.[10]

Additionally, a post-hoc analysis of the DAPA-CKD trial (presented in section B.3.3.1.5.1 Baseline characteristics in post-hoc analysisB.3.6.1.3 Post-hoc analysis from DAPA-CKD trial) aimed to assess whether the kidney protective benefits of dapagliflozin, as demonstrated in the DAPA-CKD trial, extend to participants without T2D and with lower levels of albuminuria.[11] While the trial inclusion criteria was patients with a uACR of 22.6 mg/mmol (200 mg/g) to 565 mg/mmol (5,000 mg/g), the study included 136 patients with uACR 3 to <30 mg/mmol, of whom 24 had uACR 3 to <22.6 mg/mmol at baseline. Outcomes from this analysis were consistent with those observed in the DAPA-CKD trial and, therefore, further validate the effectiveness of dapagliflozin in patients with a uACR <30 mg/mmol as demonstrated in RWE.[11]

Subgroup analysis of the DAPA-HF trial also supports the consistency of the dapagliflozin treatment effect across patients with and without T2D. The trial included patients with HFrEF across a wide range of uACR, including patients with uACR<22.6 mg/mmol, and demonstrated a significant reduction in the risk of the primary outcome of worsening HF or CV death independently of diabetes status.[12]

Evidence to support clinical efficacy in patients with an eGFR of ≥20-25 or >75-90 mL/min/1.73 m^2 with or without T2D

OPTIMISE-CKD demonstrated the consistent benefit of dapagliflozin initiation across the whole eGFR slope distribution among patients with a uACR <200mg/g (22.6 mg/mmol), thereby establishing the benefit of dapagliflozin in patients with eGFR of ≥20-25 mL/min/1.73 m^2.[8, 9]

The efficacy of dapagliflozin in the broader population of patients with CKD, regardless of uACR and eGFR category, is also supported by DECLARE-TIMI 58 and DAPA-HF. While the DAPA-CKD trial enrolled patients with an eGFR of 25–75 mL/min/1.73 m^2 and a uACR of 200–5,000 mg/g (22.6–565 mg/mmol), the extensive clinical trial program for dapagliflozin in T2D and HFrEF covers patients with a range of renal functions and provides data supporting the efficacy of dapagliflozin in patients who were not eligible for inclusion in DAPA-CKD with respect to uACR and eGFR.

Post-hoc analyses from DECLARE-TIMI 58 and DAPA-HF also provide evidence of the consistent treatment effect of dapagliflozin in patients with an eGFR ≥20 mL/min/1.73 m^2 and ≥75 mL/min/1.73 m^2, and ≥75–90 mL/min/1.73m^2, respectively.[13-15] Not only did DECLARE-TIMI 58 achieve significant treatment outcomes in patients with T2D and uACR <22.6 mg/mmol, the study also demonstrated a statistically significant improvement in the composite renal-specific outcome in patients with an eGFR of 60–<90 mL/min/1.73 m^2 (hazard ratio [HR]: 0.54; 95% confidence interval [CI]: 0·40, 0.73).[13] Similarly in DAPA-HF, dapagliflozin was associated with significant reductions in the primary endpoint of worsening HF or CV death (HR: 0.74; 95% CI: 0.65, 0.85; p<0.001), which enrolled patients across a wide range of uACR categories.[16] The efficacy of dapagliflozin in preventing the primary outcome of cardiovascular (CV) death or worsening heart failure (HF) did not differ between those with an eGFR

of <60 mL/min/1.73 m², and individuals with an eGFR ≥60 mL/min/1.73 m² (p for interaction=0.54). Additionally, between day 14 and day 720, the change in eGFR in the dapagliflozin group was about one-third of that in the placebo group (-1.09 [95% CI: -1.40, -0.77] and -2.85 [95% CI: -3.17, -2.53], respectively, p for difference in slopes <0.001). The same pattern was observed in patients with and without T2D at baseline (p for interaction=0.92) and in patients with an eGFR <60 or ≥60 mL/min/1.73 m².[15]

Collectively, evidence from these studies further supports the generalisability of the RWE and addresses the uncertainties from TA775 by:

- Demonstrating efficacy in patients with non-T2D CKD irrespective of uACR; and
- Reinforcing clinical efficacy in line with dapagliflozin's license in patients with CKD, with or without T2D, with an eGFR of 15–90 mL/min/1.73 m².

Recommendation of empagliflozin in TA942 and inconsistencies in processes and recommendations with TA775

Since TA775, empagliflozin has been evaluated as an option for the treatment of adults with CKD, with SoC, with or without dapagliflozin, as a comparator. The appraisal of empagliflozin against dapagliflozin in TA942 was conducted under the cost comparison procedure with dapagliflozin in the overlapping trial populations, during which empagliflozin demonstrated equivalent efficacy and safety to dapagliflozin through a company-sponsored ITC via network meta-analysis (NMA), and a cost utility analysis in the population not covered by the ITC to dapagliflozin.[3] This was further strengthened by a published meta-analysis showing consistent benefits and safety between SGLT2 inhibitors irrespective of diabetes status.[17] NICE recognised that results from the ITC suggested similar effectiveness and safety between dapagliflozin and empagliflozin, that both treatments would have similar costs as demonstrated in a cost-comparison, and that empagliflozin compared to SoC is an acceptable use of National Health Service (NHS) resources based on a cost-effectiveness analysis.[3] Additionally, NICE has previously recognised the similar effectiveness between the two interventions across multiple indications, demonstrated through various indirect comparisons, namely in empagliflozin's appraisals for the treatment of HFrEF and HFpEF.[18, 19] The committee in TA942 concluded that the evidence presented in empagliflozin's pivotal trial, EMPA-KIDNEY, sufficiently demonstrated that empagliflozin plus SoC was more effective than SoC alone for patients with non-T2D CKD and uACR <22.6 mg/mmol. For patients without T2D, the External Assessment Group (EAG) concluded that the ITC showed no meaningful differences between dapagliflozin and empagliflozin.

TA942 resulted in a recommendation for a substantially broader population than dapagliflozin, which is also aligned to the population enrolled in EMPA-KIDNEY:[3]

- eGFR ≥20 and <45 mL/min/1.73m²; or
- eGFR ≥45 and <90 mL/min/1.73m² and either:

- uACR ≥22.6 mg/mmol;
- T2D.

The recommendations for empagliflozin appear to be substantially based on a conclusion of similar efficacy and costs to that of dapagliflozin with an indicative ICER across the full population to inform estimates in other subgroups. Unlike in TA775, there was less focus on the assessment of cost-effectiveness in lower risk subgroups, such as in patients with greater kidney function, or in those with a low eGFR and uACR <22.6 mg/mmol, and NICE considered the decision to recommend empagliflozin in a population broader than that in TA775 (i.e., patients with an eGFR >20–90 mL/min/1.73m^2). Whilst the EAG highlighted some uncertainties in cost-effectiveness estimates in these populations, NICE considered this decision was low risk, proceeding under the accelerated streamlined committee decision-making process.

Subgroup analyses were specifically requested by NICE to explore the cost-effectiveness of dapagliflozin in three distinct cohorts (subgroups 1, 2 and 3 outlined above) in TA775. For the patients with non-T2D CKD with uACR <22.6 mg/mmol (subgroup 3 outlined above), dapagliflozin demonstrated an ICER of £17,000, indicating a cost-effective use in this patient population.[2] However, the committee did not recommend dapagliflozin in this subgroup due to the potential consequence of overprescribing, size of the population and uncertainty in the cost-effectiveness estimates. In TA942, the same subgroup analyses were not requested by NICE, but the EAG presented a cost effectiveness analysis in patients with a uACR <22.6 mg/mmol, which was based on limited data that did not include the full data from EMPA-KIDNEY. This analysis found that the cost-effectiveness in this subgroup was substantially higher than the full population. Despite this, the committee considered that a recommendation could still be made for all patients with a uACR <22.6 mg/mmol and that it was also a low-risk decision because of the fact that it was cost-effective across the full population.[3] This context is important as therefore the risk appetite in these populations appears to have evolved over time, and there is now an opportunity to broaden the original recommendations made in TA775.

Despite the potential difference in the ICERs for this subgroup in the respective appraisals, the committee considered the factors that precluded the recommendation of dapagliflozin for use in subgroup 3 were no longer a barrier to recommendation, to the extent that the decision in TA942 was low risk. The recommendation made within TA942 therefore demonstrates inconsistency in the approach adopted by NICE to inform the decisions for two similar technologies. AstraZeneca acknowledges that the risk appetite of NICE and the committee can change over time, and consequently seeks to align the recommendations in the two appraisals accordingly through this targeted review.

Conclusion

There is substantial evidence demonstrating that dapagliflozin and empagliflozin are clinically similar. NICE has previously recognised the similar effectiveness between the two interventions across multiple indications, demonstrated through various indirect comparisons, namely in empagliflozin's appraisals for the treatment of HFrEF (TA773), HFpEF (TA929), and most recently CKD (TA942). It is

recognised by clinical experts that the two products are clinically similar and, therefore, the current discrepancy in the CKD recommended populations adds unnecessary complexity for prescribers.[20]

The residual uncertainty noted by the committee in TA775 which led to the restricted recommendation has been addressed by data from the recent RWE from OPTIMISE CKD and Nakhleh *et al.,* 2024, alongside supportive subgroup analyses from DAPA-CKD, DECLARE-TIMI 58 and DAPA-HF and through the conclusions in TA942. The data across both RWE and RCTs are generalisable to the UK population and consistent with dapagliflozin trial outcomes in HFrEF, T2D and CKD, which NICE have deemed generalisable in the respective appraisals. The evidence also demonstrates a consistent treatment effect for dapagliflozin in CKD irrespective of uACR and diabetes status.

Based on the current evidence base and clinical opinion, AstraZeneca therefore, believes that NICE should expand the current recommendation for dapagliflozin to be in line with empagliflozin's recommendation in TA942. Aligning the populations will simplify the treatment pathway in both primary and secondary care and remove the current perceived complexities in prescribing for clinicians which will improve access for patients.

Table 1. The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	People with CKD who have an eGFR of: • 20 mL/min/1.73 m^2 to less than 45 mL/min/1.73 m^2 or • 45 mL/min/1.73 m^2 to 90 mL/min/1.73 m^2 and have either: ○ T2D or ○ a uACR of 22.6 mg/mmol or more	• Adults with CKD, without T2D, and with: ○ eGFR ≥20–45 mL/min/1.73m^2 and uACR <22.6 mg/mmol (200 mg/g); or ○ eGFR 20–25 mL/min/1.73m^2 and a uACR ≥22.6 mg/mmol (≥200 mg/g); or ○ eGFR >75–90 mL/min/1.73m^2 and a uACR ≥22.6 mg/mmol (≥200 mg/g). • Adults with CKD, with T2D, and with: ○ eGFR ≥20–25 mL/min/1.73m^2; or ○ eGFR >75–90 mL/min/1.73m^2.	The aim of this review is to align the populations in the recommendations for dapagliflozin and empagliflozin in TA775 and TA942 respectively. The population in the NICE scope has been partially addressed in TA775, and therefore the data presented within the company submission is aimed at the population where empagliflozin has a recommendation and dapagliflozin currently doesn't. This is because NICE have already evaluated the two technologies in cost comparison in TA942. It is expected that a positive recommendation following this review will result in a final recommendation of dapagliflozin in CKD in TA775 in the population proposed by NICE in the final scope.
Intervention	Dapagliflozin	Dapagliflozin	N/A
Comparator(s)	Empagliflozin	Empagliflozin	N/A
Outcomes	The outcome measures to be considered include: • morbidity including cardiovascular outcomes, disease	This appraisal conducts a naïve comparison of the primary endpoints in the two pivotal clinical trials for dapagliflozin and empagliflozin, DAPA-CKD and EMPA-KIDNEY, respectively.	The outcomes proposed in the scope have been included in TA775 in which dapagliflozin demonstrated effectiveness in adults with CKD. NICE has previously concluded that dapagliflozin and empagliflozin have similar effectiveness and safety based on a published ITC.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
	• progression (such as kidney replacement, kidney failure) and markers of disease progression (such as eGFR), albuminuria) • mortality • hospitalisation • adverse effects of treatment • health-related quality of life.		Additionally, it was not feasible to conduct an ITC in the specific subgroups within the decision problem versus empagliflozin due to a lack of matched cohorts and comparable datasets for analysis. For this reason, this appraisal conducts a naïve comparison of the primary endpoints in the two pivotal clinical trials for dapagliflozin and empagliflozin, DAPA-CKD and EMPA-KIDNEY, respectively, thereby addressing uncertainties raised in TA775 which led to a restricted population in the recommendation.
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. If the technology is likely to provide similar or greater health benefits at similar or lower cost than technologies recommended in published NICE technology appraisal guidance for the same indication, a cost comparison may be carried out. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or	Taking into account the previous cost-effectiveness and cost-comparison analyses completed in TA775 and TA942, a full cost comparison analysis has not been conducted for this appraisal. Instead, it is assumed that the availability of dapagliflozin in this patient population will not incur a differential cost to empagliflozin in the same group of patients. Senior leads at NICE have acknowledged that the company will make best use of the submission template but have also recognised that certain elements of the template cannot be populated.	Dapagliflozin and empagliflozin are expected to have no differences in cost or resource use in the subgroups in the decision problem. The acquisition costs of dapagliflozin and empagliflozin are equivalent at £36.59 per pack, with no confidential commercial arrangements and the same method and frequency of administration with no difference in patient monitoring, follow-up, adverse events or adherence in this population.[21, 22] The resource use of the population with non-T2D CKD and uACR <22.6 mg/mmol is estimated to have no or negligible differential considering the clinical equivalence of dapagliflozin and empagliflozin. There is no expected change

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
	outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account.		to service provision or management in this population, specifically. In patients with CKD and T2D, empagliflozin has a higher cost than dapagliflozin to the NHS. The empagliflozin SmPC states that for patients with T2D "the recommended starting dose is 10 mg empagliflozin once daily for monotherapy and add-on combination therapy with other medicinal products for the treatment of diabetes. In patients tolerating empagliflozin 10 mg once daily who have an eGFR ≥60 mL/min/1.73 m^2 and need tighter glycaemic control, the dose can be increased to 25 mg once daily".[23] Therefore, these patients in clinical practice may have their dosing up-titrated to 25 mg once daily with associated additional SoC testing and potential primary care visit, while this dosing is 10 mg for dapagliflozin.[1] Costs associated with up-titration can substantially impact the overall cost-comparison between treatments. On the other hand, dapagliflozin provides consistent and simple posology across the whole CKD population irrespective of T2D status (with the exception of patients with severe hepatic impairment who are initiated at 5 mg before increasing dose to 10 mg if tolerated), thereby alleviating pressure from an already burdened primary care system

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
			through the elimination of additional testing, patient visits, and clinician time. Additionally, dapagliflozin previously demonstrated an ICER of £17,000 in a subgroup analysis in TA775, indicating a cost effective use in this patient population.[2] While uncertainty in the estimates of empagliflozin's ICER in this patient group was much greater, , it was still included in the final recommended population.[3] Therefore, this appraisal focuses solely on demonstrating the clinical equivalency in the population within the decision problem.

Abbreviations: CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate, ICER: incremental cost effectiveness ratio; N/A: not applicable; NHS: National Health Service; SmPC: summary of medicinal product characteristics; SoC: standard of care; T2D: type 2 diabetes; uACR: urine albumin-to-creatinine ratio.

B.1.2 Description of the technology being evaluated

The summary of medicinal product characteristics (SmPC) for dapagliflozin that covers the indication of relevance to this submission (adults with CKD) is provided in Appendix C. Details of the technology being evaluated, including the method of administration, dosing and related costs, are provided in Table 2.

Table 2. Technology being evaluated

UK approved name and brand name	Dapagliflozin (Brand name: Forxiga®)
Mechanism of action	• Dapagliflozin is a highly potent, selective and reversible SGLT2 inhibitor.[1] • SGLT2 is a co-transporter protein localised primarily in the proximal tubule of the nephron in the kidney, which mediates the active transport of glucose and sodium from the filtrate into the blood, thereby controlling the level of sodium present in the filtrate.[24] • In the context of CKD, inhibition of SGLT2 is anticipated to improve renal outcomes independently of blood glucose, via mechanisms relevant to disease processes common to multiple CKD aetiologies. • In CKD, a progressive loss of nephrons triggers harmful changes such as glomerular hypertension (high pressure), single nephron hyperfiltration (abnormally high filtration rate) and glomerular hypertrophy (swelling). Resulting increases in wall tension and shear stress promote a proinflammatory and profibrotic state which together contribute to declining kidney function and disease progression.[25, 26] • SGLT2 inhibition reduces sodium reabsorption in the proximal tubule, leading to increased sodium delivery to the macula densa and altered glomerular haemodynamics, reducing glomerular hypertension and hyperfiltration.[27, 28] • The reduction of glomerular pressure alleviates hypertension-associated damage to the glomerulus, reduces urinary albumin filtration and excretion, and reduces proinflammatory pathway activation and direct tubular toxicity; these changes may contribute to reduction of tubular interstitial fibrosis.[29, 30] • SGLT2 inhibition also exerts a variety of additional systemic effects which may modify risk factors for the progression of CKD and thereby contribute to reduced kidney damage, including reduced blood pressure, albuminuria and body weight.[29, 31]
Marketing authorisation/CE mark status	Dapagliflozin was granted marketing authorisation for the treatment of adults with CKD in August 2021.
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	Dapagliflozin is also currently indicated for:[1] • Treatment of adult and children aged 10 years and above with insufficiently controlled T2D as an adjunct to diet and exercise, either as a monotherapy when metformin is

	considered inappropriate due to intolerance or in addition to other medicinal products for treatment of T2D; • Treatment of adult patients with symptomatic chronic HF. Dapagliflozin has the following contraindications:[1] • Hypersensitivity to the active substance or to any of the excipients. A full list of special warnings and precautions for use is provided in the current SmPC in Appendix C.
Method of administration and dosage	10 mg oral dapagliflozin once daily. In patients with severe hepatic impairment, a starting dose of 5 mg is recommended. If well tolerated, the dose may be increased to 10 mg.
Additional tests or investigations	No additional tests or investigations are required prior to the administration of dapagliflozin.
List price and average cost of a course of treatment	The list price of dapagliflozin is £36.59 per pack of 28 x 10 mg tablets, giving a yearly cost of £477.30.[21] Dapagliflozin is a treatment for a chronic disease, and, therefore, treatment is long-term (lifetime) or until the patient's clinician determines that treatment should be discontinued.
Patient access scheme/commercial arrangement (if applicable)	No patient access scheme is included as part of this appraisal.

Abbreviations: CKD; chronic kidney disease; eGFR: glomerular filtration rate; HF: heart failure; SGLT2: sodium-glucose co-transporter 2; SmPC: summary of Product Characteristics; T2D: type 2 diabetes; UK: United Kingdom.

B.1.3 Health condition and position of the technology in the treatment pathway

B.1.3.1 CKD overview

CKD is a complex progressive disorder defined in national and international guidelines as abnormalities of kidney structure or function present for at least three months with implications for health.[32-34] The kidneys are composed of small functional units called nephrons and are responsible for filtering the blood to remove waste products (e.g., urea) and excess water, which are converted into urine and excreted.[35] Nephrons contain a filtering unit called a glomerulus, a unit of very small blood vessels within the nephron.[35] In CKD, progressive loss of nephrons triggers harmful changes which cause kidney function to decline over time, eventually leading to kidney failure (end-stage kidney disease [ESKD]) in some patients, at which point the kidneys no longer function sufficiently to maintain health and homeostasis.[34]

CKD occurs primarily in older individuals, and may result from:[32, 36]

- Systemic disease affecting the kidney such as T2D (CKD in patients with T2D is often referred to as "diabetic kidney disease") or hypertension (HTN);
- Primary kidney disease such as glomerulonephritis (inflammation of the glomeruli, often caused by the immune system attacking healthy tissue).

A common disease pathway is shared across CKD aetiologies.[25] Progressive loss of nephrons results in hypertrophy (swelling) and hyperfiltration (abnormally high filtration rates) in the remaining functional nephrons as they compensate for reduced filtration ability.[25] Resulting increases in wall tension and shear stress promote a proinflammatory and profibrotic state which together contribute to and maintain a cycle of nephron loss, fibrosis (formation of scar tissue), declining kidney function and disease progression.[25, 26]

In addition to contributing to the development of CKD, as outlined above, conditions such as T2D, HTN and cardiovascular disease (CVD; including conditions such as HF) can also develop as a result of reduced kidney function.[37, 38] T2D and CVD, therefore, commonly co-occur with CKD both as a cause and as a result of CKD.

People with CKD do not usually have symptoms during the early stages of the disease, but symptoms such as weight loss and poor appetite, swollen ankles, feet or hands, shortness of breath, tiredness, feeling sick and itchy skin can develop as the disease progresses.[33, 39] However, even in early-stage disease, patients are at increased risk of CV events and premature mortality, with the risk increasing as CKD progresses. CKD progression may eventually lead to ESKD and a requirement for dialysis or kidney transplant in some patients.

CKD is diagnosed based on laboratory measures of kidney function and kidney damage such as eGFR (an estimation of the volume of blood filtered through the glomeruli each minute, which provides a measure of kidney function) and uACR (a measure of albuminuria [the concentration of a protein called albumin in the urine: high concentrations indicate that the kidney is damaged and too much protein is “leaking” out of the blood]).[33, 40, 41]

CKD varies in severity and can be characterised based on eGFR and uACR into one of six categories, which can be used to predict the risk of adverse disease outcomes as shown in Table 3.

ESKD, the most severe stage of CKD, is defined as eGFR consistently <15 mL/min/1.73m^2.[33] Increased uACR and decreased eGFR are independently associated with an increased risk of adverse outcomes (Table 3), and these parameters are, therefore, used to guide decisions for monitoring, treatment and referral to specialist care.[32, 33]

Table 3. Classification of CKD by risk of adverse outcomes, based on eGFR and uACR categories

		uACR categories		
		A1: normal to mildly increased <30 mg/g <3 mg/mmol	A2: moderately increased 30–299 mg/g 3–29 mg/mmol	A3: severely increased ≥300 mg/g ≥30 mg/mmol
eGFR categories	G1: normal and high (90 mL/min/1.73 m^2 or over)	Low risk[a]	Moderate risk	High risk
	G2: mild reduction related to normal range for a young adult (60 to 89 mL/min/1.73 m^2)	Low risk[a]	Moderate risk	High risk
	G3a: mild to moderate reduction (45 to 59 mL/min/1.73 m^2)	Moderate risk	High risk	Very high risk
	G3b: moderate to severe reduction (30 to 44 mL/min/1.73 m^2)	High risk	Very high risk	Very high risk
	G4: severe reduction (15 to 29 mL/min/1.73 m^2)	Very high risk	Very high risk	Very high risk
	G5: kidney failure (under 15 mL/min/1.73m^2)	Very high risk	Very high risk	Very high risk

[a]No CKD if there are no other markers of kidney damage
Footnotes: Risk categories refer to risk of adverse outcomes.
Abbreviations: CKD: chronic kidney disease; eGFR: glomerular filtration rate; uACR: urine albumin-creatinine ratio.
Source: NG203. Chronic kidney disease: assessment and management.[33]

B.1.3.2 Epidemiology and diagnosis

Over two million adults in England are recorded in the NHS Quality and Outcomes Framework (QoF) as having a diagnosis of CKD with an eGFR category of G3a–G5 (estimated prevalence: 4.19%).[42] A retrospective longitudinal study assessing primary care records from 2010 in the United Kingdom (UK) identified the prevalence of CKD stages G3a, G3b and G4 as 4%, 1.4%, and 0.4%, respectively.[43] However, a substantial proportion of patients may also remain undiagnosed; the Kidney and Liver Disease Heath Survey for England in 2016 reported that while 13% of adults surveyed had CKD (stages 1–5) based on eGFR and uACR measurements, only 2% of patients self-reported having a formal diagnosis of CKD.[44] Furthermore, a UK study estimated that the proportion of undiagnosed patients with stage 1–5 CKD could be 44%.[45] An analysis of a primary care database (CPRD) suggests that the prevalence of T2D in CKD is between 28% and 33%, and that most patients with CKD stage G4 will not have T2D (51%–65%).[46, 47]

Diagnosis of early-stage CKD (stage 1–2) is only possible using an assessment of uACR (as eGFR remains within normal ranges [≥60 mL/min/1.73 m^2]). However, rates of uACR testing for patients at

high risk of CKD are low in UK clinical practice causing most patients to be diagnosed at stage 3 or later.[48, 49] Data from the 2015/26 UK National CKD Audit of patients with CKD in primary care showed that only 54% of patients with comorbid T2D received annual uACR testing, whereas 86% received annual eGFR testing.[48] For other groups, such as patients with comorbid HTN, annual uACR testing rates were lower than 30%.[48]

B.1.3.3 Burden of CKD

Clinical burden

The clinical burden of CKD increases with albuminuria and worsening eGFR.

Patients with CKD experience worsening kidney function over time, which can be observed as declining eGFR, and this may eventually lead to ESKD where some patients will require dialysis or a kidney transplant (collectively termed renal replacement therapy).[34] eGFR may decline at different rates depending on patient characteristics, with a proportion of patients experiencing a particularly rapid decline in kidney function defined as a loss of eGFR >3 mL/min/1.73m^2 per year, in some studies.[50]

CKD is also associated with a substantial clinical burden outside of adverse renal outcomes, encompassing an increased risk of CV events, CV and all-cause mortality, and also morbidity resulting from complications such as anaemia. Despite the asymptomatic nature of early-stage CKD, even patients with earlier stages of CKD have a significantly increased risk of CV events, ESKD and premature mortality compared to the general population. However, later stages of CKD and higher albuminuria categories are associated with a particularly elevated risk compared with earlier stages.[51]

Evidence from a systematic literature review (SLR) suggests that patients with CKD with severely increased albuminuria, or who fall within the Kidney Disease Improving Global Outcomes (KDIGO) high- or very high-risk groups (Table 3), have a high presence of diabetes, CVD and HTN, especially with higher degrees of albuminuria. In fact, the prevalence of diabetes in a Spanish hypertensive cohort with CKD with eGFR below 60 mL/min/1.73m^2 increased with albuminuria (26%, 43% and 53% of individuals with normal albuminuria, moderately increased albuminuria and severely increased albuminuria, respectively).[52] Furthermore, in an analysis of a US-based hypertensive patients, the prevalence of apparent treatment-resistant HTN was found to increase with both worsening eGFR status and increasing albuminuria severity. In hypertensive patients, lower eGFR rates were attributed to the increased prevalence of apparent treatment-resistant HTN (17.2%, 26.9%, 32.2% and 50.7% in groups with uACR <10, 10–29, 30–299 and ≥300 mg/g, respectively, in those with eGFR 45–59 mL/min/1.73 m^2, versus 22.5%, 24.5%, 32.8% and 56.4% in those with eGFR <45 mL/min/ 1.73 m^2, respectively).[52]

Additionally, patients with CKD without T2D are at high risk of serious adverse clinical outcomes, including worsening of CKD stage and hospitalisation for HF, and experience the same clinical risk as those with T2D.[53] Recent real world evidence from OPTIMISE-CKD assessed the mortality, healthcare burden and treatment of CKD in 449,232 patients with CKD and with and without T2D on dapagliflozin. The observational study, which used electronic health records and claims data from Japan, Sweden, and the US, demonstrated that fatal and nonfatal risks are similar, if not slightly higher, in CKD patients without T2D compared with CKD patients with T2D, contrary to the general perception of risk among these populations.[54]

Health related quality of life burden

CKD including non-T2D CKD has a considerable impact on the health-related quality of life (HRQoL) of patients and their caregivers, including physical, emotional, and social wellbeing, which increases as the disease progresses.

An analysis of data from the 2010 Health Survey for England indicated that patients with stage 4/5 CKD reported significantly reduced European Quality of Life-5 Dimension (EQ-5D) scores for mobility, usual activity and pain/discomfort compared to those with normal kidney function and stage 1 CKD.[55] This is supported by a 2015 observational study conducted in England that reported EQ-5D utility scores to decrease from 0.85 in patients with stage 1/2 CKD to 0.73 in patients with stage 5 CKD not on dialysis.[56]

The requirement for dialysis for patients with ESKD can be distressing, and further reduces HRQoL, as patients may have to attend lengthy appointments three times a week and adhere to strict dietary and fluid restrictions.[57, 58] One study reported that patients with ESKD experienced greater decreases in HRQoL compared with the general population than patients with other chronic diseases such as arthritis and cancer.[59]

CKD and the requirement for dialysis can also affect the families and caregivers of patients, who are often responsible for providing transport to appointments and administering treatment including home dialysis, which can reduce their own HRQoL. For example, a 2019 SLR which identified 61 studies, of which two were in a UK population, found that the quality of life (QoL) for caregivers of patients with CKD receiving dialysis was poorer compared to the general population, and was largely comparable to carers of patients with other chronic conditions, such as cancer and frailty in old age.[60] As demonstrated in OPTIMISE-CKD, patients with non-T2D CKD share the same fatal and nonfatal risks as patients with CKD with T2D. Additionally, the study found that patients with non-T2D CKD are less often treated with kidney and CV protective treatments than those with T2D, therefore, potentially experiencing a worse QoL than patients with CKD and T2D who receive more optimised treatment.[54]

Economic burden

The economic burden of CKD similarly increases with CKD progression, regardless of T2D status.

Healthcare resource use and costs increase rapidly once CKD progresses beyond stage 3. Hospitalisation costs may be approximately 12 times higher in patients with pre-dialysis stage 5 CKD compared with stage 3.[61]

CKD and related complications such as HF are associated with a high hospitalisation rate. A matched cohort study of 242,349 pairs of patients in a UK primary care setting found that patients with CKD (eGFR <60 mL/min/1.73 m^2 for ≥3 months) had an increased risk of hospitalisation due to conditions such as acute kidney injury (AKI; HR: 4.90; 95% CI: 4.47, 5.38), HF (HR: 1.66; 95% CI: 1.59, 1.75) and myocardial infarction (MI; HR: 1.40; 95% CI: 1.34, 1.46) compared with individuals without CKD.[62] The relative risk (RR) for cause-specific hospitalisations between matched patients with and without CKD are summarised in Table 4.

Table 4. RR of hospitalisation cause between matched patients with and without CKD by fully adjusted HR

Cause of hospitalisation	HR (95% CI)[a]
AKI	4.90 (4.47, 5.38)
HF	1.66 (1.59, 1.75)
Venous thromboembolism	1.55 (1.46, 1.64)
MI	1.40 (1.34, 1.46)
Urinary tract infection	1.39 (1.35, 1.43)
Gastrointestinal bleeding	1.34 (1.28, 1.40)
Cerebral infarction	1.27 (1.22, 1.33)
Pneumonia	1.24 (1.20, 1.29)
Hip fracture	1.11 (1.07, 1.15)
Intracranial bleeding	1.10 (1.02, 1.19)

Footnotes: [a]Adjusted HR (patients with CKD versus those without) was estimated in a Cox regression model stratified by matched set to account for the matching on age, sex, general practice, and calendar time, with adjustment for ethnicity, socioeconomic and smoking status, body mass index, and comorbidities such as diabetes mellitus, chronic obstructive pulmonary disease, osteoporosis, stroke. Please refer to the reference for full details.
Abbreviations: AKI: acute kidney injury; CI: confidence interval; HF: heart failure; HR: hazard ratio; MI: myocardial infarction; RR: relative risk.
Source: Iwagami *et al*., 2018.[62]

In addition, the mortality and healthcare burden study from OPTIMISE-CKD found that hospitalisation rates and costs for cardiorenal complications (HF or CKD) are higher than for atherosclerotic cardiovascular disease (ASCVD) across all countries and regardless of T2D status.[54]

Therefore, timely diagnosis and treatment of CKD are key to slow disease progression and reduce the substantial clinical, HRQoL and economic burden associated with CKD, and particularly late-stage CKD.[63]

B.1.3.4 Current management

The primary goal of treatment for CKD is to slow disease progression, thereby delaying ESKD, reducing CV risk and reducing the risk of premature death. Therefore, the management of patients with CKD encompasses a variety of treatment strategies to manage both the CKD itself and any underlying conditions and complications, which are more likely in patients with CKD and comorbid T2D, HTN or CVD.[33, 34]

The management of CKD in the NHS is currently informed by NICE clinical guidelines for CKD (NG203) and T2D (NG28).[33, 64] Clinical practice is also led and informed by the NICE-accredited guidelines from the UK Kidney Association (UKKA) and KDIGO.[32, 65] Current SoC for the management of CKD in England comprises individually optimised therapy which may include a variety of treatment strategies. These include CV risk management using statins and antiplatelets, management of underlying T2D and/or HTN, ACE inhibitors or ARBs for the management of disease progression and management of additional complications such as anaemia or mineral and bone disorders as necessary.[32, 33, 64, 66]

Since the appraisal of dapagliflozin in CKD in TA775, SGLT2 inhibitors have become routinely recommended for the treatment of patients with CKD, with and without T2D, in addition to optimised SoC. However, current NICE guidelines for the management of CKD (NG203) only recommend SGLT2 inhibitors in selected CKD patients who meet uACR thresholds and/or have T2D, despite the availability of evidence demonstrating efficacy of SGLT2 inhibitors across the uACR spectrum, irrespective of diabetes status. Additionally, while NICE guidelines for T2D and CKD do not make recommendations for the use of SGLT2 inhibitors in patients with CKD without T2D or with normal to mildly elevated uACR, recent UKKA guidelines explicitly recommend SGLT2 inhibitors in a broader range of uACR and eGFR. Specifically, for people with CKD without T2D, the UKKA guidelines, which are the most widely used guidelines in UK clinical practice for CKD, recommend SGLT2 inhibitors for a uACR of 25 mg/mmol or above.[65]

Recognising the shift in the treatment landscape and the unmet need in patients with normal to mildly increased uACR, the recently published KDIGO guidelines (2024) recommend initiating SGLT2 inhibitors in CKD patients with an eGFR of 20 to 45 mL/min/1.73 m^2 and uACR <200 mg/g (<22.6 mg/mmol). While only aimed at CKD patients with T2D, this recommendation places high value on the potential for long term use of SGLT2 inhibitors in people without T2D who have a substantially decreased eGFR to reduce the risk of kidney failure.[32]

Current SoC for CKD patients without T2D and uACR <22.6 mg/mmol

Despite the investigation of many new treatments for CKD over the past two decades, ACE inhibitors and ARBs were the only treatments to demonstrate efficacy in slowing the progression of CKD to ESKD in clinical trials, until the development of SGLT2 inhibitors. In the UK, ACE inhibitors and ARBs are recommended only for patients in higher uACR categories: patients with a uACR of >70 mg/mmol

regardless of underlying comorbidities, patients with comorbid HTN and uACR >30 mg/mmol, or patients with comorbid T2D and uACR >3 mg/mmol.[33]

Data from OPTIMISE-CKD, a global burden of disease study, shows that patients with CKD without T2D are less often treated with kidney and CV protective treatments than those with T2D.[54] Considering the complex and chronic characterisation of CKD, individually optimised treatment plans are integral to management of the condition. To enable optimised treatment plans, providing both patients and physicians with choice of medications based on best available evidence is critical.

Following the recommendations made in TA942, empagliflozin is currently the only recommended treatment to modify disease progression in patients with non-T2D CKD with an eGFR of 20–45 mL/min/1.73 m^2 and a uACR <22.6 mg/mmol, and in patients with non-T2D with an eGFR of 20–25 mL/min/1.73 m^2 and a uACR ≥22.6 mg/mmol, despite both empagliflozin and dapagliflozin holding a marketing authorisation in broad CKD. Table 5 summarises the currently recommended treatments within the NHS for CKD in addition to SoC, by diabetes status and eGFR range.

Management of patients with CKD with lower levels of eGFR

Although some clinical practice guidelines have started recommending the use of SGLT2 inhibitors in T2D at eGFRs down to 20 mL/min/1.73 m^2 (based on grade B levels of evidence), many other recommendations limit initiation to those with eGFR greater than 25 mL/min/1.73 m^2 or 30 mL/min/1.73 m^2. As patients with decreased eGFR are at the highest absolute risk of kidney disease progression, findings from a meta-analysis, which demonstrated that SGLT2 inhibitors reduce the risk of kidney disease progression by 37% and AKI by 23%, emphasize the need to initiate SGLT2 inhibitors in patients with CKD down to an eGFR of 20 mL/min/1.73 m^2 with continued use below this level.[17]

Table 5. Current NICE recommended treatments for CKD in addition to SoC by eGFR and uACR

	uACR (mg/mmol)			
	With T2D		Without T2D	
eGFR range (mL/min/1.73 m^2)	**≥22.6**	**<22.6**	**≥22.6**	**<22.6**
20–25	Empagliflozin	Empagliflozin	Empagliflozin	Empagliflozin
25–<45	Dapagliflozin Empagliflozin	Dapagliflozin Empagliflozin	Dapagliflozin Empagliflozin	Empagliflozin
≥45–75	Dapagliflozin Empagliflozin	Dapagliflozin Empagliflozin	Dapagliflozin Empagliflozin	None recommended
>75–90	Empagliflozin	Empagliflozin	Empagliflozin	None recommended

Abbreviations: CKD: chronic kidney disease; eGFR: glomerular filtration rate; SoC: standard of care; T2D: type 2 diabetes; uACR: urine albumin-creatinine ratio.
Source: NG203, TA775 and TA942.[2, 3, 33]

uACR testing in clinical practice and implications on treatment

uACR testing is still not commonly used across the UK, due to lack of awareness and lack of coordinated initiatives to encourage implementation in healthcare systems, despite good evidence of its prognostic value.[52]

As part of TA775, the company cautioned against restricting access based on uACR, given that rates of uACR testing in the NHS are low; less than 30% of patients with CKD but without T2D receive a uACR test.[48] The imposed restriction by uACR on the use of dapagliflozin created an access barrier for a large proportion of patients that were unnecessarily prevented from receiving optimal treatment despite an expected treatment benefit, irrespective of their uACR level.[2] In TA942, consideration was not given to the factors that resulted in the uACR restriction being implemented in TA775. Following the recommendation in TA942, patients without T2D and with an eGFR between 20 and 45 mL/min therefore have access to empagliflozin without requiring a uACR test. The discrepancy in recommendations for this patient group across TA775 and TA942 has resulted in current NICE guidance for SGLT2 inhibitors restricting patient and clinician choice and introduces a barrier to access for dapagliflozin for patients without T2D.

Given that patients with CKD with severely increased albuminuria or who fall within the KDIGO high- or very high-risk groups have a high presence of diabetes, CVD and HTN, especially with higher degrees of albuminuria, testing for albuminuria is valuable for CKD prognosis and management, and therefore, should be more encouraged in clinical practice.

B.1.3.5 Proposed position of dapagliflozin in the treatment pathway

As summarised in Table 6, the positioning of dapagliflozin in the existing care pathway for the populations outlined in the decision problem would be in addition to optimised SoC and as an alternative to empagliflozin. This is similar to the positioning in TA775.

Evidence from OPTIMISE-CKD has demonstrated the consistent treatment benefit of dapagliflozin in patients with CKD with an eGFR of 15–60 mL/min/1.73m^2, irrespective of T2D status and uACR.[8, 9] Similar outcomes were demonstrated in Nakhleh *et al.,* 2024, a retrospective observational study from Israel, in patients with an eGFR of 25–60 mL/min/1.73m^2.[10] Moreover, a post-hoc analysis from DAPA-CKD demonstrated clinical benefit of dapagliflozin in treatment of patients with non-T2D CKD and uACR <3 mg/mmol.[11] OPTIMISE-CKD has also established that patients with CKD without T2D receive suboptimal care in the management of their disease, despite the evidence suggesting a similar, if not slightly worse, burden of disease in this patient group.[54] To improve care management, and ultimately clinical outcomes, for patients with non-T2D CKD and uACR <30 mg/mmol, enabling access to all treatment options proven to be effective in CKD regardless of T2D and uACR status is critical.

Moreover, the recent shift in both UKKA and KDIGO guidelines, in which SGLT2 inhibitors are recommended in a broader population than current NICE recommendations, indicates the overall recognition within the clinical community, both nationally and internationally, of the potential that SGLT2 inhibitors have in patients with CKD without T2D.

This review will enable dapagliflozin to become an alternative treatment option to empagliflozin for patients with CKD, with an eGFR ≥20 and <45 mL/min/1.73m^2 with or without T2D, and patients with CKD with an eGFR ≥45 and <90 mL/min/1.73m^2 and either a uACR ≥22.6 mg/mmol or T2D, thereby providing both patients and physicians with choice of medications based on best available evidence to optimise treatment plans.

A recommendation for dapagliflozin within this setting will enable continuity of care and increase clinician and patient treatment choice in a difficult to treat area, thereby optimising treatment plans based on the best available evidence. Ultimately, this will improve treatment outcomes and delay the progression of patients to ESKD and renal replacement therapy.

Table 6. Proposed positioning of dapagliflozin within this appraisal

	uACR (mg/mmol)			
	With T2D		Without T2D	
eGFR range (mL/min/1.73 m^2)	**≥22.6**	**<22.6**	**≥22.6**	**<22.6**
20–25	**Dapagliflozin** Empagliflozin	**Dapagliflozin** Empagliflozin	**Dapagliflozin** Empagliflozin	**Dapagliflozin** Empagliflozin
25–<45	Dapagliflozin Empagliflozin	Dapagliflozin Empagliflozin	Dapagliflozin Empagliflozin	**Dapagliflozin** Empagliflozin
≥45–75	Dapagliflozin Empagliflozin	Dapagliflozin Empagliflozin	Dapagliflozin Empagliflozin	None recommended
>75–90	**Dapagliflozin** Empagliflozin	**Dapagliflozin** Empagliflozin	**Dapagliflozin** Empagliflozin	None recommended

Footnote: Green border indicates the patient group in which dapagliflozin can be recommended in this review to align with the recommendation for empagliflozin in TA942.
Abbreviations: CKD: chronic kidney disease; eGFR: glomerular filtration rate; SoC: standard of care; T2D: type 2 diabetes; uACR: urine albumin-creatinine ratio.

B.1.4 Equality considerations

The use of dapagliflozin in the subgroups outlined in the decision problem is not expected to raise any issues related to equality given its clinical comparability to empagliflozin.

B.2 Key drivers of the cost effectiveness of the comparator(s)

B.2.1 Clinical outcomes and measures

Empagliflozin, the comparator in this appraisal, was recommended by NICE as a treatment option for adults with CKD in TA942.[3] This recommendation was based on both a cost utility analysis for the licensed population and a cost-comparison analysis versus dapagliflozin. Based on the cost comparison, the committee concluded that empagliflozin had similar effectiveness, safety and cost to that of dapagliflozin. Similar conclusions were made by NICE committees in TA929 and TA773, which evaluated empagliflozin in HFpEF and HFrEF, respectively.[18, 19]

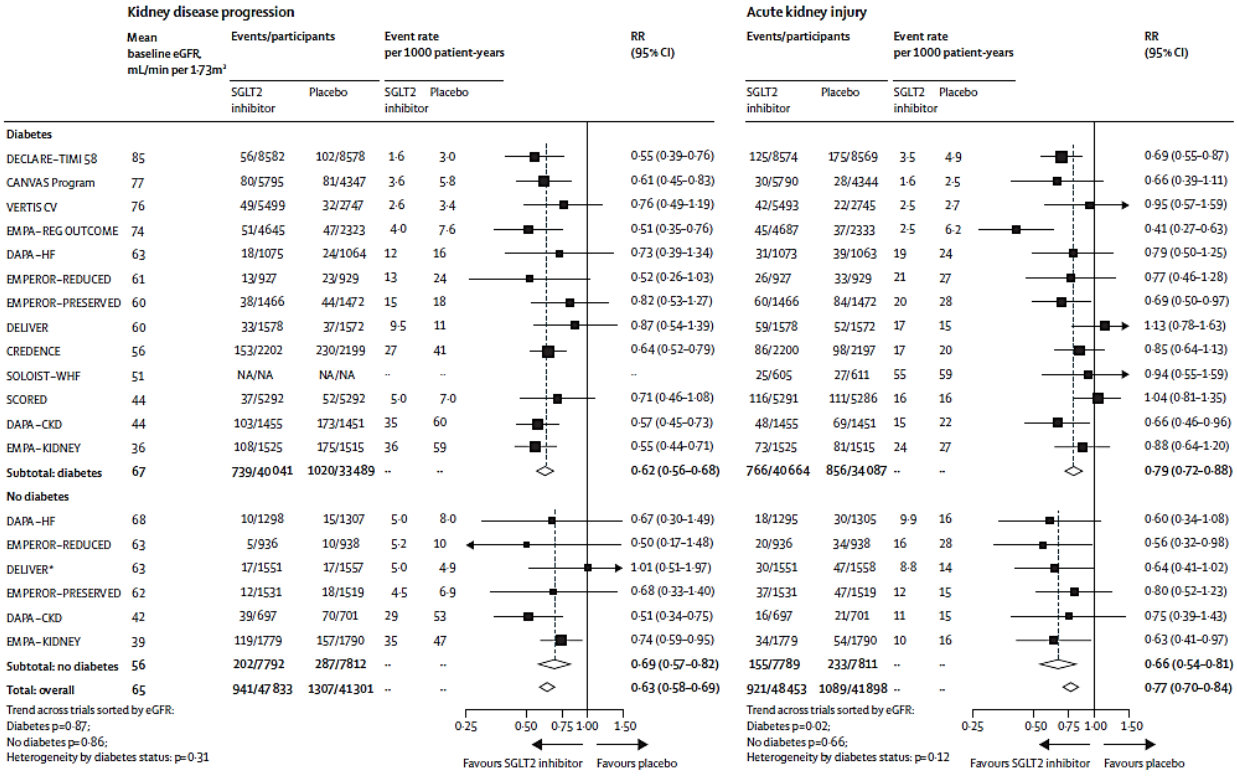
In the absence of clinical trials directly comparing empagliflozin with dapagliflozin in people with CKD, the similar clinical and safety effects of empagliflozin to dapagliflozin were demonstrated through a company sponsored ITC, in which treatment effect of the two therapies was found to be equivalent.[3] A published meta-analysis further supported this claim, showing consistent benefits in kidney disease progression, AKI, and the risk of CV death or hospitalisation for HF, as well as safety, between SGLT2 inhibitors irrespective of diabetes status.[17] Results from the meta-analysis demonstrated that SGLT2 inhibitors reduce the risk of kidney disease progression by 37% and AKI by 23%, with similar effects in patients with and without diabetes (67 While the efficacy in this population may be less certain than the overall population, the clinical assessment in the overall population was deemed to be positive by NICE.

Figure 1).[17]

The committee in TA942 concluded that the evidence presented in empagliflozin's pivotal trial, EMPA-KIDNEY, sufficiently demonstrated that empagliflozin plus SoC was more effective than SoC alone for the patient population described in section B.1.1 Decision problem. For patients without T2D, the EAG concluded that the ITC showed no meaningful differences between dapagliflozin and empagliflozin.[3]

The clinical evidence presented from EMPA-KIDNEY in TA942 included a subgroup analysis of HRs for time to the first event of kidney disease progression or adjudicated CV death. The presented HR for patients with uACR <30 mg/mmol was 1.01 (95% CI: 0.66, 1.55), which figure falls outside of the CIs of the HR for the overall trial population (0.72; 95% CI: 0.64, 0.82; p<0.001) and suggests that the treatment effect may be limited in this subgroup.[67] While the efficacy in this population may be less certain than the overall population, the clinical assessment in the overall population was deemed to be positive by NICE.

Figure 1. Effect of SGLT2 inhibition on kidney disease outcomes by diabetes status



*One participant without diabetes in DELIVER was missing a baseline creatinine measurement and was excluded.
Abbreviations: CI: confidence interval; eGFR: estimated glomerular filtration rate; RR: relative risk; SGLT2: sodium-glucose co-transporter-2
Source: Adapted from Herrington *et al*., 2022.[17]

Additionally, the EAG presented exploratory cost-effectiveness scenario in patients with a uACR <22.6 mg/mmol, which was based on limited data that did not include the full data from EMPA-KIDNEY and resulted in an ICER substantially higher than that of the full population.[3] A similar exploratory cost-effectiveness analysis was conducted in TA775, resulting in an ICER of £17,000, however, as noted above, the committee considered this estimate to be associated with uncertainties that prevented a recommendation for use in this subgroup.[2] Despite the potential difference in the ICERs for this subgroup in the respective appraisals, the committee considered the factors that precluded the recommendation of dapagliflozin for use in subgroup 3 were no longer a barrier to recommendation, and as a result, a broad positive recommendation was made for empagliflozin.

B.2.2 Resource use assumptions

Overall, the resource use associated with dapagliflozin is expected to be the same as empagliflozin which has already been appraised in TA942.

However, in patients with CKD with T2D, there is potential for empagliflozin to result in a higher cost than dapagliflozin to the NHS. The empagliflozin SmPC states that for patients with T2D "the recommended starting dose is 10 mg empagliflozin once daily for monotherapy and add-on combination therapy with other medicinal products for the treatment of diabetes. In patients tolerating empagliflozin 10 mg once daily who have an eGFR ≥60 mL/min/1.73 m^2 and need tighter glycaemic control, the dose can be increased to 25 mg once daily".[23] Therefore, these patients in clinical practice may have their dosing up-titrated to 25 mg once daily with associated additional SoC testing and potential primary care visit, while this dosing is 10 mg for dapagliflozin. Costs associated with up-titration can impact the overall cost-comparison between treatments. While up-titration of empagliflozin in this case is only relevant to patients who have T2D and require optimisation for glycaemia, and although posology in the non-T2D population for dapagliflozin and empagliflozin is similar (one tablet daily), these T2D patients will require further interventions as their conditions are treated holistically in real world practice. Specifically, when eGFR drops below 60 mL/min/1.73 m^2, patients will need to be down-titrated to the 10 mg dose as the empagliflozin SmPC states that "in patients with an eGFR <60 mL/min/1.73 m^2 the daily dose of empagliflozin is 10 mg."[23]

On the other hand, dapagliflozin provides consistent and simple posology in CKD irrespective of T2D status (with the exception of patients with severe hepatic impairment who are initiated at 5 mg before increasing dose to 10 mg if tolerated), thereby alleviating pressure from an already burdened primary care system through the elimination of additional testing, patient visits, and clinician time.

B.3 Clinical effectiveness

Summary of clinical effectiveness data

- DAPA-CKD was a large, multicentre, double-blind, placebo-controlled Phase III randomised controlled trial (RCT) which examined the effect of dapagliflozin, in addition to SoC, on renal and CV outcomes in a broad range of patients with CKD, including those with and without comorbid T2D (n=2,152).[7]
    - Dapagliflozin significantly reduced the RR of a composite outcome of sustained decline in eGFR ≥50%, ESKD or death from renal or CV causes by 39% (HR: 0.61; 95% CI: 0.51, 0.72; p<0.001).[7]
    - The positive renal treatment effect was confirmed by a significant reduction in the renal-specific composite outcome compared with placebo (HR: 0.56; 95% CI: 0.45, 0.68; p<0.001). Treatment with dapagliflozin was associated with a 29% reduction in the risk of hospitalisation for HF or CV death (HR: 0.71; 95% CI: 0.55, 0.92; p=0.0089). Dapagliflozin demonstrated a 31% RR reduction in all-cause mortality compared with placebo (HR: 0.69; 95% CI: 0.53, 0.88; p=0.004).[7]
    - A post-hoc analysis of DAPA-CKD aimed to assess whether the kidney protective benefits of dapagliflozin, as demonstrated in the DAPA-CKD trial, extend to participants without T2D and with lower levels of albuminuria.[11]
        - By week 2, dapagliflozin compared with placebo changed eGFR from baseline with similar effects in participants without T2D and with uACR <300 mg/g (−2.4 mL/min/1.73m^2; 95% CI: −4.5, −0.4) or ≥300 mg/g (−2.0 mL/min/1.73m^2; 95% CI: −2.7, −1.3; p for interaction=0.46).[11]
        - Moreover, dapagliflozin compared with placebo provided a slower decline in the chronic eGFR slope in patients without diabetes with either uACR <300 mg/g (between-group difference of 1.8 ml/min per 1.73 m^2 per year; 95% CI: 0.4, 3.1) or uACR ≥300 mg/g (between-group difference of 1.2 ml/min per 1.73 m^2 per year; 95% CI: 0.6, 1.8; p for interaction=0.62).[11]
- The OPTIMISE-CKD programme is a multinational, observational, longitudinal cohort study that uses data extracted from electronic health records and claims data sources.
    - The first observational study as part of the OPTIMISE-CKD programme used de-identified claims data from the US and aimed to compare kidney and cardiorenal protection in patients with and without T2D (eGFR 15–60 mL/min/1.73 m^2) across uACR levels after initiation of dapagliflozin for the treatment of CKD (n=1,480).[8]
        - An expected decrease associated with the mechanism of action of SGLT2 inhibitors of 3 mL/min/1.73 m^2 was observed after starting patients on dapagliflozin in both moderately increased and moderately to severely increased uACR groups (3–22.6 mg/mmol [30–200 mg/g] and >22.6 mg/mmol [>200 mg/g] respectively; described as low uACR and high uACR in the study), while change over time was consistent for both groups. Patients with normal/mildly elevated uACR (0–3 mg/mmol [0–29 mg/g]) showed similar eGFR trajectories and slopes compared to those with low uACR (3–22.6 mg/mmol [30–200 mg/g]).[8]
        - Similar hospitalisation risk for cardiorenal complications were observed during follow-up in the low and high uACR groups. There were 30.6 and 22.2 cardiorenal event rates per 100 patient-years in the low and high uACR groups, respectively (HR: 0.89; 95% CI: 0.66, 1.19; p=0.649). In addition, patients with normal/mildly

elevated uACR (0–3 mg/mmol [0–29 mg/g]) showed similar cardiorenal and mortality risk development compared to those with low and high uACR.[8]

- A second study from OPTIMISE-CKD aimed to describe the real-world utilisation of dapagliflozin following its approval for the CKD indication in the US and Japan, and to assess the effect of initiating versus not initiating dapagliflozin on kidney function decline in patients with uACR <22.6 mg/mmol (n= 20,407).[9]
  - Among dapagliflozin initiators with uACR <22.6 mg/mmol, the median eGFR slope was 1.07 mL/min/1.73m^2 per year (95% CI: 0.40, 1.74) better than in patients who did not initiate treatment. The benefit of dapagliflozin initiation was observed across the whole eGFR slope distribution among patients with uACR <22.6 mg/mmol.[9]

- Nakhleh *et al.,* 2024 (n=354) was a retrospective observational real-world study in Israel to evaluate the real-world effectiveness of SGLT2 inhibitors on the progression of CKD in patients without diabetes, with and without albuminuria, using de-identified data from the MHS central computerised database. The study measured changes in patients' annual rate of eGFR decline before and during SGLT2 inhibitor treatment (75.4% were on dapagliflozin versus 24.6% on empagliflozin). Patients included had a range of uACR levels, with 41.2% of patients with normal to mildly increased albuminuria (uACR <3mg/mmol) at baseline.[10]
  - The cohort of patients on an SGLT2 inhibitor had a mean difference in eGFR slope decline of 3.91 (95% CI: 2.81, 5.02) mL/min/1.73m^2 per year between follow -up and baseline slopes.[10]
  - eGFR decline was also influenced by baseline eGFR and uACR levels, with a lower eGFR at baseline (25–45 mL/min/ 1.73m^2) being associated with a greater decrease in slope decline following SGLT2 inhibitor initiation, with a mean change of 5.67 mL/min/1.73m^2 (95% CI: 4.03, 7.30).[10]
  - Overall, the benefit of SGLT2 inhibitors was evident across the spectrum from moderate to very high KDIGO risk categories, with or without albuminuria, and particularly in individuals without diabetes with normal to mildly increased albuminuria (uACR <3 mg/mmol; mean change in eGFR slope of 5.10 mL/min/1.74m^2 [95% CI: 3.31, 6.68]).[10]

- Subgroup analyses from two RCTs, DECLARE-TIMI-58 (n=17,160) and DAPA-HF (n=4,744), have also been considered to address uncertainty associated with treatment effect across uACR levels.
  - Firstly, [redacted] xx[68] Although the DECLARE-TIMI 58 trial enrolled only patients with T2D, results of these subgroup analyses are likely to also apply to patients with CKD without comorbid T2D.
  - Subgroup analysis of the DAPA-HF trial also support the consistency of the dapagliflozin treatment effect across patients with and without T2D, including patients with eGFR ≥60–90 mL/min/ 1.73m^2. Dapagliflozin significantly reduced the risk of the primary outcome of worsening HF or CV death independently of diabetes status.[12]
  - Overall, dapagliflozin was associated with significant reductions in the primary endpoint of worsening HF or CV death (HR: 0.74; 95% CI: 0.65, 0.85; p<0.001) in the DAPA-HF trial, which enrolled patients across a wide range of uACR categories.

B.3.1 Identification and selection of relevant studies

A SLR was not conducted for this appraisal. The evidence base for this submission is formed from key clinical studies presented in TA775 and TA942, and RWE generated for dapagliflozin that has become available since the conclusion of TA775. Additionally, two NMAs were presented in TA942 which were informed by two distinct SLRs. The first SLR, sponsored by the company for empagliflozin for the treatment of CKD in TA942, identified RCTs reporting on the efficacy and safety of potential comparators to empagliflozin, namely SGLT2 inhibitors and finerenone for the treatment of adult patients with CKD and diabetic kidney disease, and was supplemented by a targeted literature review (TLR) to identify relevant observational studies that could supplement RCT evidence.[3] The second SLR presented in TA942 aimed to evaluate the impact of diabetes on the effects of SGLT2 inhibitors on kidney outcomes.[17]

DAPA-CKD was the pivotal trial investigating the efficacy of dapagliflozin in CKD. Since TA775, additional RWE has been generated for dapagliflozin in CKD, including OPTIMISE-CKD and a retrospective study by Nakhleh *et al.,* 2024. The RWE presented in this appraisal were published in April 2024 and therefore would not have been captured in any SLR conducted beforehand due to the timelines associated with this appraisal. Additionally, EMPA-KIDNEY was the main source of clinical efficacy evidence in the cost utility model in TA942, and therefore is treated as the most relevant study for empagliflozin in this appraisal.

B.3.2 List of relevant clinical effectiveness evidence

A summary of the relevant evidence demonstrating the effectiveness of dapagliflozin in CKD, irrespective of uACR levels and diabetes status, is provided below and in Table 7:

- DAPA-CKD, a large, multicentre, double-blind, placebo-controlled Phase III RCT which examined the effect of dapagliflozin, in addition to SoC, on renal and CV outcomes in a broad range of patients with CKD, including those with and without comorbid T2D. The study is described in B.3.3.1 DAPA-CKD.

- The OPTIMISE-CKD programme, a multinational, observational, longitudinal cohort study that uses data extracted from electronic health records and claims data sources. The overall study objective is to describe the management and treatment with dapagliflozin in routine clinical practice among patients with CKD, with and without T2D across the uACR spectrum. The study is described in B.3.3.2 OPTIMISE-CKDB.3.3.2 OPTIMISE-CKD.

- Nakhleh *et al.,* 2024, a retrospective observational study in Israel that used de-identified data from the MHS central computerised database to evaluate the real-world effectiveness of SGLT2 inhibitors on the progression of CKD in patients without diabetes, with and without

albuminuria. The study is described in B.3.3.3 Nakhleh *et al.,* 2024B.3.3.3 Nakhleh *et al.,* 2024.

- DECLARE-TIMI 58, a Phase III, randomised, double-blind, multinational, placebo-controlled trial which examined the effect of dapagliflozin on CV outcomes when added to current background therapy in patients with T2D with either established CVD or CV risk factors. As the trial enrolled a proportion of patients with comorbid CKD, it is, therefore, of relevance to this appraisal. The study is described in B.3.3.4 DECLARE-TIMI 58B.3.3.4 DECLARE-TIMI 58.

- DAPA-HF, a Phase III, randomised, multinational, placebo-controlled trial which examined the effect of dapagliflozin on the incidence of worsening HF or CV death in patients with chronic HF with reduced ejection fraction. As the trial enrolled a proportion of patients with comorbid CKD, it is, therefore, of relevance to this appraisal. The study is described in B.3.3.5 DAPA-HF.

It is key to consider the inclusion of RWE studies, namely OPTIMISE-CKD and Nakhleh *et al*., 2024, to reduce uncertainties and to provide clinically important data that help to inform expectations of comparative effectiveness of dapagliflozin in CKD, irrespective of uACR levels and diabetes status, in clinical practice. Consistent with the NICE RWE framework [ECD9] commitments detailed in the NICE Board Minutes documented in December 2023, RWE can be used as the basis for decision making to reduce uncertainties and improve guidance.[69, 70] There has been a trend towards increasing use of RWE in company submissions and acceptance by committees, with NICE committees accepting RWE as primary or supportive evidence in 18 recent topics.[69, 70]

Table 7. Summary of clinical effectiveness evidence

Study	DAPA-CKD[7]	OPTIMISE CKD[8, 54] Svensson *et al.*, 2024 Tangri *et al.*, 2024	Nakhleh *et al., 2024*[10]	DECLARE-TIMI 58[13, 14]	DAPA-HF[15, 16]
Study design	Phase III, international, multi-centre, open-label RCT	Multinational, observational, longitudinal cohort study	Retrospective observational study	Phase III, randomised, multinational, double-blind, placebo-controlled trial	Phase III, randomised, multinational, placebo-controlled trial
Population	Adults aged 18 years and over at the time of consent, with an eGFR ≥25 to ≤75 mL/min/1.73 m^2 at screening, and a uACR ≥200 mg/g (≥22.6 mg/mmol) to ≤5,000 mg/g (≤565 mg/mmol), who are stable and on maximum tolerated labelled dose of an ACE inhibitor or ARB for at least four weeks before screening, if not medically contraindicated	Adults aged 18 years and over as of study index date, with first-ever registered laboratory-confirmed CKD or CKD diagnosis, defined as having either two eGFR measurements ≤60 mL/min/1.73m^2 taken ≥90 days apart or a first eGFR measurement ≤60 mL/min/1.73 m^2 followed by a first CKD diagnosis	Adults aged over 18 years, with baseline eGFR of 25–60 mL/min/1.73 m^2 and who have received an SGLT2 inhibitor (i.e., empagliflozin or dapagliflozin) between September 2020 and November 2022	Patients 40 years or older who have T2D, a glycated haemoglobin level of at least 6.5% but less than 12.0%, and a creatinine clearance of 60 ml or more per minute, with multiple risk factors for or have established atherosclerotic CV disease (defined as clinically evident ischemic heart disease, ischemic CV disease, or peripheral artery disease)	Adults aged 18 years and over, an ejection fraction of 40% or less, and NYHA class II, III, or IV HF symptoms.
Intervention(s)	Dapagliflozin 10 mg, daily	Dapagliflozin 10 mg, daily	Dapagliflozin 10 mg, daily or empagliflozin (10 or 25 mg)	Dapagliflozin 10 mg, daily	Dapagliflozin 10 mg, daily
Comparator(s)	Placebo	N/A	N/A	Placebo	Placebo

Study	DAPA-CKD[7]	OPTIMISE CKD[8, 54] Svensson *et al.*, 2024 Tangri *et al.*, 2024	Nakhleh *et al., 2024*[10]	DECLARE-TIMI 58[13, 14]	DAPA-HF[15, 16]
Indicate if study supports application for marketing authorisation (yes/no)	Yes	No	No	Yes	Yes
Reported outcomes[a]	**Primary outcomes** Time to first occurrence of any of: • ≥50% sustained decline in eGFR from baseline • Reaching ESKD • CV death • Renal death **Secondary outcomes** Time to first occurrence of any of: • ≥50% sustained decline in eGFR from baseline • Reaching ESKD • Renal death • CV death • Hospitalisation for HF • Death from any cause	• eGFR change from baseline over time following dapagliflozin initiation in patients with CKD and without T2D • Risk of cardiorenal hospitalisation in patients with CKD and without T2D initiated with dapagliflozin	• Differences in changes of eGFR slope between baseline and follow-up periods	**Primary outcomes** Time to first event of: • CV death • MI • Ischemic stroke **Secondary outcomes** • Hospitalisation for Congestive HF • The composite endpoint of CV death, MI, ischemic stroke, hospitalisation for HF, hospitalisation for unstable angina pectoris or hospitalisation for any revascularisation • All-cause mortality	**Primary outcomes** Time to first occurrence of any of: • CV death • HF Hospitalisation • Urgent HF visit **Secondary outcomes** • Time to first occurrence of any of CV death or HF hospitalisation • Total number of (first and recurrent) HF hospitalisations and CV death • Change from baseline at 8 months in the overall KCCQ summary score

Study	DAPA-CKD[7]	OPTIMISE CKD[8, 54] Svensson *et al.*, 2024 Tangri *et al.*, 2024	Nakhleh *et al., 2024*[10]	DECLARE-TIMI 58[13, 14]	DAPA-HF[15, 16]
				• Body weight change from baseline	• Time to the first occurrence of: ≥50% sustained[b] decline in eGFR, reaching ESRD (sustained[b] eGFR <15 ml/min/1.73m^2 or, chronic[b] dialysis treatment or, receiving a renal transplant), or renal death • Time to death from any cause

Footnotes: [a]Endpoints from DAPA-CKD are listed in order of the hierarchical testing sequence. [b]As defined in the Clinical Event Adjudication (CEA) charter.
Abbreviations: ACE: angiotensin-converting enzyme; ARB: angiotensin receptor blocker; CKD: chronic kidney disease; CV: cardiovascular; CVD: cardiovascular disease; eGFR: estimated glomerular filtration rate; ESKD: end stage kidney disease; ESRD: end stage renal disease; HF: heart failure; KCCQ: Kansas City cardiomyopathy questionnaire; MI: myocardial infarction; NYHA: New York Heart Association; N/A: not applicable; RCT: randomised controlled trial; T2D: type 2 diabetes; uACR: urine albumin-to-creatinine ratio.
Source: Heerspink *et al*., 2020;[7] Svensson *et al*., 2024;[8] Tangri *et al*., 2024;[54] Nakhleh *et al*., 2024;[10] Mosenzon et al., 2019;[13] Wiviott et al., 2019;[14] Jhund et al. 2021;[15] McMurray et al., 2019.[16]

Table 8 outlines how the evidence described above will address the different subgroups in the decision problem. While the evidence supports the claim that the treatment effect of dapagliflozin is consistent across eGFR and uACR ranges, irrespective of T2D, the ITC presented in TA942, as well as the published NMA, support the claim that dapagliflozin has similar effectiveness to empagliflozin in the decision problem subgroups.

Table 8. Evidence supporting the different subgroups in the decision problem

	uACR (mg/mmol)			
	With T2D		Without T2D	
eGFR range (mL/min/1.73 m^2)	**≥22.6**	**<22.6**	**≥22.6**	**<22.6**
20–25	OPTIMISE-CKD[a]	OPTIMISE-CKD[a]	OPTIMISE-CKD[a]	OPTIMISE-CKD[a]
25–<45	Recommended in TA775	Recommended in TA775	Recommended in TA775	Nakhleh *et al.*, 2024[b] DAPA-CKD[c] DAPA-HF[d]
≥45–75	Recommended in TA775	Recommended in TA775	Recommended in TA775	Not relevant for this decision problem
>75–90	DAPA-HF[d]	DAPA-HF[d] DECLARE-TIMI 58[e]	DAPA-HF[d]	Not relevant for this decision problem

Footnotes: [a]OPTIMISE-CKD includes patients with a uACR ≥3 mg/mmol (≥30 mg/g). [b]Nakhleh *et al.*, 2024 included patients with no T2D and with an eGFR of 25 – 60 mL/min/1.73m^2. [c]The post-hoc analysis from DAPA-CKD includes patients with a uACR of 3-30 mg/mmol (30-300 mg/g) only. [d]DAPA-HF includes patients with an eGFR ≥30 mL/min/1.73m^2. While uACR was not measured, it included patients with comorbid CKD and is therefore assumed to include patients with varying uACR levels. [e][redacted]

Abbreviations: eGFR: glomerular filtration rate; T2D: type 2 diabetes; uACR: urine albumin-creatinine ratio.

B.3.3 Summary of methodology of the relevant clinical effectiveness evidence

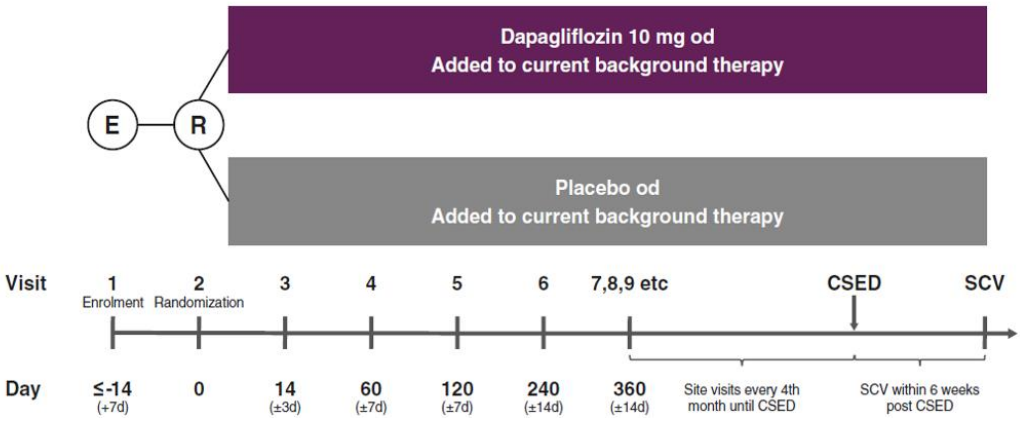
B.3.3.1 DAPA-CKD

The DAPA-CKD trial was considered as part of TA775 and provided strong clinical evidence that patients with CKD with an eGFR of 25–75 mL/min/1.73m^2 and a uACR of 22.6–565 mg/mmol (200-5,000 mg/g) would receive a significant treatment benefit from dapagliflozin. Overall, the results of the DAPA-CKD study demonstrate that dapagliflozin is an effective and well tolerated treatment across a wide range of patients, including those with and without comorbid T2D and comorbid CVD. By delaying CKD progression, reducing the risk of chronic dialysis and reducing all-cause mortality compared with SoC, dapagliflozin can reduce the burden of CKD to the NHS and improve outcomes for patients with CKD. The study is described in detail within this section.

B.3.3.1.1 Trial design

DAPA-CKD was a large, multicentre, double-blind, placebo-controlled Phase III RCT which examined the effect of dapagliflozin, in addition to SoC, on renal and CV outcomes in a broad range of patients with CKD, including those with and without comorbid T2D. An overview of the DAPA-CKD study design is shown in Figure 2. The detailed trial design, trial drugs and concomitant medications have been previously described in TA775.

Figure 2. DAPA-CKD study design



Abbreviations: CSED: common study end date (date when the predetermined number of adjudicated primary events are anticipated; E: enrolment; od: once daily; R: randomisation; SCV: study closure visit.
Source: Heerspink *et al*., 2020.[71]

B.3.3.1.2 Eligibility criteria

The eligibility criteria for the DAPA-CKD trial are presented in Table 9. Adults with or without T2D who had an eGFR of 25–75 mL/minute/1.73 m^2 of body-surface area and a uACR of 22.6–565 mg/mmol (200–5,000 mg/g) were eligible for participation.

Table 9. Inclusion and exclusion criteria of the DAPA-CKD study

Inclusion criteria	Exclusion criteria
• Adults aged ≥18 years at the time of consent • eGFR ≥25 to ≤75 mL/min/1.73 m^2 at screening • uACR ≥200 mg/g (≥22.6 mg/mmol) to ≤5,000 mg/g (≤565 mg/mmol) at screening • Stable and, for the patient, maximum tolerated labelled dose of an ACE inhibitor or ARB for at least four weeks before screening, if not medically contraindicated	• T1DM • Autosomal dominant or autosomal recessive polycystic kidney disease, lupus nephritis or ANCA-associated vasculitis • Receiving cytotoxic therapy, immunosuppressive therapy or other immunotherapy for primary or secondary renal disease within six months prior to enrolment • NYHA Class IV congestive HF at time of enrolment • MI, unstable angina, stroke or transient ischaemic attack within 12 weeks prior to enrolment • History of organ transplantation • Receiving therapy with an SGLT2 inhibitor within 8 weeks prior to enrolment or previous intolerance of an SGLT2 inhibitor • Coronary revascularisation (percutaneous coronary intervention or coronary artery bypass grafting) or valvular repair/replacement within 12 weeks prior to enrolment or is planned to undergo any of these procedures after randomisation • Any condition outside the renal and CV study area with a life expectancy of <2 years based on investigator's clinical judgement • Active malignancy requiring treatment at the time of Visit 1 (with the exception of successfully treated basal cell or treated squamous cell carcinoma) • Known blood-borne diseases • Hepatic impairment (aspartate transaminase or alanine transaminase >3 times the ULN or total bilirubin >2 times the ULN at the time of enrolment)

Abbreviations: ACE: angiotensin-converting enzyme; ANCA: anti-neutrophil cytoplasmic antibody; ARB: angiotensin receptor blocker; CV: cardiovascular; eGFR: estimated glomerular filtration rate; HF: heart failure; MI: myocardial infarction; NYHA: New York Heart Association; SGLT2: sodium glucose co-transporter 2; T1DM: type 1 diabetes mellitus; uACR: urine albumin-to-creatinine ratio; ULN: upper limit of normal.
Sources: Heerspink *et al*., 2020 (Supplemental Methods).[7]

B.3.3.1.3 Study outcomes

The primary and secondary endpoints of the DAPA-CKD study are shown in Table 10.**Table 10.**

Summary of primary and secondary endpoints from the DAPA-CKD study

Exploratory and safety outcomes have been described in detail in TA775.

Table 10. Summary of primary and secondary endpoints from the DAPA-CKD study

Priority	Objective	Endpoint measure and assessment
Primary[a]	To determine whether dapagliflozin is superior to placebo in reducing the incidence of the primary composite endpoint of ≥50% sustained decline in eGFR, reaching ESKD, CV or renal death	Time to first occurrence of any of: • ≥50% sustained decline in eGFR from baseline • Reaching ESKD • CV death • Renal death
Secondary[a]	To determine whether dapagliflozin compared with placebo will result in a reduction of the incidence of the composite endpoints of worsening of renal function	Time to first occurrence of any of: • ≥50% sustained decline in eGFR from baseline • Reaching ESKD • Renal death
	To determine whether dapagliflozin compared with placebo will result in a reduction of the incidence of the composite endpoint of hospitalisation for HF or CV death	Time to first occurrence of any of: • CV death • Hospitalisation for HF
	To determine whether dapagliflozin compared with placebo will result in a reduction of the incidence of all-cause mortality	Time to death from any cause

Footnotes: [a]Endpoints are listed in order of the hierarchical testing sequence.
Abbreviations: AE: adverse event; CKD: chronic kidney disease; CV: cardiovascular; eGFR: estimated glomerular filtration rate; ESKD: end-stage kidney disease; HF: heart failure.
Sources: Heerspink *et al*., 2020.[71]

A post hoc analysis of DAPA-CKD assessed the annual rate of eGFR decline and uACR changes in participants without T2D by baseline uACR.

B.3.3.1.4 Duration of study and follow-up

The first participant was enrolled on 2nd February 2017 and the first randomisation occurred on 13th February 2017. Recruitment closed in the majority of participating countries on 6th July 2018. Recruitment in India, the US and Canada was open until 19th October 2018. Recruitment in China opened on 2nd December 2019 and was ongoing until the trial end date of 3rd April 2020.[72]

The trial was stopped early after recommendation by the Independent Data Monitoring Committee because of clear efficacy based on 408 primary outcome events. At the end of the trial, the median follow-up was 2.4 years (interquartile range [IQR]: 2.0–2.7).[7]

B.3.3.1.5 Baseline characteristics

A total of 4,304 patients with an eGFR 25–75 mL/min/1.73 m^2 and a uACR of 22.6–565 mg/mmol (200–5,000 mg/g) were randomised in DAPA-CKD from February 2017 to October 2018.[72] The DAPA-CKD study enrolled a representative patient cohort with a broad range of comorbidities,

including patients with and without comorbid T2D.[72] An overview of baseline demographics and clinical characteristics for the DAPA-CKD study population are shown in Table 11.

Table 11. Baseline patient demographics and clinical characteristics from DAPA-CKD

Characteristic	Dapagliflozin (n=2,152)	Placebo (n=2,152)
Age, years	61.8±12.1	61.9±12.1
Female sex, n (%)	709 (32.9)	716 (33.3)
Race, n (%)[a]		
White	1,124 (52.2)	1,166 (54.2)
Black	104 (4.8)	87 (4.0)
Asian	749 (34.8)	718 (33.4)
Other	175 (8.1)	181 (8.4)
Weight, kg	81.5±20.1	82.0±20.9
BMI[b]	29.4±6.0	29.6±6.3
Current smoker, n (%)	283 (13.2)	301 (14.0)
Blood pressure, mmHg		
Systolic	136.7±17.5	137.4±17.3
Diastolic	77.5±10.7	77.5±10.3
eGFR (mL/min/1.73 m^2)		
Mean	43.2±12.3	43.0±12.4
≥60	234 (10.9)	220 (10.2)
≥45–<60	646 (30.0)	682 (31.7)
≥30–<45	979 (45.5)	919 (42.7)
<30	293 (13.6)	331 (15.4)
Haemoglobin (g/l)	128.6±18.1	127.9±18.0
Serum potassium (mEq/l)	4.6±0.5	4.6±0.6
uACR (mg/g)		
Median (IQR)	965 (472–1,903)	934 (482–1,868)
>1,000, n (%)	1,048 (48.7)	1,031 (47.9)
T2D, n (%)	1,455 (67.6)	1,451 (67.4)
CVD, n (%)[c]	813 (37.8)	797 (37.0)
HF, n (%)	235 (10.9)	233 (10.8)
Background medication at randomisation, n (%)		
ACE inhibitors	673 (31.3)	681 (31.6)
ARB	1,444 (67.1)	1,426 (66.3)
Diuretic	928 (43.1)	954 (44.3)
Statin	1,395 (64.8)	1,399 (65.0)

Footnotes: Percentages may not total 100 because of rounding. uACR of 1,000 mg/g = 113 mg/mmol. [a]Race was reported by the investigators; the designation "other" includes Native Hawaiian or other Pacific Islander, American Indian or Alaska Native, and other. [b]The BMI is the weight in kilograms divided by the square of the height in meters. [c] History of peripheral artery disease, angina pectoris, myocardial infarction, percutaneous coronary intervention, coronary-artery bypass grafting, heart failure, valvular heart disease, abdominal aorta aneurysm, atrial fibrillation, atrial flutter, ischemic stroke, transient ischemic attack, haemorrhagic stroke, carotid artery stenosis, cardiac-pacemaker insertion, vascular stent, coronary-artery stenosis, ventricular arrhythmia, implantable cardioverter–defibrillator, noncoronary revascularisation, or surgical amputation.
Abbreviations: ACE: angiotensin-converting enzyme; ARB: angiotensin receptor blocker; BMI: body mass index; CVD: cardiovascular disease; eGFR: estimated glomerular filtration rate; HF: heart failure; IQR: interquartile range; T2D; type 2 diabetes; uACR: urine albumin-to-creatinine ratio.
Source: Heerspink *et al*., 2020.[7]

Patients were well-balanced across the dapagliflozin and placebo treatment arms in terms of all demographics and characteristics.[7] The majority of patients had a baseline eGFR equivalent to stage 3 CKD (30–59 mL/min/1.73 m^2; 44.1% and 30.9% had an eGFR of 30–44 and 45–59 mL/min/1.73m^2 respectively), with a smaller group falling into stages 2 (10.5%; eGFR 60–75 mL/min/1.73 m^2) and 4 (14.5%; eGFR 25–30 mL/min/1.73 m^2).[71, 72] Mean eGFR at baseline was 43.2±12.3 mL/min/1.73 m^2 for the dapagliflozin group and 43.0±12.4 mL/min/1.73 m^2 for the placebo group.[7] All patients had at least moderately increased albuminuria at baseline, as per the study inclusion criteria (uACR ≥200 mg/g [22.6 mg/mmol]), but ~50% of patients in both treatment groups had severely increased albuminuria (uACR >1,000 mg/g [113 mg/mmol).[7] Median uACR (IQR) at baseline was 965 mg/g (472–1,903 mg/g) (109.05 mg/mmol [53.34–215.04]) for the dapagliflozin group and 934 mg/g (482–1,868 mg/g) (105.54 mg/mmol [54.47–211.08]) for the placebo group.[7]

Approximately two-thirds of patients had comorbid T2D (dapagliflozin: 67.6%, placebo: 67.4%), over a third of patients had comorbid CVD (dapagliflozin: 37.8%, placebo: 37.0%) and just over 10% had comorbid HF (dapagliflozin: 10.9%, placebo: 10.8%).[7] The use of concomitant medications was generally well balanced across treatment arms. The most common previous medications were ARBs (dapagliflozin: 67.1%, placebo: 66.3%) and statins (dapagliflozin: 64.8%, placebo: 65.0%).[7]

B.3.3.1.5.1 Baseline characteristics in post-hoc analysis

DAPA-CKD recruited 4,304 adults with an eGFR of 25–75 mL/min/1.73m^2 and a uACR between 200–5,000 mg/g (22.6 mg/mmol and 565 mg/mmol), of which 1,398 did not have T2D. This post-hoc analysis assessed the annual rate of eGFR decline and uACR changes in patients without T2D by baseline uACR.[11] An overview of baseline demographics and clinical characteristics for the DAPA-CKD study population are shown in Table 12.

Table 12. Baseline characteristics of DAPA-CKD participants without T2D and albuminuria in the post-hoc analysis

Characteristic	KDIGO stage A2 albuminuria (uACR 30 to <300 mg/g) (n=136)[a]	KDIGO stage A3 albuminuria (uACR ≥300 mg/g) (n=1,262)
Mean age, years (SD)	61 (15)	56 (15)
Female sex, n (%)	49 (36)	411 (33)
Mean eGFR (SD)	41 (11)	42 (12)
Median uACR	245	955

Footnotes: [a]Of the 136 participants with KDIGO stage A2 albuminuria, 24 had uACR 30 to <200 mg/g at baseline.
Abbreviations: eGFR: estimated glomerular filtration rate; KDIGO: Kidney Disease Improving Global Outcomes; SD: standard deviation; T2: type 2 diabetes; uACR: urine albumin-to-creatinine ratio.
Source: Heerspink *et al.,* 2022.[11]

B.3.3.2 OPTIMISE-CKD

The OPTIMISE-CKD programme is a multinational, observational, longitudinal cohort study that uses data extracted from electronic health records and claims data sources. The overall study objective is to describe the management and treatment with dapagliflozin in routine clinical practice among patients with CKD, with and without T2D across the uACR spectrum. Different analyses of the data extracted were conducted, including:

- **Svensson *et al*., 2024**: The first observational study as part of OPTIMISE-CKD included data from the US to compare estimated eGFR trajectories, eGFR slopes and cardiorenal and all-cause mortality outcomes of dapagliflozin 10 mg in patients with CKD without T2D, with low (30-200 mg/g) versus high (≥200 mg/g) uACR.[8] A summary of the methodology and results is provided in section **Error! Reference source not found.** and B.3.6.2.1 Svensson et al., 2024: dapagliflozin treatment of patients with CKD without diabetes across different albuminuria levels, respectively.

- **Tangri *et al*., 2024:** A second study from OPTMISE-CKD included data from the US and Japan to describe the real-world utilisation of dapagliflozin following its approval for the CKD indication, and to assess the effect of initiating versus not initiating dapagliflozin on kidney function decline in patients with uACR <22.6 mg/mmol (<200 mg/g).[9] A summary of the methodology and results is provided in section B.3.3.2.2 Tangri et al., 2024: dapagliflozin initiation and eGFR trajectories across uACR subgroups in clinical practice and B.3.6.2.2 Tangri et al., 2024: dapagliflozin initiation and eGFR trajectories across uACR subgroups in clinical practice, respectively.

The study supports the claim that the use of dapagliflozin in patients with CKD is associated with similar kidney protection and cardiorenal risk, irrespective of uACR levels and diabetes status. The OPTIMISE-CKD programme included patients across the uACR spectrum, with no restriction on uACR in terms of inclusion criteria; however the studies presented in this appraisal (Svensson *et al.,*

2024 and Tangri *et al*., 2024) followed different analysis plans and therefore the results presented are for different subgroups (30-200 mg/g or >200 mg/g in Svensson *et al.,* 2024, and 0-200 mg/g only in Tangri *et al*., 2024)

B.3.3.2.1 Svensson et al., 2024: dapagliflozin treatment of patients with CKD without diabetes across different albuminuria levels

B.3.3.2.1.1 Trial design

The methodology of the analysis of the OPTIMISE-CKD study of US administrative claims data is summarised in Table 13.

Table 13. Summary of trial methodology: OPTIMISE-CKD, US administrative claims data, 30 April 2021-31 March 2023

Parameter	Description
Study objective	To compare kidney and cardiorenal protection in patients without T2D across uACR levels after initiation of dapagliflozin for the treatment of CKD. Supplementary analyses included patients with CKD and T2D.
Trial design	Observational study part of the OPTIMISE-CKD study using de-identified claims data from the US.
Data source	Administrative claims database, Optum's de-identified CDM, for privately commercial or Medicare insured patients in the US.
Duration of study	Patients with CKD were indexed at the initiation of dapagliflozin 10 mg between 30 April 2021 (date of CKD marketing authorisation for dapagliflozin) and 31 March 2023 (date of data extraction).
Trial drugs	Dapagliflozin 10 mg oral once daily plus SoC.
uACR Groups	Patients were grouped based on baseline uACR levels. The "low uACR" group comprises patients with uACR 30–200 mg/g, and the "high uACR" group those with uACR >200 mg/g. Those with uACR 0–29mg/g were also assessed and classified as normal/ mildly elevated.

Abbreviations: CDM: Clinformatics® Data Mart; CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; SoC: standard of care; T2D: type 2 diabetes; uACR: urine albumin-creatinine ratio; US: United States.
Source: Svensson *et al*., 2024.[8]

B.3.3.2.1.2 Eligibility criteria

The eligibility criteria are summarised in Table 14.

Table 14. Eligibility criteria in OPTIMISE-CKD, US administrative claims data, 30 April 2021-31 March 2023

Inclusion criteria	• Age >18 years as of study index date.
	• With first ever registered laboratory confirmed CKD or CKD diagnosis, defined as at least one of:
	  ○ two eGFR measurements ≥90 days apart, of which both measurements were ≤60 mL/min/1.73m^2 or
	  ○ a first eGFR measurement ≤60 mL/min/1.73m^2 followed by a first CKD diagnosis

Exclusion criteria	• History of stage 5 CKD • Dialysis • Type 1 diabetes or gestational diabetes on or before index date

Abbreviations: CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; US: United States.
Source: Svensson *et al*., 2024.[8]

B.3.3.2.1.3 Study outcomes

The study evaluated eGFR outcomes and clinical outcomes. eGFR outcomes were reported as the absolute difference in eGFR relative to baseline, described at 3 and 6 months prior to index and 1, 3, 6, 9, and 12 months after index. The following clinical outcomes were described for each patient during the 12 months after index date: in-patient hospitalisations with a diagnosis of CKD (including diagnoses of acute kidney failure, unspecified kidney failure, diabetic kidney disease, hypertensive CKD, dialysis, glomerular diseases, renal tubulointerstitial disease or other), HF and all-cause mortality.[8]

B.3.3.2.1.4 Duration of study and follow up

Patients with CKD were indexed at the initiation of dapagliflozin 10 mg between 30 April 2021 (date of CKD marketing authorisation for dapagliflozin) and 31 March 2023 (date of data extraction), and were followed up for 12 months after the index date.[8]

B.3.3.2.1.5 Baseline characteristics

OPTIMISE-CKD patient characteristics at baseline are summarised in Table 15. In total, 28,795 new users of dapagliflozin 10 mg were identified after its approval for CKD on 30 April 2021. In those without T2D, there were 3,029 (27%) patients with a uACR reading, of which 796 (26%) had low (3–22.6 mg/mmol; 30–200 mg/g), 684 (23%) had high (>22.6 mg/mmol; >200 mg/g), and 1,549 (51%) had normal to mildly elevated (0–3 mg/mmol; 0–29 mg/g) uACR. Overall, patients without T2D with low uACR (3–22.6 mg/mmol; 30–200 mg/g) had more co-morbidities (MI, atrial fibrillation/flutter, HF) and fewer were receiving renin–angiotensin system inhibitor (RASi) compared to those with high uACR (>22.6 mg/mmol). For those with T2D, similar baseline characteristics were observed between the low and high uACR groups (3–22.6 mg/mmol and >22.6 mg/mmol respectively).[8]

Table 15. Characteristics of patients with CKD and without T2D in OPTIMISE-CKD

	Non-T2D		T2D	
Baseline characteristics	**Low uACR** (30-200 mg/g)	**High uACR** (>200 mg/g)	**Low uACR** (30-200 mg/g)	**High uACR** (>200 mg/g)
Number of patients, n	796	684	2411	1983
Age, years, mean (SD)	75 (8)	74 (9)	74 (8)	72 (8)
Female, n (%)	336 (42)	264 (39)	1079 (45)	797 (40)
Days since 1st CKD diagnosis	1347 (618-2024)	1169 (538-2067)	1064 (464-1870)	1100 (481-1931)
Co-morbidities				
ASCVD				
MI, n (%)	215 (27)	144 (21)	456 (19)	399 (20)
Stroke, n (%)	282 (35)	222 (32)	748 (31)	602 (30)
Peripheral artery disease, n (%)	318 (40)	255 (37)	826 (34)	712 (36)
Atrial fibrillation/flutter, n (%)	306 (38)	193 (28)	595 (25)	388 (20)
HF, n (%)	431 (54)	269 (39)	927 (38)	773 (39)
CKD diagnosis, n (%)	750 (94)	665 (97)	2241 (93)	1921 (97)
Cancer, n (%)	333 (42)	277 (40)	828 (34)	571 (29)
Laboratory measurements[a]				
Systolic BP, mmHg, median (IQR)	130 (120-140)	137 (124-150)	132 (122-145)	136 (126-149)
≥ 140 mmHg, n (%)	129 (29)	192 (44)	444 (34)	480 (42)
Haemoglobin, g/dL, median (IQR)	13.1 (11.9-14.4)	12.8 (11.5-14.2)	12.9 (11.8-14.2)	12.6 (11.3-13.9)
Potassium, mmol/L, median (IQR)	4.4 (4.1-4.8)	4.4 (4.1-4.8)	4.5 (4.2-4.8)	4.5 (4.2-4.9)
eGFR, mL/min/1.73 m^2, median (IQR)	47 (37-61)	41 (31-55)	50 (38-66)	44 (34-58)
45–59 (Stage 3a), n (%)	197 (25)	162 (24)	655 (28)	483 (25)
30–44 (Stage 3b), n (%)	280 (36)	241 (36)	701 (30)	687 (36)
15–29 (Stage 4), n (%)	82 (11)	143 (21)	255 (11)	325 (17)
Creatinine, mg/dL, median (IQR)	1.3 (1.0-1.6)	1.5 (1.2-1.9)	1.2 (1.0-1.6)	1.4 (1.1-1.8)
uACR, mg/g, median (IQR)	69.0 (46.0-110.0)	654.5 (360.0-1291.5)	70.0 (46.0-111.0)	623.0 (332.0-1372.0)
Renoprotective treatment				
RASi, n (%)	491 (62)	494 (72)	1860 (77)	1585 (80)
SGLT2 inhibitor, n (%)	0 (0)	0 (0)	0 (0)	0 (0)

Footnotes: [a]Laboratory measurements represent the last registered value in the year prior to incident CKD.
Abbreviations: ASCVD: atherosclerotic cardiovascular disease; BP: blood pressure; CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; HF: heart failure; IQR: interquartile range; MI: myocardial infarction; N/A: not available or not applicable; RASi: renin–angiotensin system inhibitor; SD: standard deviation; SGLT-2: sodium–glucose co-transporter-2; T2D: type 2 diabetes; uACR: urine albumin-creatinine ratio.
Source: Svensson *et al*., 2024. Supplementary material.[8]

B.3.3.2.2 Tangri et al., 2024: dapagliflozin initiation and eGFR trajectories across uACR subgroups in clinical practice

B.3.3.2.2.1 Trial design

The methodology of the analysis of the OPTIMISE-CKD study is summarised in Table 16.

Table 16. Summary of trial methodology: OPTIMISE-CKD US and Japan claims data

Parameter	Description
Study objective	To describe real-world utilisation of dapagliflozin 10 mg following its approval for the CKD indication in the US and Japan, and to assess the effect of initiating versus not initiating dapagliflozin 10 mg on kidney function decline in patients with uACR <200 mg/g.
Trial design	Observational study part of the OPTIMISE-CKD study using de-identified claims data from the US and Japan.
Data source	Administrative claims data linked with EMRs from the Optum de-identified Clinformatics® DataMart database in the US. Hospital claims database from Medical Data Vision Co. Ltd, and inpatient and outpatient data from The Real World Data Co. Ltd in Japan.
Index date	The study index date was defined as the date of first dapagliflozin 10 mg prescription (in the case of dapagliflozin initiators) or the first date on which patients met all eligibility criteria during the study period (in the case of eligible but untreated patients).
Trial drugs	Dapagliflozin 10 mg oral once daily or no treatment.

Abbreviations: CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; EMR: electronic medical records; mg: milligram; T1D: type 1 diabetes; US: United States.
Source: Tangri *et al*., 2024.[9]

B.3.3.2.2.2 Eligibility criteria

The full eligibility criteria are described in Table 17.

Table 17. Eligibility criteria for dapagliflozin 10 mg utilisation

	US (Optum Clinformatics® Data Mart)	Japan (Real World Data Co. Ltd)	Japan (Medical Data Vision Co. Ltd)
Inclusion criteria			
Age ≥18 years	X	X	X
CKD definition (any of the criteria)	•uACR ≥30 mg/g •CKD diagnosis code[a] • Two eGFR measurements at least 90 days apart, both <60 mL/min/1.73 m^2	•uACR ≥30 mg/g •CKD diagnosis code[a] • Two eGFR measurements at least 90 days apart, both <60 mL/min/1.73 m^2	•CKD diagnosis code[a] • Two eGFR measurements at least 90 days apart, both <60 mL/min/1.73 m^2
≥365 days of continuous enrolment before index date	X	X	X
Exclusion criteria			
Diagnosed with type 1 diabetes on or before index date	X		
Diagnosis of gestational diabetes mellitus on or before index date	X		
Dialysis on or before index date	X	X	X
Dapagliflozin 10 mg any time before index date	X	X	X
Diagnosis or procedure indicative of end-stage kidney disease		X	X
Polycystic kidney disease on or before index date	X		
Use of immunosuppressive drugs 6 months before or on index date	X		
Use of hydroxychloroquine on index date	X		
Not within eGFR range on or in year before index date	<25 mL/min/1.73 m^2	<15 mL/min/1.73 m^2	<15 mL/min/1.73 m^2

Footnotes: An X indicates that the criterion was applied in the database of interest. [a]Full code list is available in Table 18.
Abbreviations: CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; SGLT-2i: sodium-glucose cotransporter-2 inhibitor; uACR: urinary albumin-to-creatinine ratio; UPCR: urinary protein-to-creatinine ratio.
Source: Tangri *et al*., 2024. Supplementary material.[9]

Table 18. List of ICD-10 diagnosis codes used to define CKD

Description	ICD-10
CKD	N18
Renal tubulo-interstitial disease	N10–N16
End-stage renal disease	T86.1, Z49, Z94.0, Z99.2
Acute renal failure	N17
Hypertensive CKD	I12, I13
Diabetic CKD	E08.2, E11.2
Glomerular disease	N00, N01, N02, N03, N04, N05, N06, N07, N08, R80
CKD unspecified	N19, N25, N26, N99.0, Q60, Q62, Q63

Footnotes: All ICD-10 codes used to identify CKD were mapped to ICD-9 codes to identify cases coded using either system.
Abbreviations: CKD: chronic kidney disease; ICD: International Classification of Diseases.
Source: Tangri *et al.,* 2024. Supplementary material.[9]

B.3.3.2.2.3 Study outcomes

The primary outcome was eGFR slope between index and the end of follow-up.[9]

B.3.3.2.2.4 Duration of study and follow-up

Patients were followed from index date until the earliest of the following: loss to follow-up, death or end of the study period. Specifically in the case of comparators who became dapagliflozin initiators, the follow-up period as a comparator ended on the day that these patients initiated dapagliflozin 10 mg.[9]

B.3.3.2.2.5 Baseline characteristics

Patient characteristics at baseline for those initiating dapagliflozin are summarised in Table 19.

Table 19. Key baseline characteristics of propensity score-matched patients with CKD and uACR<200 mg/g who initiated dapagliflozin 10 mg and who did not

	uACR <200 mg/g			uACR <200 mg/g AND no T2D		
	Initiated dapagliflozin	Did not initiate dapagliflozin	SMD[a]	Initiated dapagliflozin	Did not initiate dapagliflozin	SMD[a]
	10 mg	10 mg		10 mg	10 mg	
Number of patients	2,972	2,972		275	275	
Female, n (%)	1,296 (44)	1305 (44)	0.0061	107 (39)	107 (39)	<0.0001
Age, years, median (IQR)	74 (69–79)	73 (69–78)	0.0222	75 (68–81)	76 (69–81)	0.0479
BMI available, n (%)	1,071 (36)	939 (32)		85 (31)	100 (36)	
BMI, kg/m^2, mean (SD)	31.5 (7.0)	31.0 (7.1)	0.0669	27.4 (6)	27.5 (6.4)	0.0313
BMI category, kg/m^2, n (%)						
0–18.4	<5[b]	5 (1)		<5[b]	<5[b]	
18.5–24.9	178 (17)	191 (20)		26 (31)	33 (33)	
25.0–29.9	318 (30)	257 (27)		36 (42)	40 (40)	
≥30	571 (53)	486 (52)		20 (24)	25 (25)	
Comorbidities, n (%)						
Atrial fibrillation	802 (27)	797 (27)	0.0038	99 (36)	107 (39)	0.0600
HF	1,278 (43)	1,232 (41)	0.0313	148 (54)	155 (56)	0.0511
HTN	2,890 (97)	2,885 (97)	0.0101	259 (94)	262 (95)	0.0487
MI	391 (13)	368 (12)	0.0232	29 (11)	32 (12)	0.0347
Stroke	942 (32)	892 (30)	0.0364	76 (28)	88 (32)	0.0953
Anaemia	1,602 (54)	1582 (53)	0.0135	135 (49)	133 (48)	0.0145

	uACR <200 mg/g			uACR <200 mg/g AND no T2D		
	Initiated dapagliflozin 10 mg	Did not initiate dapagliflozin 10 mg	SMD[a]	Initiated dapagliflozin 10 mg	Did not initiate dapagliflozin 10 mg	SMD[a]
T2D	2658 (89)	2667 (90)	0.0099	N/A	N/A	
Medications, n (%)						
RASi	2521 (85)	2503 (84)	0.0258	217 (79)	225 (82)	0.0731
ARNI	304 (10)	260 (9)	0.0110	32 (12)	25 (9)	0.0834
Calcium channel blockers	1269 (43)	1249 (42)	0.0027	124 (45)	123 (45)	0.0073
Diuretics	1503 (51)	1377 (46)	0.0143	159 (58)	155 (56)	0.0293
Statins	2536 (85)	2452 (83)	0.0138	173 (63)	174 (63)	0.0075
Antidiabetic treatments	2333 (79)	2283 (77)	0.0395	N/A	N/A	
eGFR						
eGFR available, n (%)	2972 (100)	2972 (100)		275 (100)	275 (100)	
eGFR, mL/min/ 1.73 m^2, median (IQR)	53.7 (42.8–71.1)	54.8 (43.2–69.1)	0.0133	50.1 (40.3–60.2)	49.5 (38.4–61.4)	0.0121
uACR						
uACR available, n (%)	2972 (100)	2972 (100)		275 (100)	275 (100)	
uACR, mg/g, median (IQR)	20.1 (7.0–55.8)	19.0 (7.0–52.0)	0.0092	8.6 (1.6–32.4)	14.0 (2.2–39.4)	0.0552
uACR category, n (%), 0–29 mg/g	1739 (59)	1813 (61)		202 (73)	189 (69)	
uACR category, n	1,233 (41)	1,159 (39)		73 (27)	86 (31)	

	uACR <200 mg/g			uACR <200 mg/g AND no T2D		
	Initiated dapagliflozin	Did not initiate dapagliflozin	SMD[a]	Initiated dapagliflozin	Did not initiate dapagliflozin	SMD[a]
	10 mg	10 mg		10 mg	10 mg	
(%), 30–200 mg/g						

Footnotes: [a]An SMD of less than 0.1 was considered good balance between covariates. [b]Exact n numbers for cohorts with n \ 5 not shown in accordance with Clinformatics Data Mart patient privacy guidelines.
Abbreviations: ARNI: angiotensin receptor/neprilysin inhibitor; BMI: body mass index; CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; HF: heart failure; HTN: hypertension; IQR: interquartile range; MI: myocardial infarction; N/A: not applicable; RASi: renin–angiotensin system inhibitor; SD: standard deviation; SMD: standardised mean difference; T2D: type 2 diabetes; uACR: urinary albumin-to-creatinine ratio.
Source: Tangri *et al.*, 2024.[9]

B.3.3.3 Nakhleh *et al.,* 2024

Nakhleh *et al.,* 2024 aimed to assess real-world effectiveness of SGLT2 inhibitors in patients with CKD and without diabetes from de-identified data. The study supports the claim that the use of SGLT2 inhibitors in this patient population provides a slower rate of kidney function decline, irrespective of baseline uACR level.[10]

B.3.3.3.1 Trial design

The methodology of Nakhleh *et al.,* 2024 including de-identified data on patients without diabetes and with an eGFR of 25–60 mL/min/1.73 m^2, who initiated dapagliflozin or empagliflozin between September 2020 and November 2022, is summarised in Table 20.[10]

Table 20. Summary of trial methodology: Nakhleh *et al*., 2024

Parameter	Description
Study objective	To assess the renal effects of SGLT2 inhibitors in patients with CKD and without diabetes in a real-world setting.
Trial design	Retrospective observational study using de-identified data on adults without diabetes and with an eGFR of 25–60 mL/min/1.73 m^2 and who received either dapagliflozin or empagliflozin.
Data source	De-identified data from the MHS, an Israeli health maintenance organisation.
Duration of study	Data from the MHS between September 2020 and November 2022 were included.
Trial drugs	Dapagliflozin and empagliflozin (drug posology is not specified in the study publication).

Abbreviations: CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; MHS: Maccabi Healthcare Service; SGLT2: Sodium-glucose cotransporter 2.
Source: Nakhleh *et al*., 2024.[10]

B.3.3.3.2 Eligibility criteria

The eligibility criteria are summarised in Table 21.

Table 21. Eligibility criteria in Nakhleh *et al*., 2024

Inclusion criteria	• Age >18 years. • Baseline eGFR of 25–60 mL/min/1.73 m^2. • Received an SGLT2 inhibitor (empagliflozin or dapagliflozin) between September 2020 and November 2022.
Exclusion criteria	• Type 1 or 2 diabetes before the index date[a] • Less than 12 months of enrolment at MHS. • Pregnancy during the past year before SGLT2 inhibitor administration. • No baseline or follow-up slopes (individuals who did not have a minimum of 2 eGFR evaluations, with at least 180 days between them in each period).

Footnotes: [a]The day of the first SGLT2 inhibitor dispensing was defined as the index date.
Abbreviations: eGFR: estimated glomerular filtration rate; MHS: Maccabi Healthcare Service; SGLT2: Sodium-glucose cotransporter 2.
Source: Nakhleh *et al*., 2024.[10]

B.3.3.3.3 Study outcomes

Nakhleh *et al.,* 2024 assessed the difference in the change of eGFR slope between baseline and follow-up periods, including:[10]

- Baseline eGFR slope calculated using eGFR values captured in the 2 years leading up to and including the index date;
- Follow up slope calculated using eGFR values between 90 and 900 days after the index date alongside baseline measurement on index date.

Treatment adherence to SGLT2 inhibitors was assessed using changes in vital signs, including systolic blood pressure (SBP), body weight, and changes in laboratory evaluations (e.g., serum albumin and haematocrit) between baseline and follow-up periods at 6 ± 3 months and 12 ± 3 months. Proportion of days covered until the end of follow-up, considered the sum of treatment days based on actual purchases, divided by the number of follow-up days (from the index date until the end of follow-up) was also used to assess treatment adherence.[10]

B.3.3.3.4 Duration of study and follow up

Patients aged >18 years, with a baseline eGFR of 25–60 mL/min/1.73 m^2, who were started on SGLT2 inhibitors (empagliflozin or dapagliflozin) between September 2020 and November 2022 were included. The day of the first SGLT2 inhibitor dispensing was defined as the index date, and the end of follow-up as either 31 May 2023, or the date of leaving MHS, whichever came first.[10]

B.3.3.3.5 Baseline characteristics

Patient characteristics at baseline are summarised in Table 22.

Table 22. Baseline patient demographics and clinical characteristics

Characteristic	Statistics (n=354)
Age, mean (SD), years	72.8 (11.8)
Female, n (%)	92 (26.0)
Age category, n (%)	
18–64 years	72 (20.3)
65–74 years	110 (31.1)
>75 years	172 (48.6)
Socioeconomic status, n (%)	
1-3	31 (8.8)
4-5	71 (20.1)
6-7	107 (30.2)
8-10	145 (41.0)
Current smoker, n (%)	
No	154 (43.5)
Yes	14 (4.0)
Missing	186 (52.5)
BMI, mean (SD), kg/m^2	29.1 (5.4)
Ejection fraction, n (%)	
<40%	77 (21.8)
40–49%	17 (4.8)
50–59%	13 (3.7)
≥60%	61 (17.2)
Missing	186 (52.5)
SBP, mean (SD), mmHg, n	127.2 (18.7), 331
DBP, mean (SD), mmHg, n	73.4 (10.9), 331
Established ASCVD, n (%)	184 (52.0)
Ischaemic heart disease, n (%)	164 (46.3)
MI or cardiac revascularisation procedure, n (%)	88 (24.9)
HF, n (%)	165 (46.6)
Atrial fibrillation, n (%)	97 (27.4)
Cerebrovascular disease, n (%)	50 (14.1)
Stroke, n (%)	20 (5.6)
Transient ischaemic attack, n (%)	16 (4.5)
Peripheral vascular disease, n (%)	31 (8.8)
HTN, n (%)	291 (82.2)
Cancer, n (%)	108 (30.5)
Liver disease, n (%)	17 (4.8)
COPD, n (%)	26 (7.3)
Urinary tract infection, n (%)	26 (7.3)
Medications for HTN, n (%)	346 (97.7)
RAS inhibitors, n (%)	322 (91.0)
ACE inhibitors, n (%)	125 (35.3)
ARBs, n (%)	244 (68.9)

Characteristic	Statistics (n=354)
Beta blockers, n (%)	253 (71.5)
Alpha blockers, n (%)	36 (10.2)
Alpha-2 receptor agonists, n (%)	11 (3.1)
Calcium channel blockers, n (%)	151 (42.7)
Thiazides, n (%)	17 (4.8)
Loop diuretics, n (%)	153 (43.2)
Aldosterone antagonists, n (%)	152 (42.9)
Nitrate, n (%)	34 (9.6)
PCSK-9 inhibitors, n (%)	9 (2.5)
Statins, n (%)	267 (75.4)
Other lipid-lowering drugs, n (%)	55 (15.5)
Antiplatelets, n (%)	178 (50.3)
Anticoagulants, n (%)	136 (38.4)
Antiarrhythmic drugs, n (%)	58 (16.4)
eGFR, mean (SD), mL/min/1.73 m^2, n	45.4 (9.5), 354
eGFR category, n (%) 45–60 mL/min/1.73 m^2 25–45 mL/min/1.73 m^2	 191 (54.0) 163 (46.0)
uACR, median (Q1–Q3), mg/g, n	36.8 (0–269.9), 301
uACR category, n (%) <30 mg/g 30–300 mg/g >300 mg/g Missing	 146 (41.2) 81 (22.9) 74 (20.9) 53 (15.0)
KDIGO risk category, n (%) Moderate High Very high	 127 (35.9) 102 (28.8) 125 (35.3)
Annual baseline eGFR slope, mean (SD), mL/min/1.73 m^2	-5.6 (7.7)
Annual baseline eGFR decline, n (%) >5 mL/min/1.73 m^2 ≤5 mL/min/1.73 m^2	 148 (41.8) 206 (58.2)
Fasting plasma glucose, mean (SD), mg/dL, n	101.7 (12.1), 340
HbA1c, mean (SD), %, n	5.7 (0.4), 270
Total cholesterol, mean (SD), mg/dL, n	153.9 (43.3), 334
Low-density lipoprotein cholesterol level, mean (SD), mg/dL, n	80.6 (32.2), 326
High-density lipoprotein level cholesterol, mean (SD), mg/dL, n	47.0 (11.6), 333
Triglyceride level, mean (SD), mg/dL, n	131.5 (99.6), 334
Serum total protein, mean (SD), g/dL, n	6.9 (0.5), 285
Serum albumin, mean (SD), g/dL, n	4.0 (0.3), 308

Characteristic	Statistics (n=354)
WBC, mean (SD), 103/µL, n	7.8 (5.3), 350
Haematocrit, mean (SD), %, n	41.1 (5.2), 350
Haemoglobin, mean (SD), g/dL, n	13.3 (1.8), 350
Platelet count, mean (SD),103/µL, n	215.4 (64.5), 350
Serum urea, mean (SD), mg/dL, n	60.9 (20.2), 352
Serum uric acid, mean (SD), mg/dL, n	7.4 (1.8), 220
Serum sodium, mean (SD), mmol/L, n	139.2 (2.7), 351
Serum potassium, mean (SD), mmol/L, n	4.6 (0.4), 352

Abbreviations: ACE: angiotensin-converting enzyme; ARB: angiotensin II receptor blocker; ASCVD: atherosclerotic cardiovascular disease; BMI: body mass index; COPD: chronic obstructive pulmonary disease; DBP: diastolic blood pressure; eGFR: estimated glomerular filtration rate; HbA1c: glycated haemoglobin; HF: heart failure; HTN: hypertension; KDIGO: Kidney Disease: Improving Global Outcomes; MI: myocardial infarction; PCSK-9: proprotein convertase subtilisin/kexin type 9; RAS: renin-angiotensin system; SBP: systolic blood pressure; SD: standard deviation; uACR: urinary albumin to creatinine ratio; WBC: white blood cell count.
Source: Nakhleh *et al*., 2024.[10]

B.3.3.4 DECLARE-TIMI 58

The Phase III DECLARE-TIMI 58 RCT (n=17,160) enrolled patients with T2D who had or were at risk of ASCVD.[13, 14] The trial enrolled a proportion of patients with comorbid CKD, and is therefore of relevance to this appraisal.

B.3.3.4.1 Trial design

Patients with T2D, glycated haemoglobin (HbA1c) 6.5–12.0% (47.5–113.1 mmol/mol), with either established ASCVD or multiple risk factors, and creatinine clearance of at least 60 mL/min were randomly assigned (1:1) to 10 mg dapagliflozin or placebo once daily.[13]

B.3.3.4.2 Eligibility criteria

Patients with T2D and either established ASCVD (age ≥40 years and either ischaemic heart disease, cerebrovascular disease, or peripheral arterial disease), or multiple risk factors for ASCVD (age ≥55 years for men or ≥60 years for women plus at least one of dyslipidaemia, HTN, or current tobacco use) were eligible to be enrolled. Participants were also required to have HbA1c between 6.5% and 12.0% (47.5–113.1 mmol/mol) and creatinine clearance (estimated by the Cockcroft-Gault equation) of 60 mL/min or higher.[13]

B.3.3.4.3 Study outcomes

The renal analysis reports findings for the components of these composite outcomes, a subgroup analysis of these composite outcomes, and changes in eGFR at different timepoints.[13] The primary safety outcome in the CV analysis was a composite of major adverse cardiovascular events (MACE), defined as CV death, MI, or ischemic stroke. The primary efficacy outcomes were MACE and a composite of CV death or hospitalisation for HF. Secondary efficacy outcomes were a renal composite (≥40% decrease in eGFR to <60 mL/min/1.73 m^2 of body-surface area, new end-stage

renal disease, or death from renal or CV causes) and death from any cause.[14] A prespecified secondary cardiorenal composite outcome was defined as a sustained decline of at least 40% in eGFR to less than 60 mL/min/1.73 m^2, end-stage renal disease (defined as dialysis for at least 90 days, kidney transplantation, or confirmed sustained eGFR <15 mL/min/1.73 m^2), or death from renal or CV causes. A prespecified renal-specific composite outcome was the same but excluding death from CV causes.[13]

B.3.3.4.4 Duration of study and follow up

The trial took place between April 25, 2013, and Sept 18, 2018; median follow-up was 4.2 years (IQR 3.9–4.4).[13]

B.3.3.4.5 Baseline characteristics

Of the 17,159 participants with available baseline eGFR data (one participant had missing data for eGFR), 8,162 (47.6%) had an eGFR of at least 90 mL/min/1.73 m², 7,732 (45.1%) had an eGFR of 60 to less than 90 mL/min/1.73 m², and 1,265 patients (7%) had an eGFR of <60 mL/min/1.73m^2 at randomisation, reflecting the enrolment criteria.[13, 14] At baseline, 11,644 (69.1%) of the 16,843 patients with available data for uACR had normal to mildly increased albuminuria (i.e., <30 mg/g), 4,030 (23.9%) had microalbuminuria (moderately increased uACR, i.e., ≥30 to ≤300 mg/g), and 1,169 (6.9%) had macroalbuminuria (severely increased uACR, i.e., >300 mg/g).[13] 6,974 patients (40.6%) had established ASCVD and 10,186 (59.4%) had multiple risk factors for ASCVD.[14]

B.3.3.5 DAPA-HF

The Phase III DAPA-HF RCT (n=4,744) enrolled patients with HFrEF, regardless of the presence or absence of comorbid T2D.[15, 16] The trial enrolled a proportion of patients with comorbid CKD, and is therefore of relevance to this appraisal. The DAPA-HF trial enrolled patients with a broad range of eGFR categories, with 41% of patients having an eGFR of <60 mL/min/1.73m^2 (CKD stage 3a and above).[15, 16]

B.3.3.5.1 Trial design

Patients were randomly assigned to receive either dapagliflozin (at a dose of 10 mg once daily) or matching placebo, in accordance with the sequestered, fixed-randomisation schedule, with the use of balanced blocks to ensure an approximate 1:1 ratio of the two regimens.[16]

B.3.3.5.2 Eligibility criteria

Eligibility requirements included an age of at least 18 years, an ejection fraction of 40% or less, and New York Heart Association (NYHA) class II, III, or IV symptoms. Patients were required to have a plasma level of N-terminal pro–B-type natriuretic peptide (NT-proBNP) of at least 600 pg/ml (or ≥400 pg/ml if they had been hospitalised for HF within the previous 12 months). Patients with atrial

fibrillation or atrial flutter on baseline electrocardiography were required to have an NT-proBNP level of at least 900 pg/ml, regardless of their history of hospitalisation for HF.[16]

B.3.3.5.3 Study outcomes

The primary outcome of DAPA-HF was the composite of worsening HF (HF hospitalisation or urgent visit for HF requiring intravenous therapy) or CV death, whichever occurred first. Prespecified secondary end points included HF hospitalisation or CV death; HF hospitalisations (first and recurrent) and CV deaths. The prespecified secondary renal outcome was a composite of ≥50% sustained decline eGFR or end-stage renal disease or renal death. Sustained was defined as lasting at least 28 days and end-stage renal disease was defined as a sustained eGFR of <15 mL/min/1.73m^2.[15]

B.3.3.5.4 Duration of study and follow up

The study ran from February 15, 2017, through to August 17, 2018.[16]

B.3.3.5.5 Baseline characteristics

At baseline, an eGFR could be calculated in 4,743 patients. 1,926 (41%) had a value <60 mL/min/1.73m^2 and 2,816 (59%) had a value of ≥ 60 mL/min/1.73m^2.[15] While uACR was not measured during the DAPA-HF trial, it is likely that the patients enrolled had a wide range of uACR categories given the lack of uACR restriction.

B.3.4 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

B.3.4.1 DAPA-CKD

A summary of the analysis populations for efficacy and safety outcomes for the DAPA-CKD study is presented in Table 23, while details of the statistical analyses conducted for DAPA-CKD are presented in Table 24.

Table 23. Summary of analysis populations in DAPA-CKD

Study population	Description
FAS	• All patients who were randomised to the dapagliflozin (n=2,152) or placebo (n=2,152) treatment arms, irrespective of their protocol adherence and continued participation in the study (the ITT population) • Patients were analysed according to their randomised therapy assignment, irrespective of the treatment actually received • The FAS was considered the primary analysis set for the primary and secondary variables and for the exploratory efficacy variables
SAS	• All patients who received at least one dose of dapagliflozin (n=2,149) or placebo (n=2,149) • Patients were analysed according to the treatment actually received[a] • The SAS was considered the primary analysis set for all safety variables

Footnotes: [a]For any patients given incorrect treatment, the treatment group was allocated as follows: patients who received both the incorrect and correct treatment were allocated to their randomised treatment group; and patients who received only the incorrect treatment were allocated to that treatment group.
Abbreviations: FAS: full analysis set; SAS: safety analysis set, ITT: intent-to-treat.
Source: Wheeler *et al.,* 2021.[73]

Table 24. Summary of statistical analyses in DAPA-CKD

DAPA-CKD	
Hypothesis objective	Treatment with dapagliflozin was hypothesised to be superior to placebo in reducing the risk of renal and CV events in patients with CKD (with or without comorbid T2D) already receiving a stable dose of an ACE inhibitor or an ARB (unless ACE inhibitors/ARBs were contraindicated)

Statistical analysis	• The primary efficacy analysis was based on the FAS. In the analysis of the primary composite endpoint, the treatments (dapagliflozin and placebo) were compared using a Cox proportional hazards regression model stratified by the factors used at randomisation (T2D and uACR) and adjusted for baseline eGFR. The analysis used each patient's last assessment as the censoring date for patients without any primary outcome event. The contribution of each component of the primary composite endpoint to the overall treatment effect were also examined and no multiplicity adjustment was made to CIs or p values
	• The secondary efficacy outcomes were tested in a similar manner as the primary efficacy outcomes using a closed testing procedure including a pre-specified hierarchical order of the primary and secondary outcomes. The secondary outcomes were tested in hierarchical order as follows:
	  ○ Composite renal endpoint consisting of 50% eGFR decline, ESKD or renal death
	  ○ Composite endpoint of hospitalisation for HF or CV death
	  ○ Time to death from any cause
	• The testing procedure continued down the hierarchy if the preceding endpoint was rejected at a one-sided 0.025 level and stopped if the null hypothesis for the preceding endpoint was not rejected
	• A mixed model for repeated measurements was used to analyse changes in the eGFR in the on-treatment population
	• Cox proportional hazards models were used to examine treatment effects within relevant subgroups separately
	• Safety data are summarised according to trial group and safety analyses were performed on all AEs occurring before or at the trial closure visit. All analyses were performed with SAS software, version 9.4 (SAS Institute)

Sample size, power calculation	• DAPA-CKD was an event-driven trial • 681 primary endpoint events were needed to provide 90% power to detect a 22% lower RR in the dapagliflozin group compared with the placebo group (HR: 0.78) using a one-sided alpha level of 0.025. Assuming an annual event rate for the primary outcome of 7.5% in the placebo group, 4,000 patients were estimated to provide the required number of primary events
Data management and patient withdrawals	• Quality of study data was assured through monitoring of investigational sites, provision of appropriate training for study personnel, and use of data management procedures. The impact of missing data with respect to the primary endpoint was assessed via a sensitivity analysis and a descriptive summary • For any patient that withdrew, the rationale for withdrawal and presence of any AE were recorded. The investigator followed up AEs reported outside of the clinical study. If a patient was lost to follow-up, the measures taken to contact the patient and determine the reason for discontinuation/withdrawal had to be documented • For incorrectly randomised patients, the study drug was discontinued in all cases where continued treatment was deemed to pose a safety risk. Where continuation with study drug was judged not to present a safety concern, the rationale for continuing study therapy was documented.

DAPA-CKD	
	Regardless of what was decided, all randomised patients were to remain in the study and the patients were to be followed up in accordance with the defined study procedures

Abbreviations: ACE: angiotensin-converting enzyme; AE: adverse event; ARB: angiotensin receptor blocker; CI: confidence interval; CKD: chronic kidney disease; CV: cardiovascular; eGFR: estimated glomerular filtration rate; ESKD: end-stage kidney disease; FAS: full analysis set; HF: heart failure; HR: hazard ratio; PTDV: premature treatment discontinuation visit; RR: relative risk; T2D: type 2 diabetes; uACR: urine albumin-to-creatinine ratio.
Source: Beernink *et al.,* 2023.[74]

B.3.4.2 OPTIMISE-CKD

B.3.4.2.1 Svensson et al., 2024: dapagliflozin treatment of patients with CKD without diabetes across different albuminuria levels

All analyses were performed in the low and high uACR groups. Baseline characteristics were described using IQRs for continuous variables and frequencies (%) for categorical variables. Change in eGFR relative to baseline was described as the mean change at each time point with 95% CI based on observed values. The individual patient slopes of post eGFR measurements were analysed using quantile regression, where the median slopes (per year) were estimated and presented with 95% CI. Three models were used: unadjusted, eGFR adjusted (adjusted by baseline eGFR), and multivariable adjusted (baseline eGFR, age, sex, HF and RASi [including angiotensin receptor–neprilysin inhibitors]). The time to clinical outcomes was analysed using Cox regression models, where time since index was the primary timescale. The models were adjusted for age, sex, HF, CKD diagnosis, MI, stroke and peripheral arterial disease. The results were presented as the HR with 95% CI for the RR of high uACR (>22,6 mg/mmol) relative to low uACR (3–22.6 mg/mmol; 30–200 mg/g). The crude event rates were presented as number of events per 100 patient-years. In all analyses, the primary cohorts were patients with CKD without T2D, grouped by low and high uACR. All analyses have also been performed within patients with CKD and with T2D.[8]

B.3.4.2.2 Tangri et al., 2024: dapagliflozin initiation and eGFR trajectories across uACR subgroups in clinical practice

Each dapagliflozin initiator was matched 1:1 with a potential comparator who had not initiated treatment on the same date and had the closest matching propensity score. Nearest neighbour matching was performed using logistic regression within the MatchIt package (version 4.5.4) in R (version 4.0.2). A propensity score model, which included all variables in the full baseline table (Table 19) and an interaction between angiotensin receptor/neprilysin inhibitor (ARNI) and HF for matching patients, was developed to maximise the balance between groups. Covariates were considered well balanced if standardised mean differences were less than 0.1 after propensity score matching. The statistical methodology described in this section applies only to the effectiveness analysis, using the prevalent new user design.[9]

B.3.4.3 Nakhleh *et al.*, 2024

Continuous variables with approximately normal distribution are reported as mean and standard deviation (SD; or standard error of the mean [SEM], if otherwise stated), and those with skewed distributions as median and IQR. Categorical variables are reported as the number of observations and proportions. Baseline characteristics were compared across uACR categories using chi-squared tests for categorical variables and one-way analysis of variance (ANOVA) or t tests for continuous variables, as appropriate.[10]

The eGFR annual slope per participant was calculated for baseline and follow-up periods by fit to a linear regression. The difference in eGFR annual slope between these two periods was calculated using a paired t test and presented as the mean difference between these two periods with 95% CIs. Heterogeneity between subgroups was evaluated by one-way ANOVA tests. The eGFR value and change in eGFR from baseline in each time window were presented as the mean and SD or the mean and SEM, according to the context.[10]

Changes in SBP (mmHg), body weight (kg), haematocrit (%) and serum albumin (g/dL) from baseline to follow-up periods (at 6 ±3 months and 12 ± 3 months after index date) were estimated using paired t tests and presented as mean change and 95% CI. Analyses were performed using SAS version, version 9.4. Figures were created using SAS, version 9.4 or R software (package ggplot2). A p value of <0.05 was taken to indicate statistical significance.[10]

B.3.4.4 DECLARE-TIMI 58

In the subgroup analysis presented in this document, cardiorenal and renal-specific composite outcomes and their components, subgroup analyses of these composite outcomes, and comparison of eGFR change by treatment group at different timepoints were reported.

Analyses were done according to the intention-to-treat principle, using data for all randomly assigned participants. Adjudicated outcome data were used to define CV death and renal death events. The Kaplan-Meier method was used to generate cumulative incidence curves for the cardiorenal and renal-specific composite outcomes and for sustained decrease in eGFR by at least 40% to less than 60 mL/min/1.73 m². HRs and 95% CIs were calculated with the Cox proportional-hazard model for the cardiorenal and renal-specific composite outcomes and their individual components, both in the entire population and in prespecified subgroups according to patients' baseline demographics, medical histories, background medications, and baseline measurements.[13]

B.3.4.5 DAPA-HF

Time-to-event data were evaluated with the use of Kaplan–Meier estimates and Cox proportional-hazards models, stratified according to diabetes status, with a history of hospitalisation for HF and treatment-group assignment as fixed-effect factors; for the renal outcome, the baseline eGFR was included instead of a history of hospitalisation for HF. Cox models were used to calculate HRs, 95%

CIs, and two-sided p values and used a semiparametric proportional-rates model to calculate total (including recurrent) events.[16]

B.3.5 Critical appraisal of the relevant clinical effectiveness evidence

B.3.5.1 DAPA-CKD

A quality assessment for DAPA-CKD, in accordance with the NICE-recommended checklist for assessment of bias in RCTs is provided in Table 25.

Table 25. Overview of quality assessment for DAPA-CKD

DAPA-CKD (NCT03036150)	Risk of bias
Was randomisation carried out appropriately?	Yes. Patients were randomised in a 1:1 ratio stratified by comorbid T2D status and uACR at baseline. Randomisation was performed based on a sequestered, fixed randomisation schedule using balanced blocks.[7]
Was the concealment of treatment allocation adequate?	Yes. An interactive voice/web-response system was used to determine treatment assignment and matching placebo was used.[7]
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes. The baseline characteristics, including medications for comorbid T2D and kidney disease, were balanced between the dapagliflozin and placebo groups.[7]
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes. This study had a double-blind design. No trial personnel had access to the randomisation scheme. Dapagliflozin and placebo were packaged identically, with uniform tablet appearance, labelling, and administration schedules.[75]
Were there any unexpected imbalances in drop-outs between groups?	No. Discontinuations of study medication were low and well-balanced between treatment arms.[7]
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No. Based on the clinical study report all outcomes are reported in detail.[76]
Did the analysis include an ITT analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes. Efficacy analysis was performed on the FAS.[7]
Did the authors of the study publication declare any conflicts of interest?	Yes, the DAPA-CKD trial was sponsored by AstraZeneca. The sponsor was involved in the design and write up of the trial.[72]

Abbreviations: FAS: full analysis set; ITT: intention-to-treat; uACR: urine albumin-to-creatinine ratio; T2D: type 2 diabetes.

B.3.5.2 OPTIMISE-CKD

A quality assessment for OPTIMISE-CKD is provided in Table 26.

Table 26. Overview of quality assessment for OPTIMISE-CKD

OPTIMISE-CKD	Risk of bias
Was the cohort recruited in an acceptable way	Yes – cohort was representative of a defined population.
Was the exposure accurately measured to minimise bias	Yes – all adult patients in the databases used in the study were included in the descriptive analysis if they initiated or were eligible for dapagliflozin 10 mg during the study period.
Was the outcome accurately measured to minimise bias?	Yes – the study outcome measures were objective measures and calculated through a reliable system using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation to ensure that a consistent and recognised method was used across patients.
Have the authors identified all confounding factors?	Yes – the study used databases that collected information on a range of clinical variables identified as potential confounders.
Have the authors taken account of the confounding factors in the design and/or analysis?	Yes – the sample size of the study allowed for propensity score matching to be used to adjust for confounding variables.
Was the follow-up of patients complete?	Yes - Patients were followed from index date until the earliest of the following: loss to follow-up, death or end of the study period. In the case of comparators who became dapagliflozin initiators, the follow-up period as a comparator ended on the day that these patients initiated dapagliflozin 10 mg.
How precise (for example, in terms of confidence and p-values) are the results?	95% CIs and p-values to two decimal points were reported alongside HRs for the reported outcomes.

Adapted from critical appraisal skills programme (CASP): Making sense of evidence. 12 questions to help you make sense of a cohort study.
Abbreviations: CI: confidence interval; HR: hazard ratio

B.3.5.3 Nakhleh *et al.,* 2024

A quality assessment for Nakhleh *et al.,* 2024 is provided in Table 27.

Table 27. Overview of quality assessment for Nakhleh *et al.*, 2024

Nakhleh *et al.*, 2024	Risk of bias
Was the cohort recruited in an acceptable way	Yes – cohort was representative of a defined population.
Was the exposure accurately measured to minimise bias	Yes – all adult patients in the databases used in the study were included in the descriptive analysis if they initiated dapagliflozin or empagliflozin during the study period.
Was the outcome accurately measured to minimise bias?	Yes – the study outcome measures were objective measures.
Have the authors identified all confounding factors?	No
Have the authors taken account of the confounding factors in the design and/or analysis?	No
Was the follow-up of patients complete?	Yes - Patients were followed from index date (day of the first SGLT2 inhibitor dispensing) until the earliest of the following: the end of follow-up (31 May 2023), or the date of leaving MHS, whichever came first.
How precise (for example, in terms of confidence and p-values) are the results?	95% CIs and p-values to two decimal points were reported alongside HRs for the reported outcomes.

Adapted from critical appraisal skills programme (CASP): Making sense of evidence. 12 questions to help you make sense of a cohort study.
Abbreviations: CI: confidence interval; HR: hazard ratio; MHS: Maccabi Healthcare Service; SGLT2: sodium-glucose co-transporter-2.

B.3.5.4 DECLARE-TIMI 58

The critical appraisal of the dapagliflozin clinical trial programme in T2D is available in TA288.[4]

B.3.5.5 DAPA-HF

A summary of quality assessment results for DAPA-HF is provided in Table 28.

Table 28. Overview of quality assessment for DAPA-HF

DAPA-HF (NCT03036124)	Risk of bias
Was randomisation carried out appropriately?	Yes. Patients were randomised in a 1:1 ratio stratified by diabetes status at baseline based on a computer-generated randomisation schedule prepared before the study by or under the supervision of the sponsor.
Was the concealment of treatment allocation adequate?	Yes. An interactive voice/web-response system was used to determine treatment assignment and matching placebo was used.
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes. Demographics and disease characteristics were balanced between the groups and patients were stratified according to baseline diabetes status.
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes. This was a double-blind study. The interactive voice/web-response system was used to manage study agent inventory while ensuring that no one at the sites had to be unblinded. The investigator was not provided with the treatment randomisation codes. The investigators and the site personnel were blinded to the treatment assignment.
Were there any unexpected imbalances in drop-outs between groups?	No. Discontinuations of study medication were low and well-balanced between treatment arms.
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No. Based on the clinical study report all outcomes are reported in detail.
Did the analysis include an ITT analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes. Efficacy analyses were performed on the full analysis set.
Did the authors of the study publication declare any conflicts of interest?	Yes, the DAPA-CKD trial was sponsored by AstraZeneca. The sponsor was involved in the design and write up of the trial.

Abbreviations: ITT: intention to treat

B.3.5.6 Applicability of the evidence in clinical practice

The patient population enrolled in the DAPA-CKD trial is considered broadly similar to the CKD patient population seen in UK clinical practice. While minor differences were noted in the age and ethnicity of the trial population, and in the background therapies received by patients enrolled in the trial compared to clinical practice, these differences were deemed to not significantly affect the applicability of the DAPA-CKD trial results to the UK setting. TA775 addressed the specific differences in detail, and why they were not considered of great impact on the applicability of DAPA-CKD to the UK clinical setting.[2]

Additionally, following the positive recommendation of dapagliflozin in CKD in TA775, which was the first SGLT2 inhibitor to be recommended in CKD with and without T2D, the rapid uptake of dapagliflozin in CKD in UK clinical practice has been indicative of the acceptability of the clinical evidence demonstrated in DAPA-CKD and the applicability of this evidence to the UK patient population.

AstraZeneca acknowledges that the RWE presented in this appraisal is from varying geographies outside the UK. However, the data presented is from multiple countries and shows consistent results across all geographies and populations. Additionally, outcomes from RWE are consistent with evidence from RCTs (DAPA-CKD, DAPA-HF, DECLARE-TIMI-58) which NICE have already deemed generalisable, and have been ratified by clinical experts in previous appraisals (TA775 and TA773) and are therefore generalisable to the UK population.

B.3.6 Clinical effectiveness results of the relevant studies

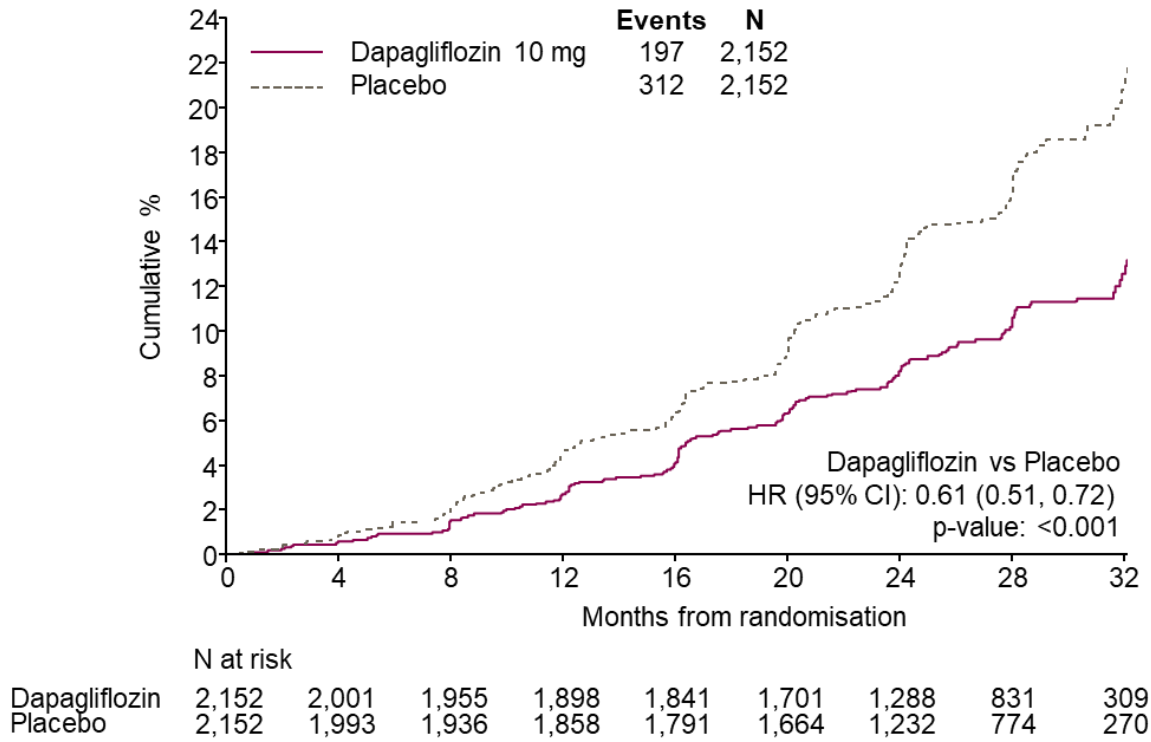
B.3.6.1 DAPA-CKD trial

B.3.6.1.1 Primary endpoint

The DAPA-CKD trial met its primary efficacy endpoint. Dapagliflozin significantly reduced the RR of a composite outcome of sustained decline in eGFR ≥50%, ESKD or death from renal or CV causes by 39% (HR: 0.61; 95% CI: 0.51, 0.72; p<0.001).[7] Patients treated with dapagliflozin gained an early and sustained treatment benefit as demonstrated in the Kaplan-Meier plot (Figure 3), showing the early separation of the treatment curves for the DAPA-CKD primary endpoint.[7]

Fewer patients in the dapagliflozin group experienced significant kidney decline than those in the placebo group, and they were also less likely to reach ESKD.[7] Importantly, a 34% reduction in the RR of chronic dialysis was observed with dapagliflozin compared with placebo.[7]

Figure 3. Kaplan-Meier plot of the composite of ≥50% eGFR decline, ESKD and renal or CV death



Footnotes: N at risk is the number of patients at risk at the beginning of the period. One month corresponds to 30 days. 2-sided p value is displayed. HR, CI and p value are from the Cox proportional hazard model.
Abbreviations: CI: confidence interval; CV: cardiovascular; D: dapagliflozin 10 mg; eGFR: estimated glomerular filtration rate; ESKD: end stage kidney disease; HR: hazard ratio; P: placebo.
Source: Heerspink *et al.,* 2020.[7]

B.3.6.1.2 Secondary endpoint

Secondary endpoints were also met and supported the clinical benefit of dapagliflozin observed in the primary composite endpoint:[7, 76]

- The positive renal treatment effect was confirmed by a significant reduction in the renal-specific composite outcome compared with placebo (HR: 0.56; 95% CI: 0.45, 0.68; p<0.001).
- Treatment with dapagliflozin was associated with a 29% reduction in the risk of hospitalisation for HF or CV death (HR: 0.71; 95% CI: 0.55, 0.92; p=0.0089).
- Dapagliflozin demonstrated a 31% RR reduction in all-cause mortality compared with placebo (HR: 0.69; 95% CI: 0.53, 0.88; p=0.004).

In addition, DAPA-CKD demonstrated substantial treatment benefit of dapagliflozin on progression of CKD compared with placebo in the exploratory analyses of surrogate endpoints for CKD progression. The full results of the primary and secondary endpoints, as well as the exploratory analysis have been detailed in section B.2 of TA775.

B.3.6.1.3 Post-hoc analysis from DAPA-CKD trial

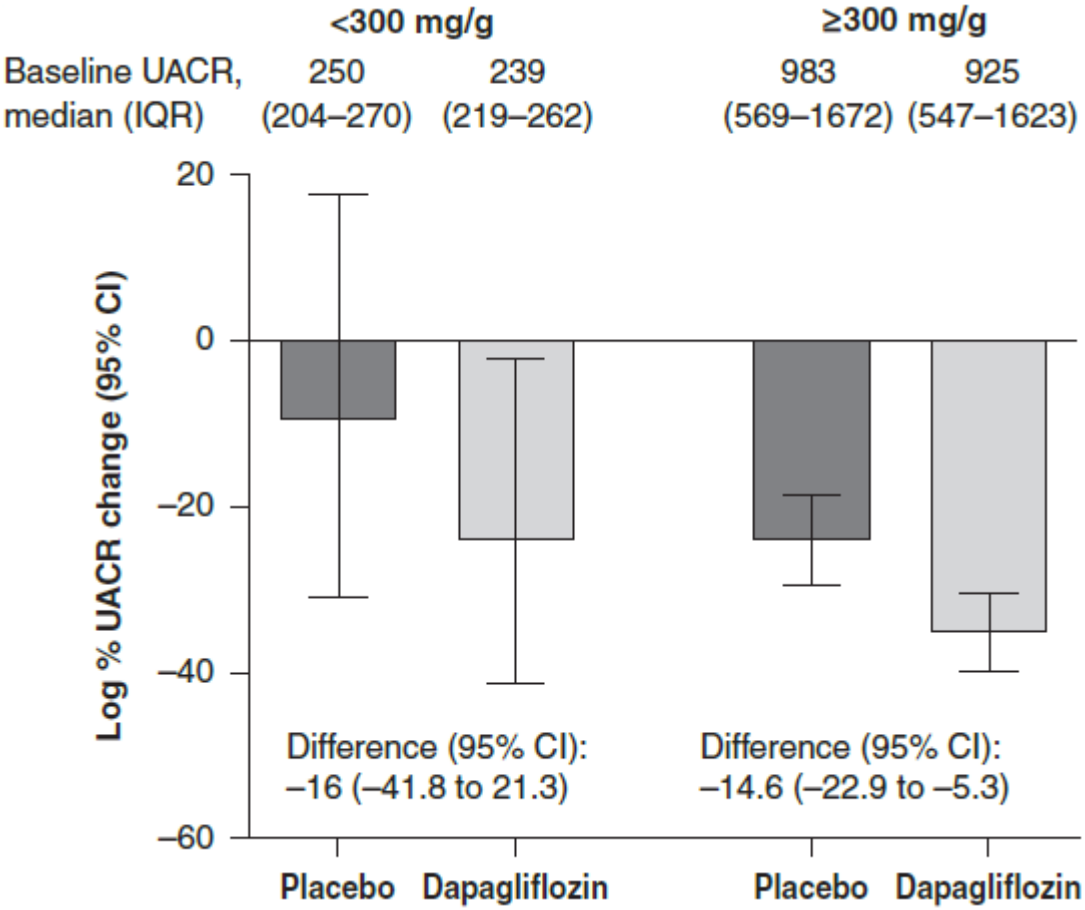
A post-hoc analysis of DAPA-CKD aimed to assess whether the kidney protective benefits of dapagliflozin, as demonstrated in the DAPA-CKD trial, extend to participants without T2D and with lower levels of albuminuria (30–<300 mg/g; 3–<30 mg/mmol). Of all participants in DAPA-CKD without T2D, at baseline, 136 had KDIGO stage A2 albuminuria (microalbuminuria; uACR 30–<300 mg/g or 3 to <30 mg/mmol, 24 of whom had uACR 30–<200 mg/g or 3 to <22.6 mg/mmol at baseline), and 1,262 had KDIGO stage A3 albuminuria (macroalbuminuria; uACR ≥300 mg/g or ≥30 mg/mmol).[11]

B.3.6.1.3.1 Outcomes

By week 2, dapagliflozin compared with placebo changed eGFR from baseline with similar effects in participants without T2D and with uACR <30 mg/mmol (−2.4 mL/min/1.73m^2; 95% CI: −4.5, −0.4) or ≥30mg/mmol (−2.0 mL/min/1.73m^2; 95% CI: −2.7, −1.3; p for interaction =0.46). Thereafter, dapagliflozin compared with placebo led to a slower decline in the chronic eGFR slope in participants without T2D with uACR <300mg/g (between-group difference of 1.8 mL/min/1.73m^2 per year; 95% CI: 0.4, 3.1) and in participants without T2D with uACR ≥300mg/g (between-group difference of 1.2 mL/min/1.73m^2 per year; 95% CI: 0.6, 1.8; p for interaction =0.62).[11]

Reductions in uACR were also observed, with percentage reductions of 16% (95% CI: −21, 42) and 15% (95% CI: 5, 23; p for interaction =0.36) in stage A2 albuminuria and stage A3 albuminuria groups, respectively (Figure 4).[11]

Figure 4. Effects on albuminuria



Abbreviations: CI: confidence interval; IQR: interquartile range; uACR: urine albumin-to-creatinine ratio.
Source: Heerspink *et al.*, 2022.[11]

Across the two uACR subgroups, there were no differences in the risk of adverse events (AEs) leading to drug discontinuation or serious adverse events (SAEs; Table 29 and Table 30). Incidences of the kidney composite end point among participants without T2D and with uACR <300 mg/g, defined as sustained ≥50% eGFR decline, kidney failure, or death due to kidney failure, were infrequent during follow-up (one in the dapagliflozin group and three in the placebo group).[11]

Table 29. AEs in participants with stage A2 albuminuria

Characteristic	Dapagliflozin (n=72)	Placebo (n=64)
Drug discontinuation due to AE	2/72	1/64
Serious AE	18/72	14/64

Abbreviations: AE: adverse event.
Source: Heerspink *et al.*, 2022.[11]

Table 30. AEs in participants with stage A3 albuminuria

Characteristic	Dapagliflozin (n=624)	Placebo (n=635)
Drug discontinuation due to AE	34/624	28/ 635
SAE	132	153

Abbreviations: AE: adverse event; SAE: serious adverse event.
Source: Heerspink *et al*., 2022.[11]

B.3.6.1.3.2 Robustness of evidence

Additional analysis was conducted to assess robustness, in which participants without T2D were stratified by baseline uACR <600 or ≥600 mg/g. In the subgroup of 489 participants with baseline uACR <600 mg/g, dapagliflozin compared with placebo led to a slower decline in the chronic eGFR slope (between-group difference of 0.8 mL/min/1.73m^2 per year; 95% CI: 0.0, 1.6). In the subgroup with 909 participants without T2D with uACR ≥600 mg/g, the between-group difference was 1.6 mL/min/1.73m^2 per year (95% CI: 0.9, 2.3; p for interaction =0.26).[11]

B.3.6.1.3.3 Conclusion

Dapagliflozin attenuated the decline in kidney function (week 2 to the end of the study) in participants without T2D whether there was stage A2 or stage A3 albuminuria at baseline. The evidence from this post-hoc analysis suggests that the kidney-protective effects of dapagliflozin is likely to extend to patients with CKD without T2D and with lower levels of albuminuria, as has been reported in patients with CKD with T2D.[11] This evidence was recognised by NICE in TA775 as being generalisable to the UK population, and is also consistent with recent RWE findings (section B.3.6.2 OPTIMISE-CKD and B.3.6.3 Nakhleh *et al.,* 2024).

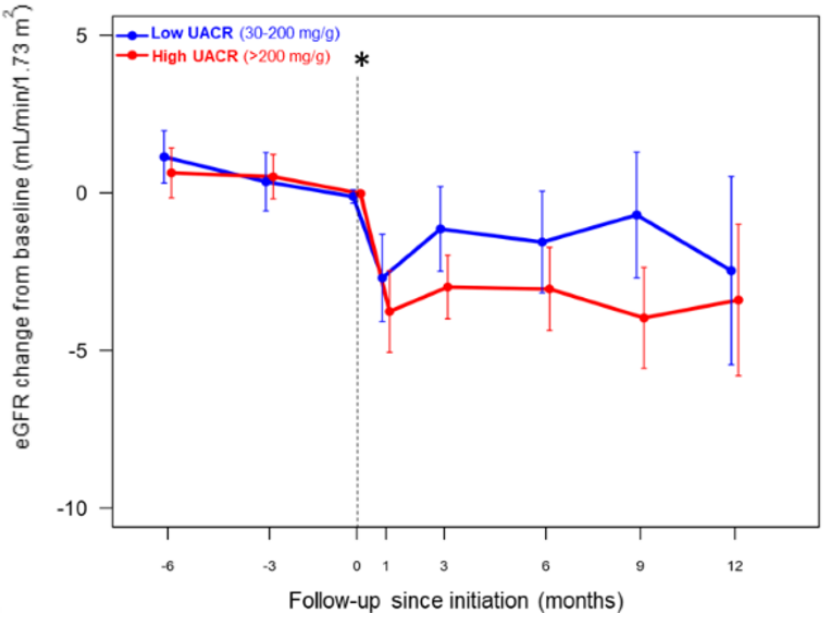
B.3.6.2 OPTIMISE-CKD

B.3.6.2.1 Svensson et al., 2024: dapagliflozin treatment of patients with CKD without diabetes across different albuminuria levels

eGFR trajectories and slopes

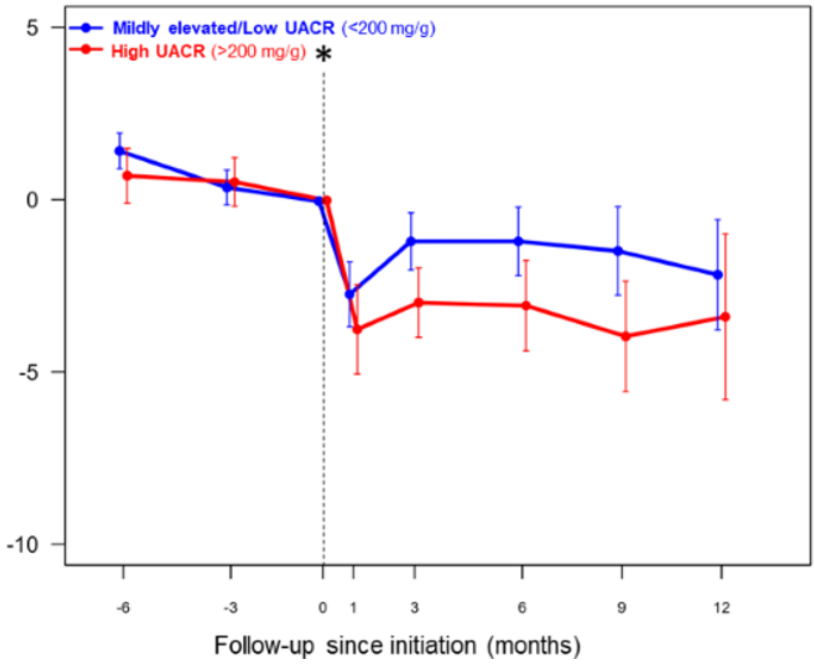
An expected decrease associated with the mechanism of action of SGLT2 inhibitors of 3 mL/min/1.73 m^2 was observed after starting patients on dapagliflozin in both the low and high uACR groups without T2D, while change over time was consistent for both groups (Figure 5). Similar effects were observed when patients with normal/ mildly elevated uACR were added into the low uACR group (Figure 6). In patients with T2D, eGFR trajectories were similar between the low and high uACR groups (Figure 7).[8] Interestingly, patients with normal/mildly elevated uACR (0–29 mg/g) showed similar eGFR trajectories and slopes compared to those with low uACR (3–22.6 mg/mmol; 30–200 mg/g). These data suggest that eGFR-associated kidney protection with dapagliflozin is reproduceable in a real-world setting, and extends to patients with CKD without T2D, regardless of uACR status.

Figure 5. eGFR change from baseline over time following dapagliflozin initiation in patients with CKD and without T2D, uACR ≥30mg/g



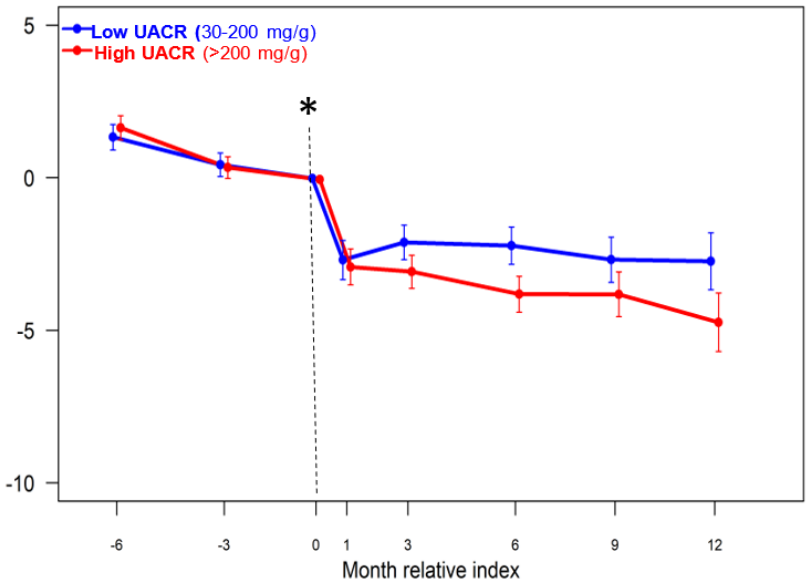
Footnote: * Initiation of dapagliflozin.
Abbreviations: CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; T2D: type 2 diabetes; uACR: urine albumin-creatinine ratio.
Source: Svensson *et al*., 2024. Supplementary material.[8]

Figure 6. eGFR change from baseline over time following dapagliflozin initiation in patients with CKD and without T2D, all uACR



Footnote: * Initiation of dapagliflozin.
Abbreviations: CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; T2D: type 2 diabetes; uACR: urine albumin-creatinine ratio.
Source: Svensson *et al*., 2024. Supplementary material.[8]

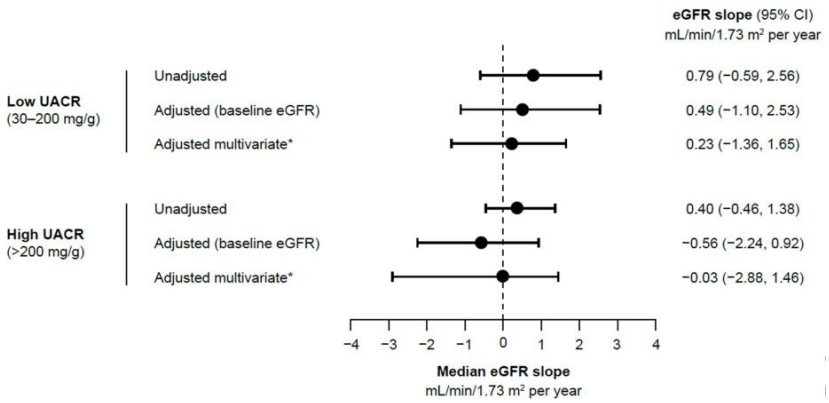
Figure 7. eGFR change from baseline over time following dapagliflozin initiation in patients with CKD and T2D



Footnote: * Initiation of dapagliflozin.
Abbreviations: CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; T2D: type 2 diabetes; uACR: urine albumin-creatinine ratio.
Source: Svensson *et al*., 2024. Supplementary material.[8]

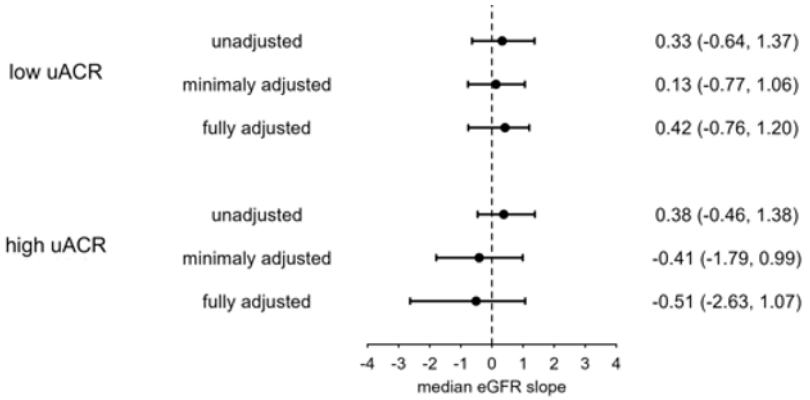
Moreover, there was a flat eGFR slope (95% CI) for the low uACR group (0.79 mL/min/1.73 m^2 per year [–0.59, 2.56]), and similar to the high uACR group (0.40 mL/min/1.73 m^2 per year [–0.46, 1.38]) as seen in Figure 8. Similar effects were observed when patients with normal/ mildly elevated uACR were added into the low uACR group (Figure 9). For patients with T2D, comparable trends were observed for the low uACR group, while a downward slope was seen for the high uACR group (Figure 10).[8]

Figure 8. eGFR slopes in patients with CKD and without T2D initiated with dapagliflozin, uACR ≥30mg/g



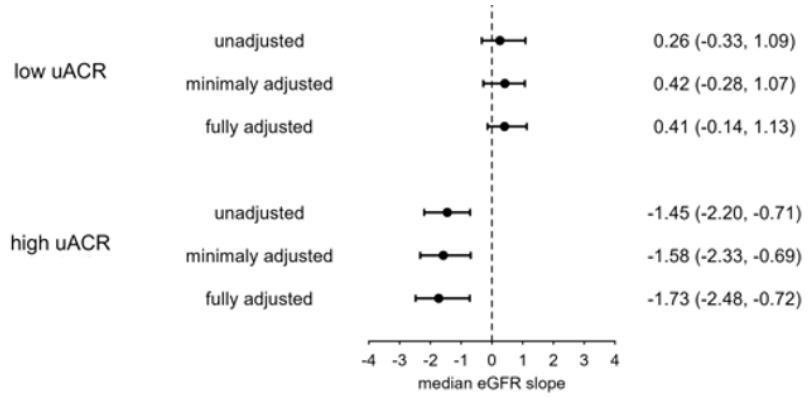
Footnotes: * Adjusted for baseline eGFR, age and sex, HF and RASi.
Abbreviations: CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; HF: heart failure; RASi: renin–angiotensin system inhibitor; T2D: type 2 diabetes; uACR: urine albumin-creatinine ratio.
Source: Svensson *et al*., 2024.[8]

Figure 9. eGFR slopes in patients with CKD and without T2D initiated with dapagliflozin, all uACR



Abbreviations: CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; RASi: renin–angiotensin system inhibitor; T2D: type 2 diabetes; uACR: urine albumin-creatinine ratio.
Source: Svensson *et al*., 2024. Supplementary material.[8]

Figure 10. eGFR slopes in patients with CKD and T2D initiated with dapagliflozin

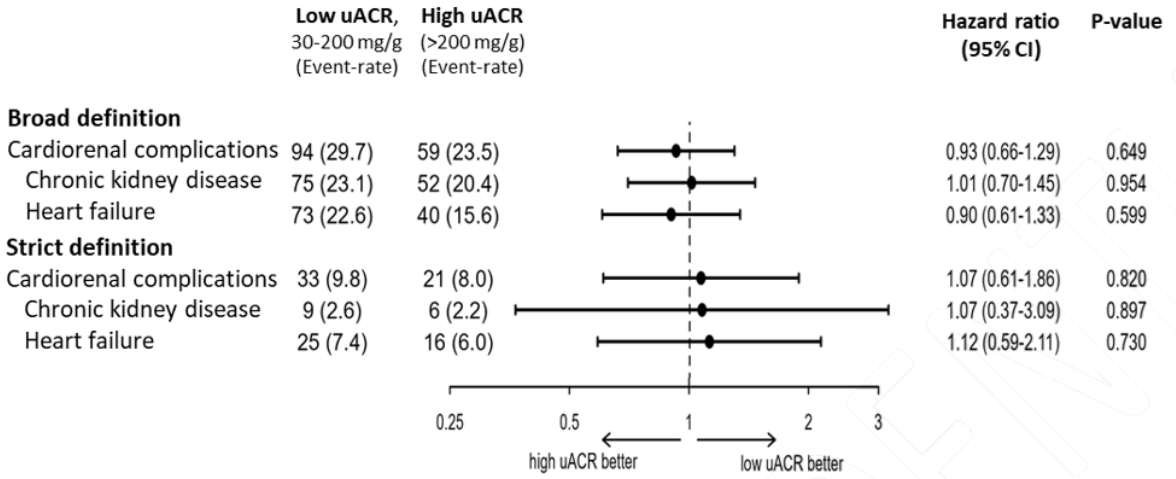


Abbreviations: CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; RASi: renin–angiotensin system inhibitor; T2D: type 2 diabetes; uACR: urine albumin-creatinine ratio.
Source: Svensson *et al*., 2024. Supplementary material.[8]

Cardiorenal outcomes

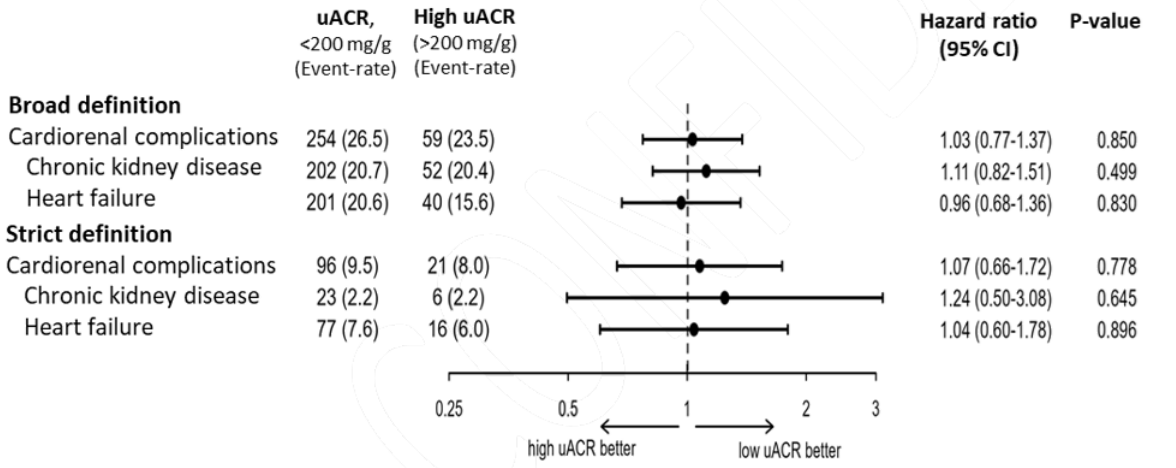
As presented in Figure 11, similar hospitalisation risk for cardiorenal complications were observed during follow-up in the low and high uACR groups. There were 29.7 and 23.5 cardiorenal event rates per 100 patient-years in the low and high uACR groups, respectively (HR: 0.93; 95% CI: 0.66, 1.29; p=0.649). After applying strict criteria, results remained close to the line of unity (HR: 1.07; 95% CI: 0.61, 1.86, p=0.820). Both CKD and HF, the separate components of the combined cardiorenal outcomes, had consistent rates in the low (23.1 and 22.6, respectively) and the high (20.4 and 15.6, respectively) uACR groups. The pattern of risk did not change when the normal/ mildly elevated uACR group were added onto the low uACR group (Figure 12). Hospitalisation risk for patients with T2D were comparable to those without T2D (Figure 13).[8]

Figure 11. Risk of cardiorenal hospitalisation in patients with CKD and without T2D initiated with dapagliflozin



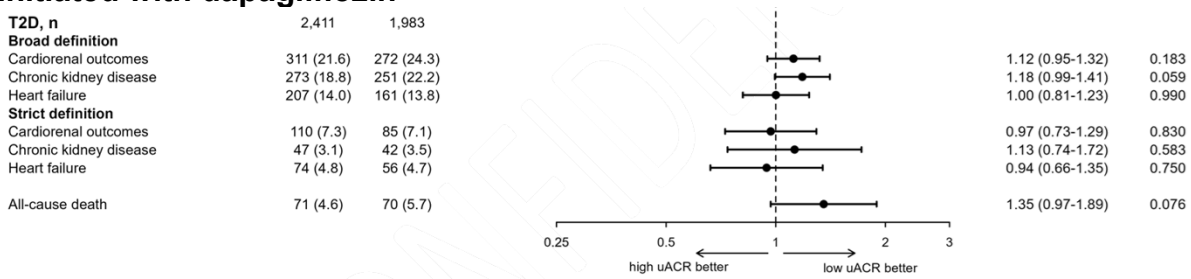
Footnotes: Broad definition: patients with a diagnosis of cardiorenal complication (CKD or HF) in an in-hospital setting. Strict definition: restricted to patients with a hospital admission where a cardiorenal complication was the main diagnosis. The diagnosis of CKD includes diagnoses of acute kidney failure, unspecified kidney failure, diabetic kidney disease, hypertensive CKD, dialysis, glomerular diseases, renal tubulointerstitial disease, or other. Adjusted for age and sex, history of MI, stroke, peripheral artery disease, atrial fibrillation, HF, RAS inhibitors.
Abbreviations: CI: confidence interval; CKD: chronic kidney disease; HF: heart failure; MI: myocardial infarction; T2D: type 2 diabetes; uACR, urine albumin-creatinine ratio.
Source: Svensson *et al*., 2024. Supplementary material.[8]

Figure 12. Risk of cardiorenal hospitalisation in patients with CKD and without T2D initiated with dapagliflozin, all uACR



Footnotes: Broad definition: patients with a diagnosis of cardiorenal complication (CKD or HF) in an in-hospital setting. Strict definition: restricted to patients with a hospital admission where a cardiorenal complication was the main diagnosis. The diagnosis of CKD includes diagnoses of acute kidney failure, unspecified kidney failure, diabetic kidney disease, hypertensive CKD, dialysis, glomerular diseases, renal tubulointerstitial disease, or other. Adjusted for age and sex, history of MI, stroke, peripheral artery disease, atrial fibrillation, HF, RAS inhibitors.
Abbreviations: CI: confidence interval; CKD: chronic kidney disease; HF: heart failure; MI: myocardial infarction; T2D: type 2 diabetes; uACR, urine albumin-creatinine ratio.
Source: Svensson *et al*., 2024. Supplementary material.[8]

Figure 13. Risk of cardiorenal hospitalisation in patients with CKD and T2D initiated with dapagliflozin



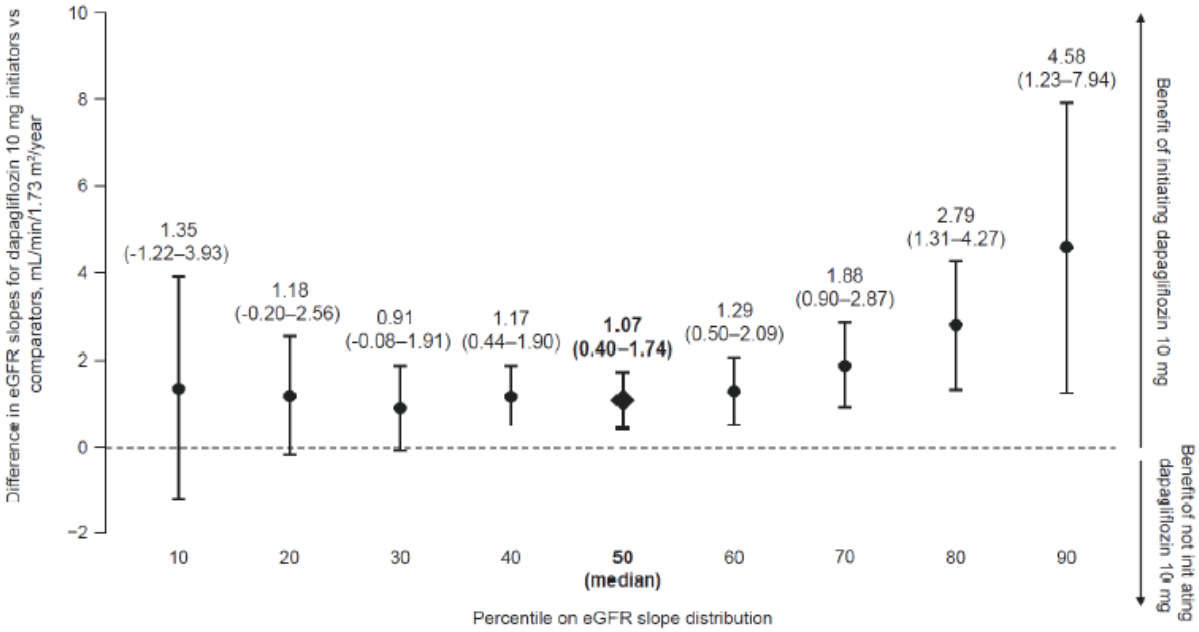
Footnotes: Broad definition: patients with a diagnosis of cardiorenal complication (CKD or HF) in an in-hospital setting. Strict definition: restricted to patients with a hospital admission where a cardiorenal complication was the main diagnosis. The diagnosis of CKD includes diagnoses of acute kidney failure, unspecified kidney failure, diabetic kidney disease, hypertensive CKD, dialysis, glomerular diseases, renal tubulointerstitial disease, or other. Adjusted for age and sex, history of MI, stroke, peripheral artery disease, atrial fibrillation, HF, RAS inhibitors.
Abbreviations: CI: confidence interval; CKD: chronic kidney disease; HF: heart failure; MI: myocardial infarction; T2D: type 2 diabetes; uACR, urine albumin-creatinine ratio.
Source: Svensson *et al*., 2024. Supplementary material.[8]

B.3.6.2.2 Tangri et al., 2024: dapagliflozin initiation and eGFR trajectories across uACR subgroups in clinical practice

eGFR trajectories

Among dapagliflozin initiators with uACR <200mg/g, the median eGFR slope was 1.07 mL/min/1.73m^2 per year (95% CI: 0.40, 1.74) better than in patients who did not initiate treatment. The benefit of dapagliflozin initiation was observed across the whole eGFR slope distribution among patients with uACR <200 mg/g (Figure 14). In the subgroup of patients with CKD without T2D, the difference was 1.28 mL/min/1.73m^2 per year (95% CI: -1.56, 4.12) in favour of dapagliflozin initiation.[9]

Figure 14. Quantile regression per decile among patient with uACR <200 mg/g



Abbreviations: eGFR: estimated glomerular filtration rate; uACR: urinary albumin-to-creatinine ratio.
Source: Tangri *et al*., 2022.[9]

Given the small sample size for patients with uACR <200 mg/g without T2D, a post-hoc analysis was performed which used information from the total cohort of patients with uACR <200 mg/g to inform estimates of treatment effect among these patients. Results from this analysis found that a weight of 30% on the information from the total cohort was sufficient to result in a significant effect of dapagliflozin initiation (versus non-initiation) on eGFR slope in patients without T2D (1.09 mL/min/1.73m^2 per year; 95% credibility interval: 0.02, 2.51).[9]

B.3.6.2.3 Conclusions from OPTIMIZE-CKD

In addition to the meta-analyses reviewed as part of empagliflozin TA942 concluding equivalent efficacy and safety between dapagliflozin and empagliflozin, which was recognised by NICE, the OPTIMISE-CKD evidence presented demonstrates the consistent treatment effect of dapagliflozin in CKD, irrespective of diabetes status and albuminuria. Dapagliflozin initiation was also associated with a clinically meaningful attenuation in eGFR slope (1.07 mL/min/1.73m^2 per year) among patients with CKD and uACR <200 mg/g compared to non-initiators, and a similar hospitalisation risk for cardiorenal complications in the low and high uACR groups. Patients with normal/mildly elevated uACR had similar eGFR slops and trajectories and cardiorenal and mortality risk development compared to those with low and high uACR. Therefore, it is reasonable to assume a consistent treatment effect for dapagliflozin initiation in these patients.

It is important to note that the estimated difference of initiating dapagliflozin 10mg on eGFR slope in Tangri *et al.,* 2024 was similar to the benefit observed with dapagliflozin (vs placebo) on total slope among patients enrolled in DAPA-CKD (0.95 mL/min/1.73 m^2/year [95% CI: 0.63;1.27]), and

directionally consistent with findings from EMPA-KIDNEY, both of which NICE deemed generalisable to the UK population in TA775 and TA942 respectively. The acute eGFR dip following dapagliflozin initiation seen in Svensson *et al.,* 2024 is also analogous with that shown in the DAPA-CKD trial, as well as the post-hoc analysis from DAPA-CKD in patients with microalbuminuria. The consistent treatment effect of dapagliflozin addresses uncertainties raised in TA775, including the potential for decision errors and overprescribing in those with CKD without T2D and with a uACR of less than 22.6 mg/mmol. This is further supported by the empagliflozin TA942, in which such uncertainties were not explored.

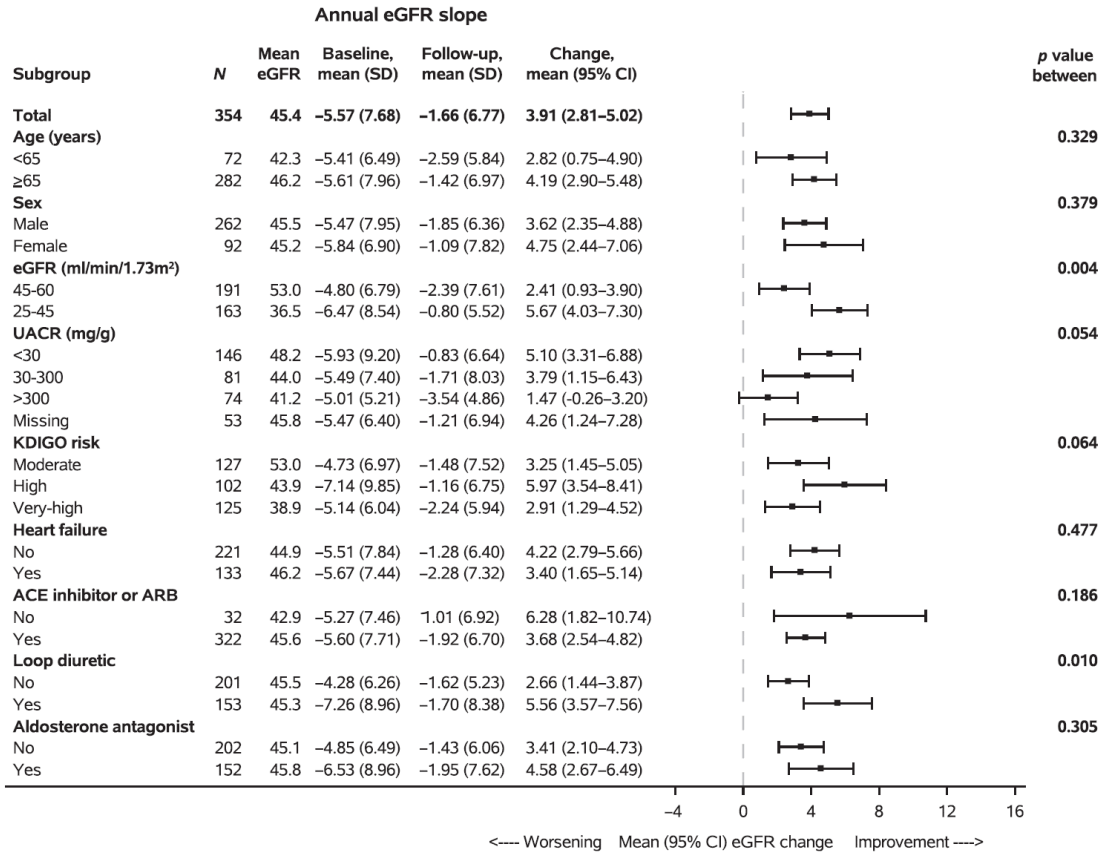
B.3.6.3 Nakhleh *et al.,* 2024

B.3.6.3.1 Change in eGFR slope from baseline to follow-up

Both baseline eGFR and uACR levels influence decline in eGFR with SGLT2 inhibitors (Figure 15 and Figure 16). Lower baseline eGFR is associated with greater decrease in eGFR slope; eGFR of 25–45 mL/min/1.73 m^2 per year provided a 87.6% reduction in eGFR slope (from -6.47 ± 8.54 to -0.80 ± 5.52), a mean change of 5.67 (95% CI: 4.03, 7.30) mL/min/1.73 m^2 per year, compared to a 50.2% reduction (from -4.80 ± 6.79 to -2.39 ± 7.61) and a mean change of 2.41 (95% CI: 0.93, 3.90) mL/min/1.73 m^2 per year with eGFR of 45–60 mL/min/1.73 m^2 (p value between subgroups =0.004).[10]

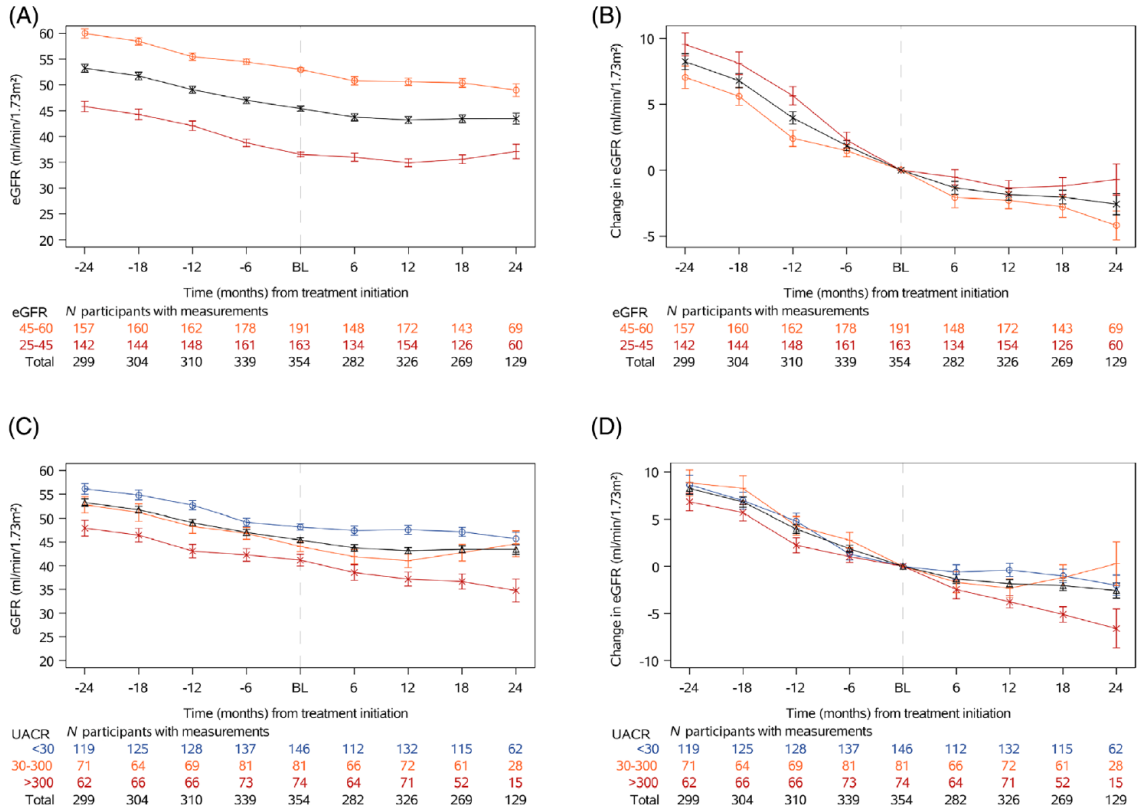
Similarly, lower levels of uACR are also associated with greater decrease in eGFR slope; uACR <30 mg/g (<3 mg/mmol) provided 86.0% reduction in the eGFR slope after SGLT2 inhibitor administration (mean change: 5.10; 95% CI: 3.31, 6.88 mL/min/1.73 m^2 per year), compared with a 69.0% reduction (mean change: 3.79; 95% CI: 1.15, 6.43 mL/min/1.73 m^2 per year) in uACR of 30–300 mg/g (3–30 mg/mmol) and a 29.3% reduction (mean change: 1.47; 95% CI: -0.26, 3.20 mL/min/1.73 m^2 per year) with a uACR >300 mg/g (>30 mg/mmol) (p value between subgroups =0.054).[10]

Figure 15. Forest plot of change in eGFR slope from baseline to follow-up



Footnote: Differences between subgroups were assessed using a one-way analysis of variance test. A p value <0.05 was considered statistically significant.
Abbreviations: ACE: angiotensin-converting-enzyme; ARB: angiotensin II receptor blocker; CI: confidence interval; eGFR: estimated glomerular filtration rate; KDIGO: Kidney Disease: Improving Global Outcomes; SD: standard deviation; uACR: urine albumin to creatinine ratio.
Source: Nakhleh *et al*., 2024.[10]

Figure 16. Mean (SEM) eGFR change during the study period by baseline eGFR (mL/min/1.73 m^2) and uACR (mg/g)

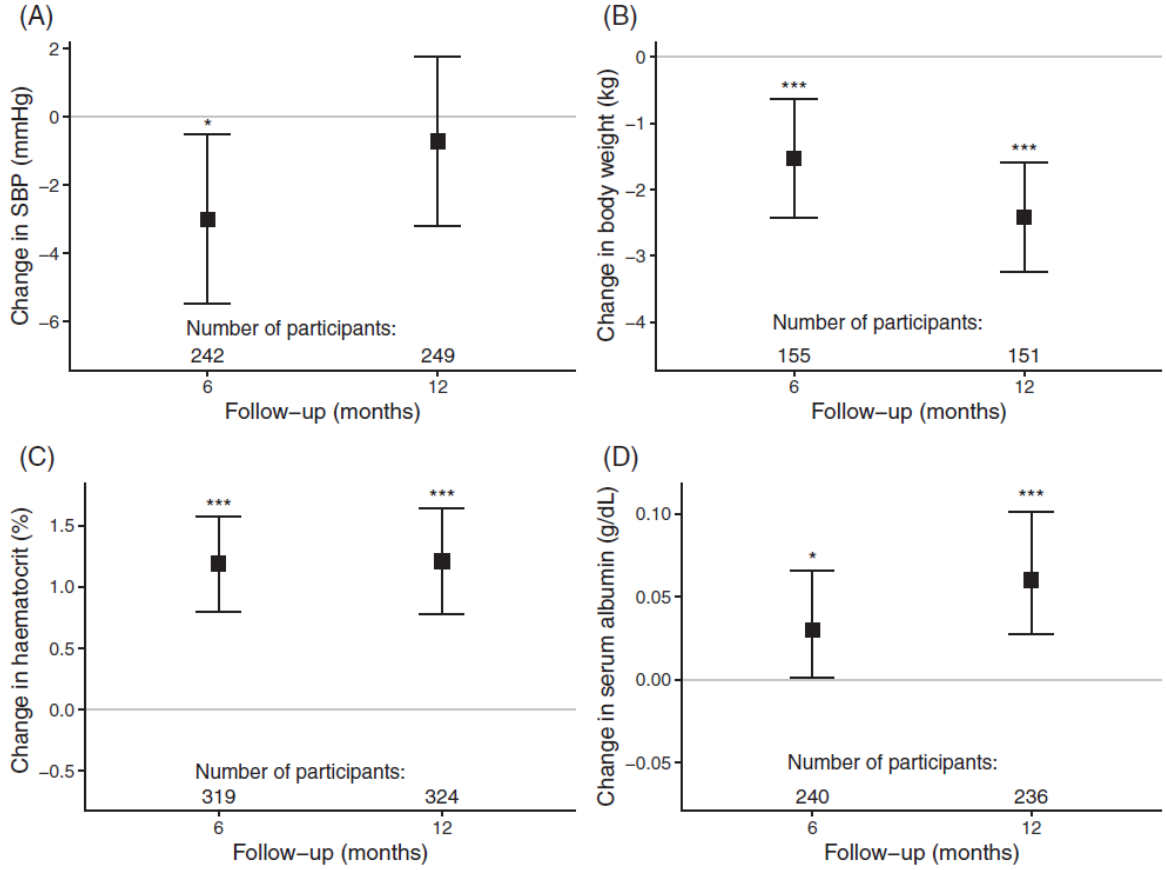


Footnote: A, B, Stratification by baseline eGFR. C, D, Stratification by baseline urine albumin to creatinine ratio (uACR). A, C, eGFR values over time windows. B, D, Absolute change from baseline evaluation over time windows.
Abbreviations: BL: baseline; eGFR: estimated glomerular filtration rate; SEM: standard error of the mean; uACR: urine albumin to creatinine ratio.
Source: Nakhleh *et al*., 2024.[10]

B.3.6.3.2 Adherence to SGLT2 inhibitors

A high adherence to SGLT2 inhibitors was observed with a median proportion of days covered (PDC) of (Q1–Q3) 87.2% (36.7%– 96.3%). Moreover, SBP was significantly reduced by 3.01 (95% CI: -5.50, -0.52) mmHg at 6 month and body weight by 1.53 (95% CI: -2.43, -0.64) kg. Both serum albumin and haematocrit rose by 0.03 (95% CI: 0.00, 0.07) g/dl and 1.19% (95% CI: 0.80%, 1.57%), respectively.[10] Change in clinical indicators associated with adherence to SGLT2 inhibitors from baseline to follow-up evaluation is presented in Figure 17.

Figure 17. Mean (95% CI) change in clinical indicators associated with adherence to SGLT2 inhibitors from baseline to follow-up evaluation - 6 months or 12 months after the index date



Footnote: A, SBP. B, Body weight. C, Haematocrit. D, Serum albumin. Significant correlations are indicated by asterisks; * and *** denote p values of <0.05 and <0.001, respectively.
Abbreviations: CI: confidence interval; SBP: systolic blood pressure; SGLT2: sodium-glucose co-transporter-2.
Source: Nakhleh *et al*., 2024.[10]

B.3.6.4 Supporting RCT outside of the DAPA-CKD trial

The efficacy of dapagliflozin in the broader population of patients with CKD, regardless of uACR and eGFR category, is further supported by DECLARE-TIMI 58 and DAPA-HF. While the DAPA-CKD trial enrolled patients with an eGFR of 25–75 mL/min/1.73 m^2 and a uACR of 200–5,000 mg/g (22.6–565 mg/mmol), the extensive clinical trial program for dapagliflozin in T2D and HFrEF covers patients with a range of renal functions and provides data supporting the efficacy of dapagliflozin in patients who were not eligible for inclusion in DAPA-CKD with respect to uACR and eGFR.

As part of the appraisal process in TA775, the company presented additional evidence from two RCTs to address uncertainty associated with treatment effect across uACR levels, DECLARE-TIMI-58 (n=17,160) and DAPA-HF (n=4,744).

B.3.6.4.1 DECLARE-TIMI 58

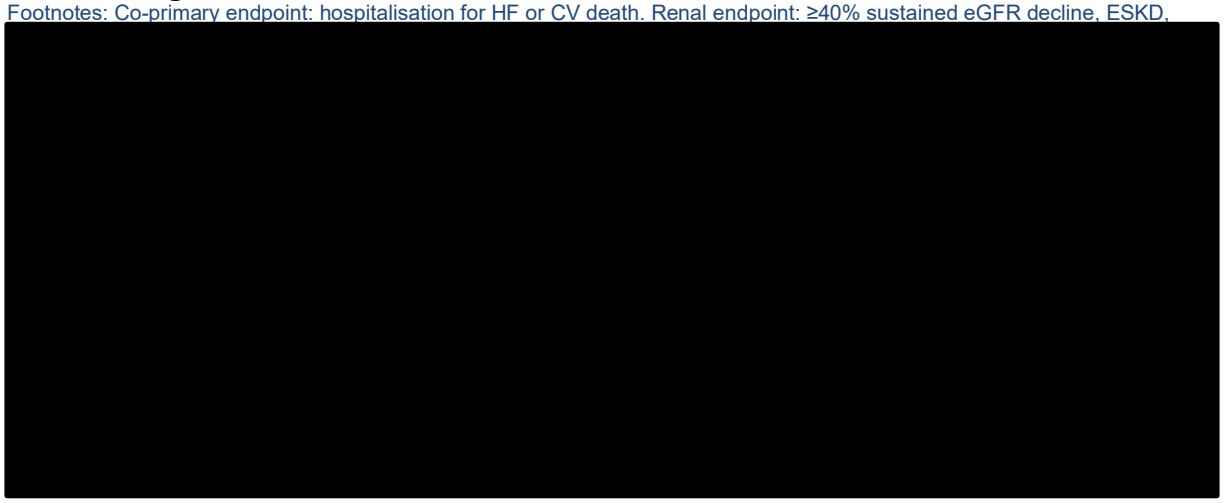
[redacted][68]

Figure 18. Relevant subgroup analyses from the DECLARE-TIMI 58 study by uACR categories

Footnotes: Co-primary endpoint: hospitalisation for HF or CV death. Renal endpoint: ≥40% sustained eGFR decline, ESKD, renal death. Cardiorenal endpoint: ≥40% sustained eGFR decline, renal death, ESKD, CV death.
Abbreviations: CI: confidence interval; CV: cardiovascular; eGFR: estimated glomerular filtration rate; ESKD: end-stage kidney disease; HF: heart failure; HR: hazard ratio; uACR: urine albumin-to-creatinine ratio.
Source: AstraZeneca UK Ltd. Data on File. ID: REF-231259. May 2024.[68]

Figure 19. Relevant subgroup analyses from the DECLARE-TIMI 58 study by eGFR categories

Footnotes: Co-primary endpoint: hospitalisation for HF or CV death. Renal endpoint: ≥40% sustained eGFR decline, ESKD, renal death. Cardiorenal endpoint: ≥40% sustained eGFR decline, renal death, ESKD, CV death.



Abbreviations: CI: confidence interval; CV: cardiovascular; eGFR: estimated glomerular filtration rate; ESKD: end-stage kidney disease; HF: heart failure; HR: hazard ratio.

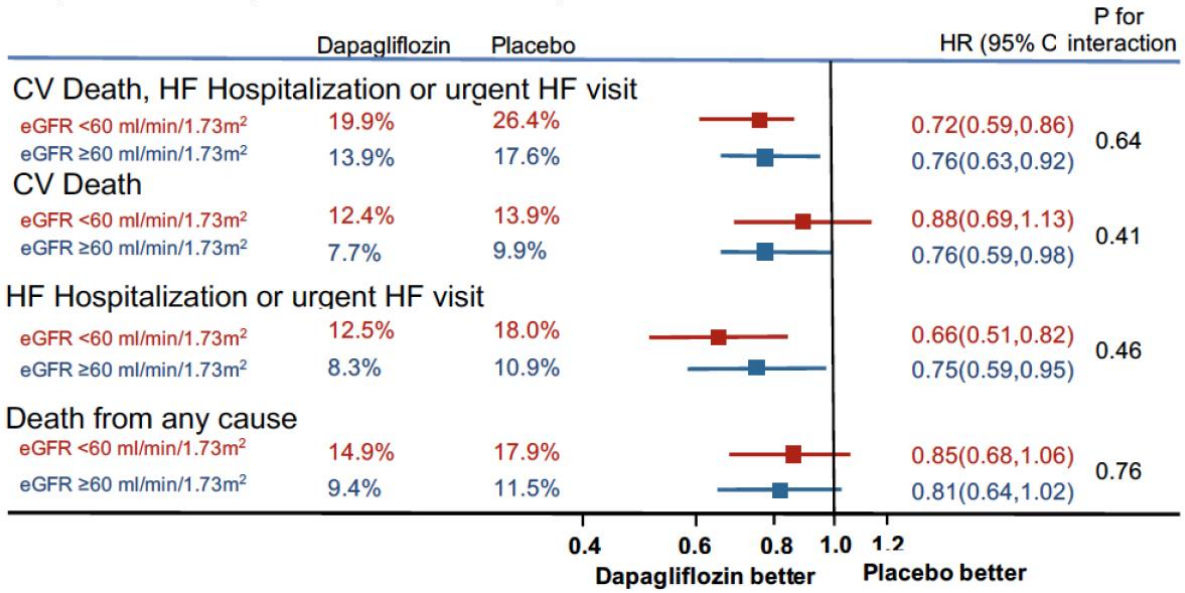
Source: AstraZeneca UK Ltd. Data on File. ID: REF-231259. May 2024.[68]

B.3.6.4.2 DAPA-HF

The incidence rates of the primary and secondary outcomes of the trial were higher in those with CKD at baseline. The efficacy of dapagliflozin in preventing the primary outcome of CV death or worsening HF did not differ between those with an eGFR of <60 mL/min/1.73m^2 and individuals with an eGFR ≥60 mL/min/1.73m^2 (p for interaction=0.64).[15] The efficacy of dapagliflozin in preventing CV death, HF hospitalisations, or urgent HF visits, the total HF hospitalisations and all-cause death also did not differ by eGFR group (Figure 20).

The incidence of the prespecified renal composite outcome was higher in the patients with lower eGFR at baseline than in those with an eGFR ≥60 mL/min/1.73m^2. Although the rate was lower in those randomly assigned to dapagliflozin, the difference was not statistically significant (HR: 0.71; 95% CI: 0.44, 1.16; p=0.17).[15]

Figure 20. Effect of dapagliflozin on the primary and secondary outcomes in DAPA-HF according eGFR group at baseline (*rate ratio and N provided for total hospitalizations or CV death outcome).



Abbreviations: CI: confidence interval; CV: cardiovascular; eGFR: estimated glomerular filtration rate; HF: heart failure; HR: hazard ratio.
Source: Jhund *et al*., 2020.[15]

B.3.6.4.3 Conclusions from subgroup analyses

The treatment effect observed in DAPA-CKD versus placebo is expected to be generalisable to patients in moderately increased uACR categories or below, and higher eGFR categories

Analyses from both DECLARE-TIMI 58 and DAPA-HF (which would have enrolled patients with a wide range of uACR categories) suggest that the treatment effect observed in DAPA-CKD extends to patients in lower uACR categories than patients enrolled in DAPA-CKD (i.e., with a uACR <200 mg/g [22.6 mg/mmol]: patients with less kidney damage). Overall, outcomes from DECLARE-TIMI-58 and DAPA-HF showed that dapagliflozin in combination with SoC was more effective than SoC alone across the CKD population, irrespective of uACR levels. Additionally, the subgroup analyses from both trials provide evidence that the treatment effect observed in DAPA-CKD extends to patients within higher eGFR categories (i.e., patients with better kidney function) than patients enrolled in DAPA-CKD (eGFR >75 mL/min/1.73m²).

Additionally, evidence from OPTIMISE-CKD demonstrates the consistent treatment effect of dapagliflozin irrespective of T2D status and uACR, thereby further validating the generalisability of the treatment effect observed in DAPA-CKD versus placebo to patients in lower uACR categories.

B.3.7 Subgroup analysis

As this evaluation is a cost-comparison based on the recommendation and decision-making in TA942, which did not consider subgroup analyses necessary for decision-making, no further subgroup analyses will be considered. Therefore, this section will not be populated for this appraisal.

B.3.8 Meta-analysis

This section will not be populated for this appraisal.

B.3.9 Indirect and mixed treatment comparisons

An ITC has not been conducted for this appraisal as one has already been conducted for TA942. The ITC via NMA of empagliflozin and dapagliflozin conducted as part of TA942 aimed to examine the relative efficacy of empagliflozin to comparators for the treatment of patients with CKD/diabetic kidney disease, with or without other comorbidities such as T2D or HF, and considered the effect of SGLT2 inhibitors on kidney disease progression for patients with prevalent CKD from multiple trials; subgroup analyses were not conducted. The results of the NMA were considered by the EAG, which reached the following conclusions[3]:

- "Empagliflozin was superior to placebo for some of the outcomes in the CKD + T2D subgroup and was non-inferior to dapagliflozin for all outcomes".

- "The NMA showed a borderline meaningful difference between empagliflozin and dapagliflozin for the composite renal outcome definition, in favour of dapagliflozin. For patients with CKD but without T2D there were no meaningful differences between dapagliflozin and empagliflozin" (emphasis in original).

The conclusion that the NMA demonstrated similar effectiveness and safety between dapagliflozin and empagliflozin was supported by a published meta-analysis showing that SGLT2 inhibitors reduce the risk of kidney disease progression by 37% and AKI by 23%, with similar effects in patients with and without diabetes.[17] The meta-analysis also demonstrated the safety of SGLT2 inhibitors at low levels of kidney function down to an eGFR of at least 20 mL/min/1.73 m^2 with patients without diabetes being at particularly low risk of ketoacidosis or amputation (whether receiving an SGLT2 inhibitor or not). As patients with decreased eGFR are at the highest absolute risk of kidney disease progression, outcomes from this meta-analysis should encourage the initiation of SGLT2 inhibitors in patients with CKD down to an eGFR of 20 20 mL/min/1.73 m^2 with continued use below this level.[17]

As a result of the above ITC, an ITC specific to the population being appraised has not been conducted for this appraisal. Producing an ITC in the specific sub-groups is not feasible due to the heterogeneity in populations enrolled in RCTs for SGLT2 inhibitors which has resulted in data availability restrictions: a lack of matched cohorts and comparable datasets for analysis precludes the execution of a robust ITC in the subgroups for consideration in this appraisal. Whilst a formal ITC

cannot be conducted, RWE demonstrating efficacy in these subgroups for dapagliflozin has been provided and naive comparisons (see below) versus the original source of data from DAPA-CKD and compared versus empagliflozin have been evaluated. The clinical similarity of dapagliflozin and empagliflozin in this population has already been acknowledged by NICE and confirmed by the clinical community in response to the draft scope.

B.3.9.1 Naïve comparison of dapagliflozin and empagliflozin HRs

As outlined in section B.2.1 Clinical outcomes and measuresB.2.1 Clinical outcomes and measures, the HR in patients with uACR <30 mg/mmol in the pivotal trial for empagliflozin, EMPA-KIDNEY, was 1.01 (CI: 0.66, 1.55) and fell outside of the CI for the HR for the overall trial population.[3] While the efficacy in this population may be less certain than the overall population, the clinical assessment in the overall population was deemed to be positive by NICE. In the DAPA-CKD post-hoc analysis, dapagliflozin significantly reduced eGFR by week 2, with no statistically significant difference in the different uACR groups without diabetes (uACR <30 mg/mmol: -2.4 mL/min/1.73 m^2; 95% CI: -4.5, -0.4; uACR ≥30 mg/mmol: -2.0 mL/min/1.73 m^2; 95%CI: -2.7, -1.3; p for interaction=0.46).[11] Additionally, RWE from OPTIMISE-CKD and Nakhleh *et al.,* 2024 demonstrated the consistent treatment effect of dapagliflozin with respect to eGFR slope and cardiorenal outcomes irrespective of uACR.[8-10]

B.3.10 Adverse reactions

Dapagliflozin and empagliflozin have been established to have similar safety profiles in the population in scope according to the ITC presented in TA942.[3] This has also been ratified by clinical experts who have responded to the draft scope consultation for this appraisal.

B.3.11 Conclusions about comparable health benefits and safety

Overall, the clinical evidence shows that dapagliflozin and empagliflozin have similar treatment effects in CKD patients with CKD, without T2D, with an eGFR between 20 and 45 mL/min/1.73m^2 and a uACR <22.6 mg/mmol (<200 mg/g), patients with CKD without T2D and an eGFR >75–90 mL/min/1.73m^2, and patients with CKD with T2D with an eGFR 20–25 mL/min/1.73m^2 or >75–90 mL/min/1.73m^2. The ITC presented as part of TA942 demonstrated no difference in clinical effectiveness between dapagliflozin and empagliflozin in patients without T2D and a naïve comparison of HRs from the DAPA-CKD post-hoc analysis and EMPA-KIDNEY in patients with uACR <30 mg/mmol favours dapagliflozin. RWE from OPTIMISE-CKD and Nakhleh *et al*., 2024, as well as subgroup analyses from DAPA-HF and DECLARE-TIMI 58, further support the use of dapagliflozin in a broad CKD population, including patients without T2D with normal to mildly increased uACR.

B.3.12 Ongoing studies

There are no ongoing studies of dapagliflozin relevant for this appraisal.

B.4 Cost-comparison analysis

B.4.1 Changes in service provision and management

No change in service provision and management is expected to result from this appraisal (see section B.4.6 Interpretation and conclusion of economic evidenceB.4.6 Interpretation and conclusion of economic evidence).

B.4.2 Cost-comparison analysis inputs and assumptions

A cost comparison analysis has not been conducted for this appraisal (see section B.4.6 Interpretation and conclusion of economic evidenceB.4.6 Interpretation and conclusion of economic evidence).

B.4.3 Base-case results

This section is not relevant for this decision problem.

B.4.4 Sensitivity and scenario analyses

This section is not relevant for this decision problem.

B.4.5 Subgroup analysis

This section is not relevant for this decision problem.

B.4.6 Interpretation and conclusion of economic evidence

A cost comparison of empagliflozin versus dapagliflozin has already been demonstrated in TA942 and a cost comparison approach has been accepted for decision making for this appraisal. In TA942, the cost comparison analysis conducted confirmed no meaningful differences in cost between the two treatments, and therefore it is assumed that a cost comparison analysis in this appraisal would result in a similar outcome. Therefore, a cost comparison analysis has not been conducted for this appraisal.

Dapagliflozin and empagliflozin are expected to have no differences in cost or resource use. The acquisition costs of dapagliflozin and empagliflozin are equivalent at £36.59 per pack, with no confidential commercial arrangements and the same method and frequency of administration.[21, 22] There is no difference in patient monitoring or follow-up, adverse events or patient adherence. The resource use of the population in scope is estimated to have no or negligible differential considering the clinical equivalence of dapagliflozin and empagliflozin,[3] therefore there is no expected change to service provision or management.

However, in patients with CKD with T2D, there is potential for empagliflozin to result in a higher cost than dapagliflozin to the NHS. The empagliflozin SmPC states that for patients with T2D "the recommended starting dose is 10 mg empagliflozin once daily for monotherapy and add-on combination therapy with other medicinal products for the treatment of diabetes. In patients tolerating empagliflozin 10 mg once daily who have an eGFR ≥60 mL/min/1.73 m^2 and need tighter glycaemic control, the dose can be increased to 25 mg once daily".[23] Therefore, these patients in clinical practice may have their dosing up-titrated to 25 mg once daily with associated additional SoC testing and potential primary care visit, while this dosing is 10 mg for dapagliflozin. Costs associated with up-titration can impact the overall cost-comparison between treatments. While up-titration of empagliflozin in this case is only relevant to patients who have T2D and require optimisation for glycaemia, and although posology in the non-T2D population for dapagliflozin and empagliflozin is similar (one tablet daily), these patients with T2D will require further interventions as their conditions are treated holistically in real world practice. Specifically, when eGFR drops below 60 mL/min/1.73 m^2, patients will need to be down-titrated to the 10 mg dose as the empagliflozin SmPC states that "in patients with an eGFR <60 mL/min/1.73 m^2 the daily dose of empagliflozin is 10 mg."[23]

On the other hand, dapagliflozin provides consistent and simple posology across the whole CKD population irrespective of T2D status, with the exception of patients with severe hepatic impairment who are initiated at 5 mg before increasing dose to 10 mg if tolerated, thereby alleviating pressure from an already burdened primary care system through the elimination of additional testing, patient visits, and clinician time.[1]

The clinical effectiveness of dapagliflozin is comparable to empagliflozin as demonstrated previously. Additionally, outcomes from recent RWE, combined with the subgroup analyses from DECLARE-TIMI 58, DAPA-HF and DAPA-CKD, demonstrate the benefit of dapagliflozin in the subgroups currently not included in the recommendation in TA775, and address the uncertainties that led to that recommendation, thereby eliminating the need for any restriction in the NICE recommendation.

Clinicians also acknowledge that the two drugs are clinically similar and therefore there is a need to have the recommendations aligned to alleviate any complexity and confusion around the prescribing particularly in primary care.[20] Additionally, guidelines used in UK clinical practice recommend both treatment options equally.[32, 65] In light of the recent RWE demonstrating consistent treatment effect irrespective of T2D status and uACR levels, and given the proven clinical similarity between dapagliflozin and empagliflozin via ITC in TA942 and previous appraisals, there is an opportunity to align the populations in the recommendations for the two therapies via cost comparison.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal: cost-comparison

Dapagliflozin for the treatment of adults with chronic kidney disease – Review of TA775 [ID6411]

Addendum

Company evidence submission

July 2024

File name	Version	Contains confidential information	Date
ID6411_Dapagliflozin_CKD_TA775 review_Addendum [CON]	Final	Yes	31st July 2024

Summary of evidence provided in this addendum

In response to the queries from the EAG, this response provides an overview of the data sources and available effect estimates for dapagliflozin in the specific subgroups of interest in this review of TA775 (Questions 1 and 2). In line with the submission, the data sources included for dapagliflozin in this review are: OPTIMISE–CKD (Svensson *et al.* 2024; Tangri *et al.* 2024), Nakhleh *et al.* 2024, DECLARE–TIMI 58, DAPA–HF and DAPA–CKD.[1-6]

Effect estimates for empagliflozin in each specific subgroup in this review are not publicly available. However, this response presents the totality of available evidence that demonstrates the consistency of the treatment effect of dapagliflozin across the subgroups, and the clinical equivalence of dapagliflozin and empagliflozin, using evidence on the mechanism of action (Question 4), clinical expert opinion (Question 3), meta-analyses and indirect treatment comparisons (ITCs; Questions 5 and 6). This response discusses evidence of the clinical equivalence of dapagliflozin and empagliflozin as treatments for chronic kidney disease (CKD), as well as other relevant indications (namely, type 2 diabetes [T2D] and heart failure [HF]).

To further support this response, a cost-comparison model has been developed (from the perspective of the UK National Health Service and Personal Social Services [NHS and PSS]), which demonstrates that empagliflozin and dapagliflozin are associated with equivalent costs when used as a treatment for CKD (Question 10). As such, dapagliflozin can be considered a clinically effective and safe treatment option in the specific subgroups of interest in this review, associated with equivalent costs as empagliflozin.

Alignment between dapagliflozin evidence and decision problem

The lack of detail provided in the CS makes it difficult to assess the extent to which the evidence for dapagliflozin provided by the company informs each of the outcomes listed in the NICE scope for:

- *the population as defined in the NICE scope*
- *the subgroups listed in the company's proposed positioning of dapagliflozin*

1. *Please provide precise information on:*
    a. *the number of study participants that fall within the subgroups listed in the company's proposed positioning of dapagliflozin, for each dapagliflozin study included in the CS (CS Document B, Table 6 may be used as a template);*
    b. *effect estimates for dapagliflozin and comparators specifically for these subgroups for all outcomes specified in the NICE scope, (e.g. from post–hoc analyses and using individual patient data where available).*
2. *In the absence of trial data or real–world evidence directly informing the subgroups listed in the company's decision problem, please provide a detailed and balanced discussion of the applicability of the submitted evidence to these subgroups, using appropriate evidence (e.g. from the broader literature on SLGT2 inhibitors).*

Overview of response

The aim of this submission is to review the current recommendation from the National Institute for Health and Care Excellence (NICE) for dapagliflozin in CKD and align it with the NICE recommendation for empagliflozin to ensure a unified approach in the treatment of CKD across different patient subgroups. Therefore, the subgroups within this targeted review have been identified on this basis (i.e., subgroups of patients which are currently recommended for empagliflozin in TA942, but not currently recommended for dapagliflozin in TA775), and therefore do not necessarily directly align with the populations within the presented studies supporting this submission. Nonetheless, there is a combination of randomised controlled trial (RCT) and real-world evidence (RWE) data which provides evidence of a consistent treatment effect in subgroups which includes those included within the scope of this review.

This targeted review addresses five subgroups:

Adults with CKD without T2D

- **Subgroup 1**: Adults with CKD without T2D and with an estimated glomerular filtration rate (eGFR) ≥20–45 mL/min/1.73m^2 and a urine albumin-creatinine ratio (uACR) <22.6 mg/mmol (200 mg/g)
- **Subgroup 2**: Adults with CKD without T2D and with an eGFR ≥20–25 mL/min/1.73m^2 and a uACR ≥22.6 mg/mmol (≥200 mg/g)
- **Subgroup 3**: Adults with CKD without T2D and an eGFR >75–90 mL/min/1.73m^2 and a uACR ≥22.6 mg/mmol (≥200 mg/g)

Adults with CKD with T2D

- **Subgroup 4:** Adults with CKD, with T2D, and with an eGFR ≥20–25 mL/min/1.73m^2 (irrespective of uACR)

- **Subgroup 5:** Adults with CKD, with T2D, and with an eGFR >75–90 mL/min/1.73m^2 (irrespective of uACR)

The combined evidence from DAPA–CKD, DAPA–HF, DECLARE–TIMI 58, OPTIMISE CKD and Nakhleh *et al*., 2024 demonstrates that dapagliflozin is associated with similar kidney protective effects among patients with CKD irrespective of T2D status, uACR category or eGFR category.[1-8] It is therefore reasonable to conclude that patients outside of the DAPA–CKD study eligibility criteria, including those captured in the five subgroups listed above, are expected to benefit from treatment with dapagliflozin. This is further supported by the scientific merit around the mechanism of action and the similarities of this between dapagliflozin and empagliflozin, alongside a consistent conclusion of similar clinical efficacy between both sodium-glucose co-transporter-2 (SGLT2) inhibitors, as evidenced by ITCs, including matching-adjusted indirect comparison (MAICs), for CKD and other indications, and further supported by expert clinical opinion and non-differentiation between SGLT2 inhibitors as a class within clinical guidelines (discussed in response to Questions 3, 4, 5 and 6).

This response focuses on the available evidence demonstrating the efficacy of dapagliflozin within each subgroup specifically. In response to Question 1, Table 1 outlines which studies provide effect estimates for each subgroup, with the corresponding number of study participants for each dapagliflozin study for each subgroup provided in Table 2. The following text provides effect estimates for dapagliflozin across the five specified subgroups. These estimates highlight dapagliflozin's consistent efficacy in CKD treatment, regardless of T2D status, uACR category and eGFR category. Detailed discussions on the available data for each subgroup are provided, which addresses the External Assessment Group's (EAG's) requests in Question 1b and Question 2. Effect estimates for empagliflozin in each subgroup are not provided in this response as they are not publicly available, but the available subgroup analyses which provide insight into the expected efficacy of empagliflozin in the relevant subgroups are summarised in the response to Question 5.

Table 1. Studies providing effect estimates relevant to the 5 subgroups addressed in this review

Study	Relevant eligibility criteria	Subgroup 1	Subgroup 2	Subgroup 3	Subgroup 4	Subgroup 5
		• Without T2D • eGFR ≥20–45 mL/min/1.73m^2 • uACR <22.6 mg/mmol	• Without T2D • eGFR ≥20–25 mL/min/1.73m^2 • uACR ≥22.6 mg/mmol	• Without T2D • eGFR >75–90 mL/min/1.73m^2 • uACR ≥22.6 mg/mmol	• With T2D • eGFR ≥20–25 mL/min/1.73m^2 • irrespective of uACR	• With T2D • eGFR >75–90 mL/min/1.73m^2 • irrespective of uACR
OPTIMISE–CKD (Svensson et al 2024)[1]	• Without T2D (supportive analysis with T2D) • uACR unrestricted • eGFR 15–60 mL/min/1.73 m^2 • Dapagliflozin initiators only	**Yes** *for eGFR 15–60 mL/min/1.73 m^2*	**Yes** *for eGFR 15–60 mL/min/1.73 m^2*	N/A	**Yes** *for eGFR 15–60 mL/min/1.73 m^2*	N/A
OPTIMISE–CKD (Tangri et al 2024)[2]	• without T2D • uACR of 3-22.6 mg/mmol (30-200 mg/g) • eGFR 25–60 mL/min/1.73 m^2 • Dapagliflozin initiators and matched non-initiators	**Yes** *for eGFR 25–60 mL/min/1.73 m^2 and uACR of 3-22.6 mg/mmol*	N/A	N/A	N/A	N/A
Nakhleh et al 2024[3]	• without T2D • uACR unrestricted • eGFR 25–60 mL/min/1.73 m^2 • SGLT2i initiators only	**Yes** •*for eGFR 25–60 mL/min/1.73 m^2 and uACR of either <3 or 3–30 mg/mmol*	N/A	N/A	N/A	N/A
DECLARE–TIMI 58[4]	• with or without T2D • uACR unrestricted • Creatinine clearance >60 mL/min[a]	N/A	N/A	N/A	N/A	**Yes** *for eGFR ≥60–<90 mL/min/1.73m^2*
DAPA–HF[5]	• with or without T2D • uACR unrestricted • eGFR >30 mL/min/1.73 m^2	N/A	N/A	**(Yes)[b]** *for eGFR ≥60 mL/min/1.73 m^2 irrespective of uACR or T2D*	N/A	**(Yes)[b]** *for eGFR ≥60 mL/min/1.73 m^2 irrespective of uACR or T2D*
DAPA–CKD[6]	• with or without T2D • uACR 22.6–565 mg/mmol (200–5,000 mg/g) • eGFR 25–75 mL/min/1.73 m^2	**Yes** *for eGFR 25–75 mL/min/1.73 m^2 and uACR of 3–<30 mg/mmol*	N/A	N/A	N/A	N/A

Footnotes: [a] Patients discontinued treatment with dapagliflozin if creatinine clearance fell below 30 ml/min/1.73 m^2. [b] While the results of the DAPA–HF study are not reported separately by T2D status and eGFR category, this study enrolled a substantial number of patients with an eGFR ≥60 mL/min/1.73m^2 both with and without T2D (n=1,157 patients with eGFR ≥60 mL/min/1.73m^2 and T2M at baseline, n=1,659 patients with eGFR ≥60 mL/min/1.73m^2 without T2M at baseline) and did not restrict enrolment by uACR

category. As such, effect estimates provided for the eGFR ≥60 mL/min/1.73m^2 subgroup represent a group of patients with a range of uACR categories, including a proportion of patients with uACR ≥22.6 mg/mmol.[5]
Abbreviations: eGFR: estimated glomerular filtration rate; N/A: not applicable; T2D: type 2 diabetes; uACR: urine albumin–creatinine ratio.

Table 2. Number of study participants that fall within the subgroups in the decision problem

Study	Subgroup 1 • Without T2D • eGFR ≥20–45 mL/min/1.73m^2 • uACR <22.6 mg/mmol	Subgroup 2 • Without T2D • eGFR ≥20–25 mL/min/1.73m^2 • uACR ≥22.6 mg/mmol	Subgroup 3 • Without T2D • eGFR >75–90 mL/min/1.73m^2 • uACR ≥22.6 mg/mmol	Subgroup 4 • With T2D • eGFR ≥20–25 mL/min/1.73m^2 • irrespective of uACR	Subgroup 5 • With T2D • eGFR >75–90 mL/min/1.73m^2 • irrespective of uACR
OPTIMISE–CKD (Svensson et al 2024)[1]	**Dapagliflozin n=796** *eGFR 15–60 mL/min/1.73 m^2 and uACR 3–22.6 mg/mmol (30–200 mg/g)*	**Dapagliflozin n=648** *eGFR 15–60 mL/min/1.73 m^2*	N/A	**Dapagliflozin n=4,394[a]** *eGFR 15–60 mL/min/1.73m^2*	N/A
OPTIMISE–CKD (Tangri et al 2024)[2]	**Dapagliflozin n=275** **SOC n=275** *eGFR 25–60 mL/min/1.73 m^2 and uACR 3-22.6 mg/mmol (30-200 mg/g)*	N/A	N/A	N/A	N/A
Nakhleh et al 2024[3]	**Dapagliflozin n=146** *eGFR 25–60 mL/min/1.73 m^2 and uACR <30 mg/g* **Dapagliflozin n=81** *eGFR 25–60 mL/min/1.73 m^2 and uACR 30–300 mg/g*	N/A	N/A	N/A	N/A
DECLARE–TIMI 58[4]	N/A	N/A	N/A	N/A	**Dapagliflozin n=3,838** **Placebo n=3,894** *eGFR ≥60–<90 mL/min/1.73m^2*
DAPA–HF[5]	N/A	N/A	**Dapagliflozin n=1,410** **Placebo n=1,406** • *eGFR ≥60 mL/min/1.73m^2* • *irrespective of T2D or UACR*	N/A	**Dapagliflozin n=1,410** **Placebo n=1,406** • *eGFR ≥60 mL/min/1.73m^2* • *irrespective of T2D or UACR*
DAPA–CKD[6]	**Dapagliflozin n=69** **Placebo n=63** *eGFR 25–75 mL/min/1.73 m^2 and uACR 3–<30 mg/mmol*	N/A	N/A	N/A	N/A

Footnotes: [a] Results are reported separately by uACR category. n=2,411 patients with T2D and uACR <22.6 mg/mmol; n=1,983 patients with T2D and uACR ≥22.6 mg/mmol.
Abbreviations: eGFR: estimated glomerular filtration rate; N/A: not applicable; T2D: type 2 diabetes; SOC: standard of care; uACR: urine albumin–creatinine ratio.

Subgroup 1: Adults with CKD without T2D and with an eGFR ≥20–45 mL/min/1.73m² and a uACR <22.6 mg/mmol (<200 mg/g)

Subgroup 1 consists of adults with a lower uACR than the enrolment criteria in DAPA–CKD. Direct effect estimates for dapagliflozin from clinical trials or real-world evidence are not available for this specific subgroup. However, subgroup analyses of DAPA-CKD and DECLARE-TIMI 58 strongly suggest that dapagliflozin's kidney protective benefits are consistent regardless of uACR category and therefore extend to this subgroup (see Supporting Data).

Specific evidence from the DAPA-CKD, DECLARE-TIMI 58 and OPTIMISE CKD studies further suggest that dapagliflozin's kidney protective benefits extend to this subgroup of patients, and provides effect estimates for dapagliflozin in patients with a wider range of uACR categories than were included in the DAPA-CKD study. For example:

- **DAPA–CKD post–hoc subgroup analysis**: a post-hoc analysis of DAPA-CKD demonstrated that dapagliflozin effectively slowed eGFR decline in a subgroup of patients without T2D with a uACR of 3–<30 mg/mmol (30–<300 mg/g) and eGFR of 25–75 mL/min/1.73 m^2: a between-group difference in eGFR decline of 1.8 ml/min/1.73m² per year (95% CI 0.4 to 3.1) was reported for dapagliflozin vs placebo in this subgroup.[6]

- **OPTIMISE–CKD**:
    - In an analysis of 275 dapagliflozin initiators and 275 matched non-initiators without T2D with an eGFR of 25–60 mL/min/1.73 m^2 and a uACR 3–22.6 mg/mmol (30-200 mg/g), initiation of dapagliflozin was associated with clinically meaningful attenuation of eGFR decline compared with non–initiation (eGFR slope difference 1.28 [95% CI: –1.56 to 4.12] mL/min/1.73m^2/year).[2]
    - An analysis of 796 dapagliflozin initiators without T2D with an eGFR of 15–60 mL/min/1.73 m^2 and uACR of 3–22.6 mg/mmol (30–200 mg/g) demonstrated a flat eGFR slope after initiation of dapagliflozin (0.79 mL/min/1.73m^2 per year [95% CI: –0.59 to 2.56]).[1]
- **Nakhleh et al 2024**:
    - Analysis of de-identified data from Israeli patients with CKD without T2D and with an eGFR of 25–60 mL/min/1.73 m^2 demonstrated that SGLT2 inhibitor administration was associated with a decrease in eGFR slope across uACR subgroups, including <3 and <3–30 mg/mmol (<30 and <30–300 mg/g) subgroups.[3]
    - SGLT2 inhibitor administration was also associated with an 87.6% reduction in eGFR slope (mean change: 5.67 [95% CI: 4.03 to 7.30] mL/min/1.73 m^2 per year) among patients with an eGFR of 25–45 mL/min/1.73 m^2 (regardless of uACR).[3]

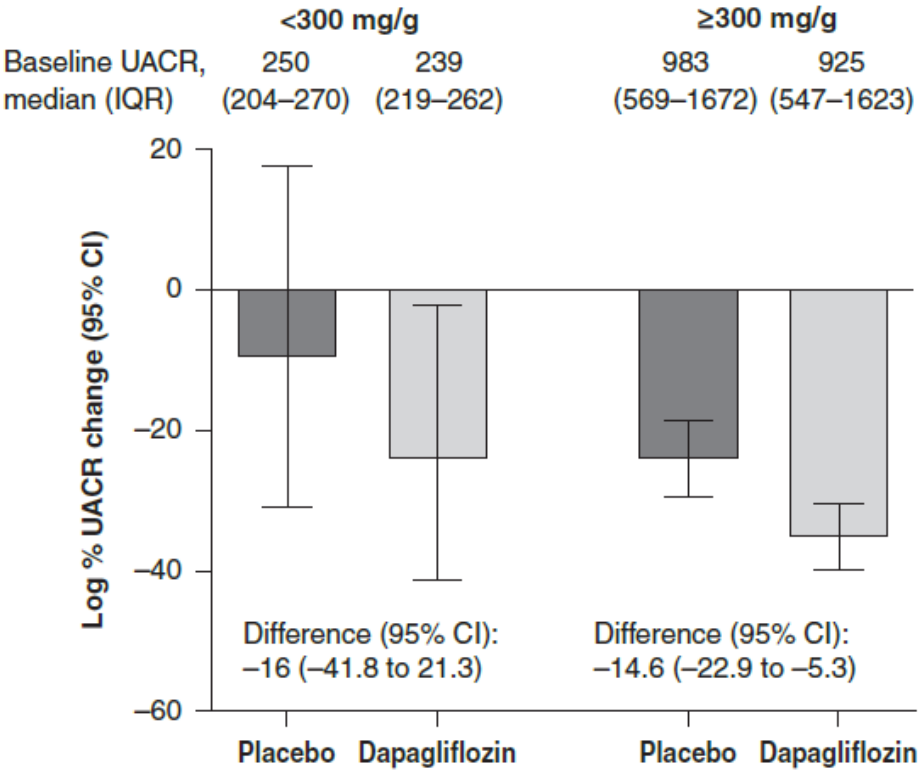
These results are presented in more detail in the following sections.

DAPA–CKD[6]

A post–hoc subgroup analysis of the Phase III DAPA–CKD RCT (n=1,398) provides an effect estimate for eGFR slope and uACR decline among patients without T2D with a uACR of 3–<30 mg/mmol (30–<300 mg/g) and eGFR of 25–75 mL/min/1.73 m^2, and demonstrates a consistent treatment effect of dapagliflozin across uACR subgroups:

- eGFR slope: Among patients with uACR 3–<30 mg/mmol (30–<300 mg/g; n=136, including 24 patients with a uACR of 3–<22.6 mg/mmol [30–<200 mg/g] at baseline), dapagliflozin resulted in a slower decline in chronic eGFR slope compared with placebo: between–group difference in eGFR decline after Week 2 was 1.8 ml/min per 1.73 m^2 per year (95% CI, 0.4 to 3.1).
    - The treatment effect of dapagliflozin in reducing eGFR decline was consistent regardless of uACR category: the between–group difference in eGFR decline for dapagliflozin vs placebo after Week 2 among patients with uACR ≥30 mg/mmol (≥300 mg/g; n=1,262) was 1.2 ml/min per 1.73 m^2 per year (95% CI, 0.6 to 1.8; p–value for interaction 0.36).
    - The effect of dapagliflozin on eGFR change from baseline to Week 2 was also similar across uACR subgroups (−2.4 mL/min/1.73m^2; 95% CI: −4.5 to −0.4 vs −2.0 mL/min/1.73m^2; 95% CI: −2.7 to −1.3; for patients with uACR 3–<30 mg/mmol and ≥30mg/mmol respectively. P value for interaction=0.46).
- uACR decline: among patients with uACR 3–<30 mg/mmol (30–<300 mg/g; n=136, including 24 patients with a uACR of 3 to <22.6 mg/mmol at baseline), the percentage reduction in uACR was 16% (95% CI, –21 to 42).
    - The treatment effect of dapagliflozin on uACR reduction was consistent regardless of uACR category (Figure 1).

Figure 1. Effects of dapagliflozin on albuminuria in a post-hoc analysis of DAPA-CKD



Abbreviations: CI: confidence interval; IQR: interquartile range; uACR: urine albumin–to–creatinine ratio.
Source: Heerspink *et al.,* 2022.[6]

OPTIMISE–CKD

As outlined in Document B, Section B.3.3.2, the OPTIMISE-CKD programme is a multinational, observational, longitudinal cohort study that uses data extracted from electronic health records and claims data sources. The overall study objective is to describe the management and treatment with dapagliflozin in routine clinical practice among patients with CKD, with and without T2D across the uACR spectrum, as well as facilitating assessment of the real-world effectiveness of dapagliflozin. Two analyses of the data extracted are presented in this response: Tangri et al. 2024 (comparative effectiveness study: dapagliflozin initiators vs matched non-initiators)[2] and Svensson et al. 2024[1] (dapagliflozin initiators only).

These complementary analyses were conducted separately due to the challenges associated with assessing the real-world effectiveness of dapagliflozin across the uACR spectrum, including limited availability of registry data with sufficient follow-up after the approval of dapagliflozin for CKD in 2021, limited availability of registry data for patients without T2D that included uACR measurements (due to limited recording of uACR in clinical practice), the lack of a natural comparator for dapagliflozin in CKD at the time the study was conducted and the existing approvals for and widespread use of dapagliflozin to treat T2D and HF (populations which include a high proportion of patients with CKD) prior to the approval of dapagliflozin in CKD. Conducting a comparative effectiveness study with an untreated comparator group (Tangri et al 2024) and a second innovative effectiveness study comparing the effectiveness of dapagliflozin in low vs high uACR subgroups of non-diabetic patients (based on the assumption that dapagliflozin's kidney-protective effect in patients with CKD without T2D and high UACR from DAPA-CKD translates into a real-world setting) was the most suitable way to demonstrate the effectiveness of dapagliflozin in patients without T2D.

Tangri et al. 2024[2]

The first study from OPTMISE–CKD included data from patients in the US and Japan who either initiated dapagliflozin or were eligible to initiate dapagliflozin during the study period to describe the real–world utilisation of dapagliflozin following its approval for the CKD indication, and to assess the effect of initiating versus not initiating dapagliflozin on kidney function decline in patients with uACR <22.6 mg/mmol (<200 mg/g). The study period for the effectiveness analysis was from 30 August 2020 (i.e. the first release of the DAPA-CKD results) until the end of the data available for each dataset, and the study population included patients with or without T2D, with an eGFR of 25–60 mL/min/1.73 m^2 and a uACR of 3–22.6 mg/mmol (30-200 mg/g).

While results are not reported specifically for patients without T2D with an eGFR ≥20–45 mL/min/1.73m^2 and a uACR <22.6 mg/mmol (<200 mg/g), this analysis provides an effect estimate for eGFR slope among patients without T2D with a uACR of 3-22.6 mg/mmol (30-200 mg/g) and eGFR 25–60 mL/min/1.73 m^2, and also suggests that the treatment effect of dapagliflozin is consistent across uACR subgroups:

- Among the subgroup of patients without T2D with a uACR 3–22.6 mg/mmol (30-200 mg/g; n=275 dapagliflozin initiators; n=275 matched non–initiators) initiation of dapagliflozin was associated with clinically meaningful attenuation of eGFR decline

compared with non-initiation; eGFR slope difference 1.28 (95% CI: –1.56, 4.12) mL/min/1.73m^2/year.

- This was similar to the overall study population of patients with a uACR 3-22.6 mg/mmol (30-200 mg/g) with or without T2D (n=2,972 dapagliflozin initiators; n=2,972 matched non–initiators): initiation of dapagliflozin was associated with an eGFR slope difference of 1.07 (95% CI: 0.40 to 1.74) mL/min/1.73m^2/year compared with non-initiation in this subgroup.
- Given the small sample size for patients with uACR 3–22.6 mg/mmol (30-200 mg/g; n=275) without T2D, a post–hoc analysis was also performed which used information from the total cohort of patients with uACR 3–22.6 mg/mmol (30-200 mg/g) (i.e. including patients with T2D) to inform estimates of treatment effect among patients without T2D. Results from this analysis found that a weight of 30% on the information from the total cohort was sufficient to result in a significant effect of dapagliflozin initiation (versus non–initiation) on eGFR slope in patients without T2D (1.09 mL/min/1.73m^2 per year; 95% credibility interval: 0.02, 2.51).

Svensson et al. 2024[1]

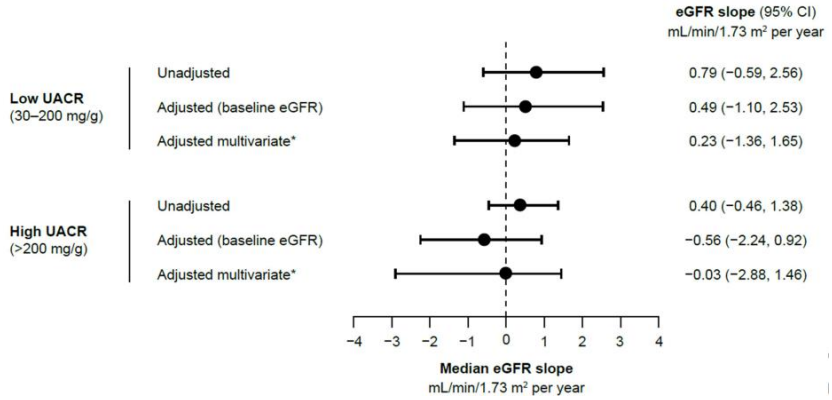
The second observational study as part of OPTIMISE–CKD included data from US patients with CKD without T2D and with an eGFR of 15–60 mL/min/1.73 m^2 who initiated dapagliflozin 10 mg between 30th April 2021 and 31st March 2023 (i.e. after the approval of dapagliflozin for CKD) to compare estimated eGFR trajectories, eGFR slopes and cardiorenal and all–cause mortality outcomes of dapagliflozin 10 mg in patients with low 3–<22.6 mg/mmol (30–200 mg/g) versus high >22.6 mg/mmol (>200 mg/g) uACR during the 12 months after the index date; a supplementary analysis also included patients with uACR of 0–2.9 mg/mmol (0–29 mg/g) within the “low” uACR subgroup, this group in the publication are defined as normal/mildly elevated uACR. The results with this group included in the supplementary information. An additional supportive analysis also enrolled patients with T2D. While results are not reported separately for patients without T2D with an eGFR ≥20–45 mL/min/1.73m^2 and a uACR <22.6 mg/mmol (200 mg/g) specifically, this analysis provides an effect estimate for eGFR slope among individuals without T2D with a uACR of 3–22.6 mg/mmol (30–200 mg/g) and an eGFR 15–60 mL/min/1.73 m^2, and also suggests that the treatment effect of dapagliflozin is consistent across uACR subgroups:

- eGFR slope for patients without T2D with a uACR of 3–22.6 mg/mmol (30–200 mg/g; n=796) was flat at 0.79 mL/min/1.73m^2 per year (95% CI: –0.59 to 2.56), suggesting a beneficial effect of dapagliflozin in slowing renal decline.
    - This was similar to the eGFR slope observed among patients without T2D with a uACR >22.6 mg/mmol (>200 mg/g; n=684; 0.40 mL/min/1.73m^2 [95% CI: 0.46 to 1.38]); Figure 2)
    - A supplementary analysis which included patients with uACR of 0–2.9 mg/mmol (0–29 mg/g) within the “low” uACR subgroup (i.e. comparing patients with a uACR of <22.6 mg/mmol [<200 mg/g] vs a uACR of >22.6 mg/mmol [>200 mg/g]) also demonstrated no significant difference in the treatment effect of dapagliflozin between uACR subgroups (Figure 3).
- The risks of hospitalisation for cardiorenal complications over 12 months of follow up were similarly consistent among patients with a uACR of 3–22.6 mg/mmol (30–200 mg/g) compared with patients with a uACR of >22.6 mg/mmol (>200 mg/g; Figure 4) using both broad (patients with a diagnosis of cardiorenal complication (CKD or HF) in an in–hospital setting) and strict (restricted to patients with a hospital admission where a

cardiorenal complication was the main diagnosis) definitions of cardiorenal hospitalisation.

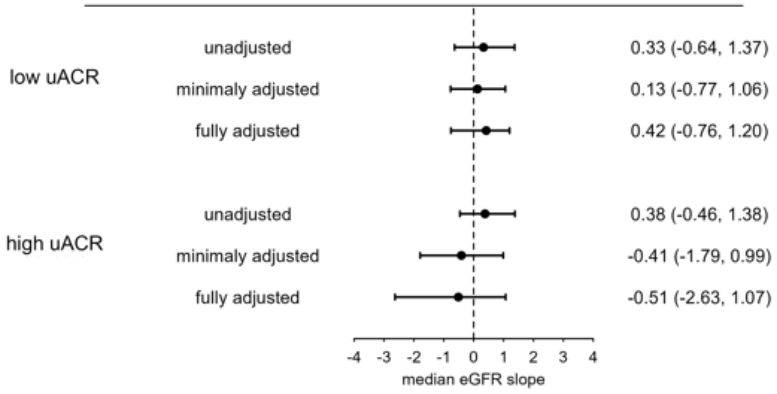
- A supplementary analysis which included patients with uACR of 0–2.9 mg/mmol (0–29 mg/g) within the "low" uACR subgroup (i.e. comparing patients with a uACR of <22.6 mg/mmol [<200 mg/g] vs a uACR of >22.6 mg/mmol [>200 mg/g]) also demonstrated no significant difference in the risk of cardiorenal hospitalisation or all-cause mortality between uACR subgroups.
- Given that dapagliflozin was associated with a significant reduction in cardiorenal complications among patients with a uACR of >22.6 mg/mmol (>200 mg/g in the DAPA-CKD trial), the similarities in cardiorenal complications and all-cause mortality between the low and high uACR groups in the OPTIMISE study suggest that the cardiorenal protective effects of dapagliflozin may extend to patients with a uACR of <22.6 mg/mmol (>200 mg/g).

Figure 2. eGFR slopes in patients with CKD and without T2D initiated with dapagliflozin, uACR ≥ 3 mg/mmol (30mg/g).



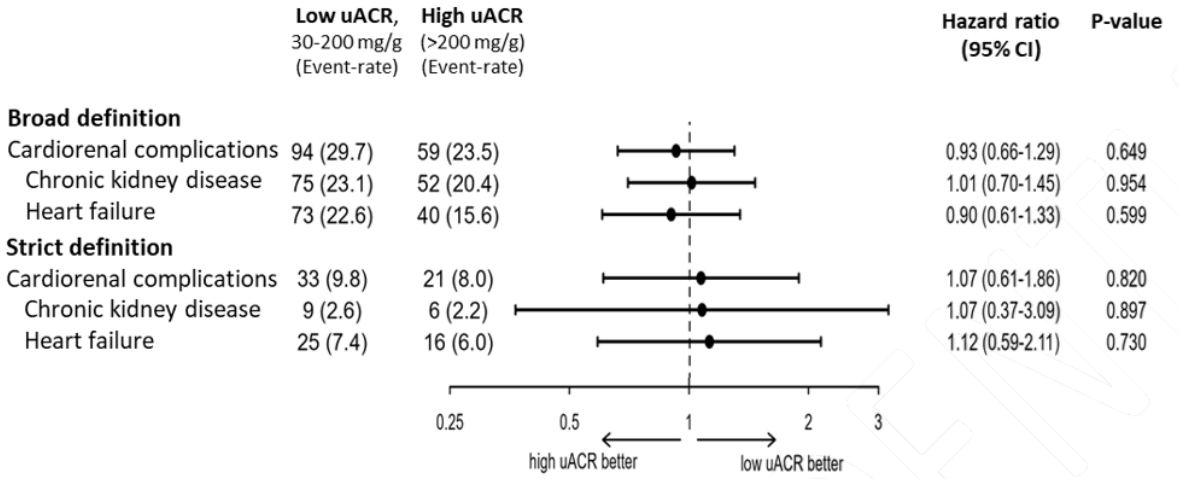
Footnotes: * Adjusted for baseline eGFR, age and sex, HF and RASi.
Abbreviations: CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; HF: heart failure; RASi: renin–angiotensin system inhibitor; T2D: type 2 diabetes; uACR: urine albumin–creatinine ratio.
Source: Svensson *et al*., 2024.[1]

Figure 3. eGFR slopes in patients with CKD and without T2D initiated with dapagliflozin



Footnotes: low uACR: 0–22.6 mg/mmol (0–200 mg/g), high uACR: >22.6 mg/mmol (>200 mg/g).
Abbreviations: CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; HF: heart failure; RASi: renin–angiotensin system inhibitor; T2D: type 2 diabetes; uACR: urine albumin–creatinine ratio.
Source: Svensson *et al*., 2024.[1]

Figure 4. Risk of cardiorenal hospitalisation in patients with CKD and without T2D initiated with dapagliflozin



Footnotes: Broad definition: patients with a diagnosis of cardiorenal complication (CKD or HF) in an in–hospital setting. Strict definition: restricted to patients with a hospital admission where a cardiorenal complication was the main diagnosis. The diagnosis of CKD includes diagnoses of acute kidney failure, unspecified kidney failure, diabetic kidney disease, hypertensive CKD, dialysis, glomerular diseases, renal tubulointerstitial disease, or other. Adjusted for age and sex, history of MI, stroke, peripheral artery disease, atrial fibrillation, HF, RAS inhibitors.
Abbreviations: CI: confidence interval; CKD: chronic kidney disease; HF: heart failure; MI: myocardial infarction; T2D: type 2 diabetes; uACR, urine albumin–creatinine ratio.
Source: Svensson *et al*., 2024. Supplementary material.[1]

Nakhleh et al. 2024[3]

The observational study published by Nakhleh et al. (2024) aimed to assess the real–world effectiveness of SGLT2 inhibitors (dapagliflozin or empagliflozin) in patients with CKD, without T2D and with an eGFR of 25–60 mL/min/1.73 m^2 using de–identified Israeli patient data; 267 participants (75.4%) were started on dapagliflozin, the remaining 87 (24.6%) received empagliflozin. While results are not reported separately for patients without T2D with an eGFR ≥20–45 mL/min/1.73m^2 and a uACR <22.6 mg/mmol (<200 mg/g) specifically, this analysis provides an effect estimate for eGFR slope among patients without T2D with a uACR of <3 or 3–30 mg/mmol (<30 or 30–300 mg/g) and an eGFR 25–60 mL/min/1.73 m^2, as well as among patients without T2D and with eGFR 25–45 mL/min/1.73 m^2 regardless of uACR category, and also suggests that the treatment effect of dapagliflozin is consistent across uACR subgroups.

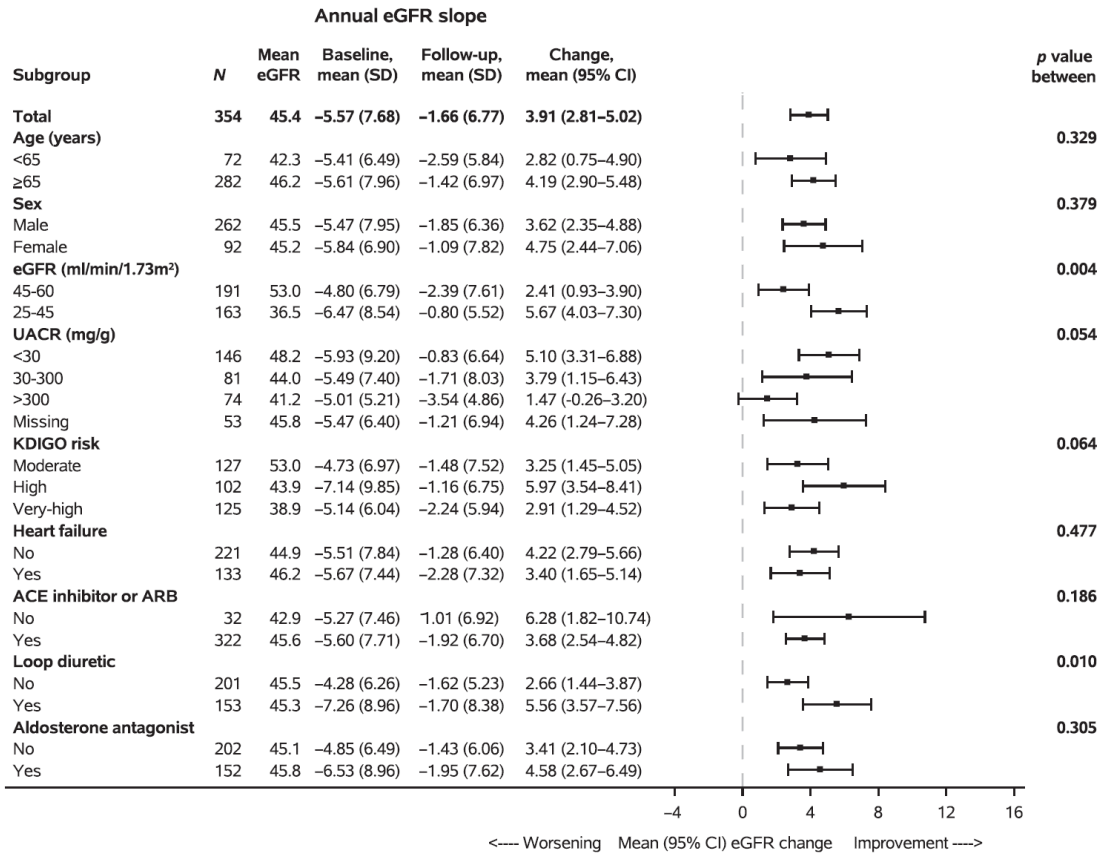
The study included patients with a wide range of uACR measurements, and reported effect estimates by uACR category (53 patients were missing a uACR measurement):

- Among patients with an eGFR of 25–60 mL/min/1.73 m^2, SGLT2 inhibitor administration was associated with a decrease in eGFR slope in all uACR subgroups, including the <3 and 3–30 mg/mmol (<30 and 30–300 mg/g) subgroups most relevant to subgroup 1 (Figure 5).
    - uACR <3 mg/mmol (<30 mg/g; n=146): 86.0% reduction in eGFR slope after SGLT2 inhibitor administration (mean change: 5.10; 95% CI: 3.31 to 6.88 mL/min/1.73 m^2 per year)
    - uACR of 3–30 mg/mmol (30–300 mg/g; n= 81): 69.0% reduction after SGLT2 inhibitor administration (mean change: 3.79; 95% CI: 1.15 to 6.43 mL/min/1.73 m^2 per year)

- uACR >30 mg/mmol (>300 mg/g; n=74): 29.3% reduction after SGLT2 inhibitor administration (mean change: 1.47; 95% CI: –0.26 to 3.20 mL/min/1.73 m^2 per year)
- Although the eGFR slope decrease was numerically greater among patients with lower uACR compared with patients with higher uACR, this difference was not statistically significant (p–value between subgroups =0.054)

- Among patients with an eGFR of 25–45 mL/min/1.73 m^2 regardless of uACR, SGLT2 inhibitor administration was associated with an 87.6% reduction in eGFR slope (mean change: 5.67 (95% CI: 4.03 to 7.30) mL/min/1.73 m^2 per year (Figure *5*).

Figure 5. Forest plot of change in eGFR slope from baseline to follow–up



Footnote: Differences between subgroups were assessed using a one–way analysis of variance test. A p value <0.05 was considered statistically significant.
Abbreviations: ACE: angiotensin–converting–enzyme; ARB: angiotensin II receptor blocker; CI: confidence interval; eGFR: estimated glomerular filtration rate; KDIGO: Kidney Disease: Improving Global Outcomes; SD: standard deviation; uACR: urine albumin to creatinine ratio.
Source: Nakhleh *et al.,* 2024.[3]

Subgroup 2: Adults with CKD without T2D and with an eGFR ≥20–25 mL/min/1.73m^2 and a uACR ≥22.6 mg/mmol (≥200 mg/g)

Subgroup 2 consists of adults with a lower eGFR than patients enrolled in DAPA–CKD. Direct effect estimates for dapagliflozin from clinical trials or real-world evidence are not available for this specific subgroup. However, subgroup analyses of DAPA-CKD and DECLARE-TIMI 58 strongly suggest that dapagliflozin's kidney protective benefits are consistent regardless of eGFR category and therefore extend to this subgroup (see Supporting Data).

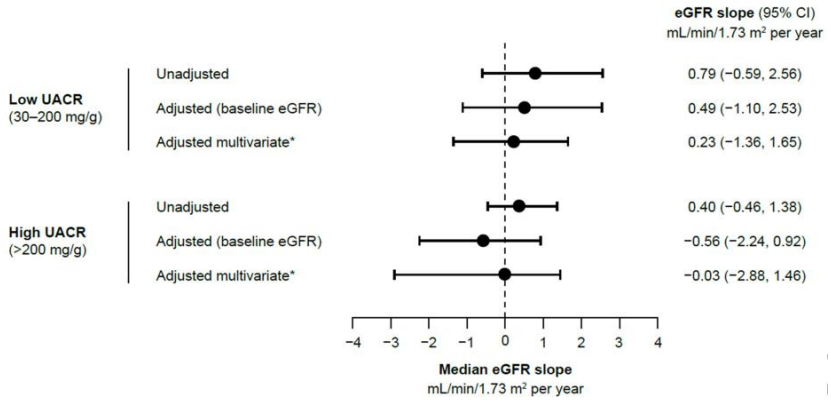
Evidence from the OPTIMISE CKD study further suggests that dapagliflozin's kidney protective benefits extend to this subgroup of patients, and provides an effect estimate for dapagliflozin in patients with a wider range of eGFR categories than were included in the DAPA-CKD study, as outlined below. Specifically, in an analysis of 684 dapagliflozin initiators without T2D with an eGFR 15–60 mL/min/1.73 m^2 and a uACR of >22.6 mg/mmol (>200 mg/g), a flat eGFR slope of 0.40 mL/min/1.73m^2 (95% CI: 0.46 to 1.38) was observed after dapagliflozin initiation.[1]

OPTIMISE–CKD (Svensson et al. 2024)[1]

While the results of the OPTIMISE-CKD study are not reported separately for patients without T2D with an eGFR 20–25 mL/min/1.73 m^2 and a uACR of ≥22.6 mg/mmol (≥200 mg/g) specifically, this analysis provides an effect estimate for eGFR slope among patients without T2D with an eGFR 15–60 mL/min/1.73 m^2 and a uACR of >22.6 mg/mmol (>200 mg/g):

- eGFR slope after dapagliflozin initiation was flat at 0.40 mL/min/1.73m^2 (95% CI: 0.46, 1.38) for patients without T2D with a uACR of >22.6 mg/mmol (>200 mg/g; n=684), suggesting a beneficial effect of dapagliflozin in slowing renal decline.
- This was similar to the eGFR slope observed among patients with uACR 3–22.6 mg/mmol (30–200 mg/g; n=796) of 0.79 mL/min/1.73m^2 per year (95% CI: –0.59, 2.56; Figure 6).

Figure 6. eGFR slopes in patients with CKD and without T2D initiated with dapagliflozin, uACR ≥ 3 mg/mmol (30mg/g)



Footnotes: * Adjusted for baseline eGFR, age and sex, HF and RASi.
Abbreviations: CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; HF: heart failure; RASi: renin–angiotensin system inhibitor; T2D: type 2 diabetes; uACR: urine albumin–creatinine ratio.
Source: Svensson *et al*., 2024.[1]

Subgroup 3: Adults with CKD without T2D and an eGFR >75–90 mL/min/1.73m² and a uACR ≥22.6 mg/mmol (≥200 mg/g)

Subgroup 3 consists of adults with a higher eGFR than patients enrolled in DAPA–CKD. Direct effect estimates for dapagliflozin from clinical trials or RWE are not available for this specific subgroup. However, subgroup analyses from DAPA–CKD, DAPA–HF and DECLARE–TIMI 58 indicate that the efficacy of dapagliflozin is consistent across various eGFR categories and therefore strongly suggest that dapagliflozin's kidney protective benefits extend to this subgroup (see Supporting Data).

In addition, specific evidence from the DAPA-HF study further suggests that dapagliflozin's treatment effect is consistent in this subgroup of patients. While the results of the DAPA–HF study are not reported separately by T2D status and eGFR category, this study enrolled a substantial number of patients with an eGFR ≥60 mL/min/1.73m^2 both with and without T2D. As such, DAPA-HF provides effect estimates for dapagliflozin in patients with a wider range of eGFR categories than were included in the DAPA-CKD study. Given that DAPA-HF did not restrict enrolment by uACR category, these effect estimates are from a group of patients which includes a proportion of patients with uACR ≥22.6 mg/mmol, making them relevant to subgroup 3.[5]

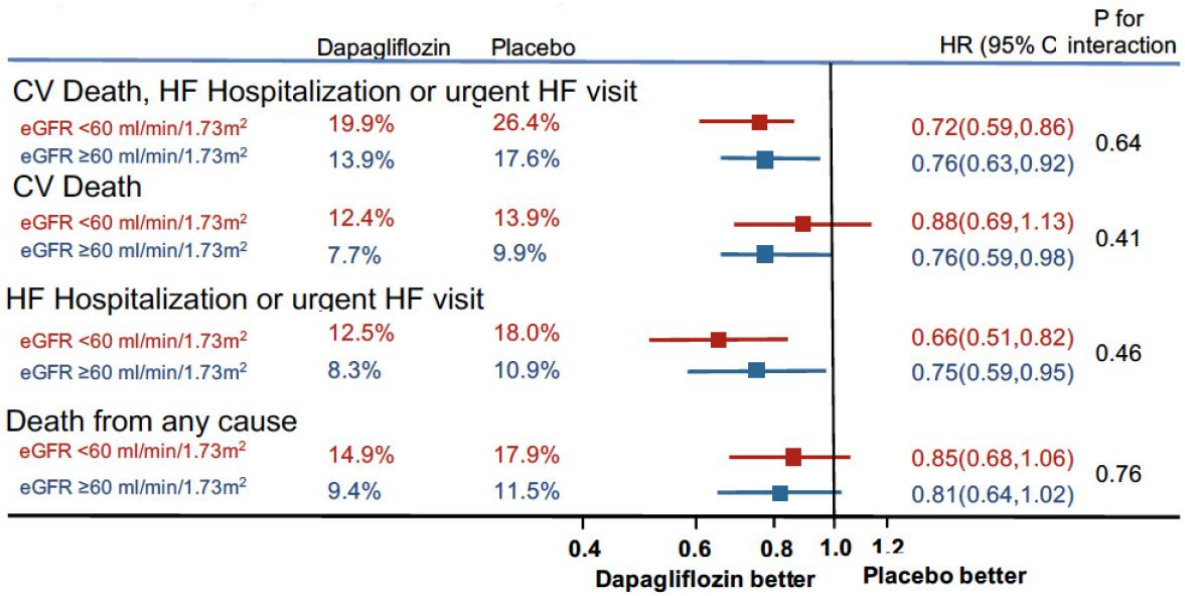
DAPA-HF[5]

The Phase III DAPA-HF RCT (n=4,743) enrolled patients with HF with reduced ejection fraction (HFrEF) and an eGFR of ≥30 mL/min/1.73m^2, regardless of the presence or absence of comorbid T2D. As outlined above, DAPA-HF enrolled a substantial number of patients with an eGFR ≥60 mL/min/1.73m^2 (n=2,816, 59%) both with and without T2D (n=1,157 patients with eGFR ≥60 mL/min/1.73m^2 and T2M at baseline, n=1,659 patients with eGFR ≥60 mL/min/1.73m^2 without T2M at baseline).

A clear treatment benefit for dapagliflozin was observed among patients with eGFR ≥60 mL/min/1.73m^2 (n=2,816) for the primary outcome of cardiovascular (CV) death or worsening HF, as well as other outcomes including CV death, hospitalisation for HF or urgent HF visit, or death from any cause (Figure 7). The efficacy of dapagliflozin in preventing the primary outcome of CV death or worsening HF, as well as other outcomes including CV death, hospitalisation for HF or urgent HF visit, or death from any cause was consistent between those with an eGFR of <60 mL/min/1.73m^2 and those with an eGFR ≥60 mL/min/1.73m^2 (Figure 7).

The incidence of the prespecified renal composite outcome did not differ between the treatment groups in the DAPA-HF trial in the total study population (HR: 0.71; 95% CI: 0.44 to 1.16; p=0.17). Among patients with an eGFR ≥60 mL/min/1.73m^2, the rate of the prespecified renal composite outcome was lower in those randomly assigned to dapagliflozin, but the difference was not statistically significant (HR: 0.49; 95% CI: 0.23 to 1.06). There was no effect of eGFR subgroup on the dapagliflozin effect on the renal composite (p-value for interaction=0.19).

Figure 7. Effect of dapagliflozin on the primary and secondary outcomes in DAPA-HF according to eGFR group at baseline (*rate ratio and N provided for total hospitalizations or CV death outcome).



Abbreviations: CI: confidence interval; CV: cardiovascular; eGFR: estimated glomerular filtration rate; HF: heart failure; HR: hazard ratio.
Source: Jhund *et al*., 2020. Supplementary materials.[5]

Subgroup 4: Adults with CKD, with T2D, and with an eGFR ≥20–25 mL/min/1.73m² (irrespective of uACR)

Subgroup 4 consists of adults with a lower eGFR than patients enrolled in DAPA–CKD. Direct effect estimates for dapagliflozin from clinical trials or real-world evidence are not available for this specific subgroup. However, subgroup analyses from DAPA–CKD, DAPA–HF and DECLARE–TIMI 58 indicate that the efficacy of dapagliflozin is consistent across various eGFR categories and therefore strongly suggest that dapagliflozin's kidney protective benefits extend to this subgroup (see Supporting Data).

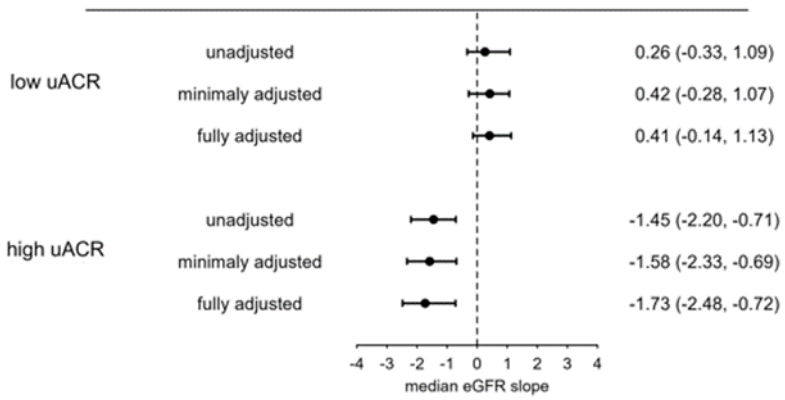
Evidence from the OPTIMISE CKD study further suggests that dapagliflozin's kidney protective benefits extend to this subgroup of patients, and provides an effect estimate for dapagliflozin in patients with a wider range of eGFR categories than were included in the DAPA-CKD study. Specifically, in an analysis of 4,394 dapagliflozin initiators with T2D and an eGFR of 15–60 mL/min/1.73 m^2, a flat eGFR slope of 0.26 mL/min/1.73 m^2 per year (–0.64, 2.47) was reported for patients with a uACR of 3–22.6 mg/mmol (30–200 mg/g). eGFR slope for patients with a uACR of >22.6 mg/mmol (>200 mg/g) was –1.45 mL/min/1.73 m^2 per year [–2.20, –0.71]).[1]

OPTIMISE–CKD (Svensson et al. 2024)[1]

While the results of the OPTIMISE-CKD are not reported separately for patients with T2D and an eGFR 20–25 mL/min/1.73 m^2 specifically, the supportive analysis based on patients with T2D provides an effect estimate for eGFR slope among patients with T2D and an eGFR 15–60 mL/min/1.73 m^2 (effect estimates are reported separately by uACR category; Figure 8):

- Among patients with a uACR of 3–22.6 mg/mmol (30–200 mg/g), the eGFR slope was flat at 0.26 mL/min/1.73 m^2 per year (95% CI:–0.33 to 1.09), suggesting a beneficial effect of dapagliflozin in slowing renal decline.
- Among patients with a uACR of >22.6 mg/mmol (>200 mg/g), eGFR slope results indicated that a small degree of renal decline continued to occur (–1.45 mL/min/1.73 m^2 per year [95% CI –2.20 to –0.71]), but results were similar to the eGFR slope observed in the ITT population of the DAPA-CKD trial (-2.86 ± 0.11 and -3.79 ± 0.11 ml/min/1.73 m^2/year in the dapagliflozin and placebo groups, respectively between baseline and 30 months).[6]

Figure 8. eGFR slopes in patients with CKD and with T2D initiated with dapagliflozin in OPTIMISE CKD



Footnotes: Minimally adjusted: adjusted for baseline eGFR; Fully adjusted: adjusted for baseline eGFR, age and sex, HF and RASi.
Abbreviations: CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; HF: heart failure; RASi: renin–angiotensin system inhibitor; T2D: type 2 diabetes; uACR: urine albumin–creatinine ratio.
Source: Svensson *et al*., 2024.[1]

Subgroup 5: Adults with CKD, with T2D, and with an eGFR >75–90 mL/min/1.73m^2 (irrespective of uACR)

Subgroup 5 consists of adults with a greater eGFR than patients enrolled in DAPA–CKD. Direct effect estimates for dapagliflozin from clinical trials or real-world evidence are not available for this specific subgroup. However, subgroup analyses from DAPA–CKD, DAPA–HF and DECLARE–TIMI 58 indicate that the efficacy of dapagliflozin is consistent across various eGFR categories and therefore strongly suggest that dapagliflozin's kidney protective benefits extend to this subgroup (see Supporting Data).

Specific evidence from the DECLARE-TIMI 58 study further suggest that dapagliflozin's kidney protective benefits extend to this subgroup of patients, and provides an effect estimate for dapagliflozin in patients with a wider range of eGFR categories than were included in the DAPA-CKD study; [redacted], among patients with an eGFR of ≥60–<90 mL/min/1.73m^2.[4, 8] Further evidence from the DAPA-HF study also suggests that dapagliflozin's treatment effect extends to this subgroup of patients. While the results of the DAPA–HF study are not reported separately by T2D status and eGFR category, this study enrolled a substantial number of patients with an eGFR ≥60 mL/min/1.73m^2 both with and without T2D (n=1,157 patients with eGFR ≥60 mL/min/1.73m^2

and T2M at baseline, n=1,659 patients with eGFR ≥60 mL/min/1.73m^2 without T2M at baseline). As such, DAPA-HF provides effect estimates for dapagliflozin in patients with a wider range of eGFR categories than were included in the DAPA-CKD study; a clear dapagliflozin treatment benefit was observed among patients with eGFR ≥60 mL/min/1.73m^2 on the primary outcome of CV death or worsening HF, as well as other outcomes including CV death, hospitalisation for HF or urgent HF visit, or death from any cause. Given that DAPA-HF did not restrict enrolment by uACR category, these effect estimates represent a group of patients which inherently includes a proportion of patients with uACR ≥22.6 mg/mmol.[5]

DECLARE–TIMI 58[8, 9]

The Phase III DECLARE–TIMI 58 RCT (n=17,160) enrolled patients with T2D and either established atherosclerotic cardiovascular disease (ASCVD; age ≥40 years and either ischaemic heart disease, cerebrovascular disease, or peripheral arterial disease), or multiple risk factors for ASCVD (age ≥55 years for men or ≥60 years for women plus at least one of dyslipidaemia, hypertension, or current tobacco use). Participants were also required to have HbA1c between 6.5% and 12.0% (47.5–113.1 mmol/mol) and creatinine clearance (estimated by the Cockcroft–Gault equation) of 60 mL/min or higher.

While results are not reported for patients with T2D and an eGFR >75–90 mL/min/1.73 m^2 specifically, a post-hoc subgroup analysis of DECLARE–TIMI 58 provides an effect estimate for renal and cardiorenal outcomes among a similar subgroup of patients: individuals with T2D and eGFR ≥60–<90 mL/min/1.73m^2 irrespective of uACR:

- Effect estimates for the composite primary endpoint (hospitalisation for HF or CV death), the renal composite endpoint (eGFR ≥40%, ESKD, or death from renal causes) and the cardiorenal endpoint (≥40% sustained eGFR decline, renal death, ESKD, CV death) among patients with T2D and ≥60–<90 mL/min/1.73m^2 are presented in Figure 9.
    - The treatment effect of dapagliflozin was consistent between patients with eGFR <60 mL/min/1.73m^2, ≥60–<90 mL/min/1.73m^2 and ≥90 mL/min/1.73m^2 (Figure 9).

Figure 9. Relevant subgroup analyses from the DECLARE–TIMI 58 study by eGFR categories

Patient subgroup	Dapagliflozin n/N	Placebo n/N	HR (95% CI)	p-value (interaction)
Co-primary endpoint				
eGFR ≥ 90 ml/min/1.73m²	163/4137	163/4025	0.96 (0.77-1.19)	
eGFR ≥60 to <90 ml/min/1.73m²	199/3838	252/3894	0.79 (0.66-0.95)	0.37
eGFR < 60 ml/min/1.73m²	55/606	81/659	0.78 (0.55-1.09)	
Overall	**417/8581**	**496/8578**	**0.84 (0.74-0.96)**	
Renal endpoint				
eGFR ≥ 90 ml/min/1.73m²	41/4137	79/4025	0.50 (0.34-0.73)	
eGFR ≥60 to <90 ml/min/1.73m²	65/3838	121/3894	0.54 (0.40-0.73)	0.87
eGFR < 60 ml/min/1.73m²	21/606	38/659	0.60 (0.35-1.02)	
Overall	**127/8581**	**238/8578**	**0.53 (0.43-0.66)**	
Cardiorenal endpoint				
eGFR ≥ 90 ml/min/1.73m²	135/4137	164/4025	0.79 (0.63-0.99)	
eGFR ≥60 to <90 ml/min/1.73m²	182/3838	240/3894	0.76 (0.63-0.93)	0.97
eGFR < 60 ml/min/1.73m²	53/606	76/659	0.77 (0.54-1.09)	
Overall	**370/8581**	**480/8578**	**0.77 (0.68-0.89)**	

Footnotes: Co–primary endpoint: hospitalisation for HF or CV death. Renal endpoint: ≥40% sustained eGFR decline, ESKD, renal death. Cardiorenal endpoint: ≥40% sustained eGFR decline, renal death, ESKD, CV death.
Abbreviations: CI: confidence interval; CV: cardiovascular; eGFR: estimated glomerular filtration rate; ESKD: end–stage kidney disease; HF: heart failure; HR: hazard ratio; uACR: urine albumin–to–creatinine ratio.
Source: Mosenzon *et al.* 2019;[9] Wiviott *et al.* 2018.[8]

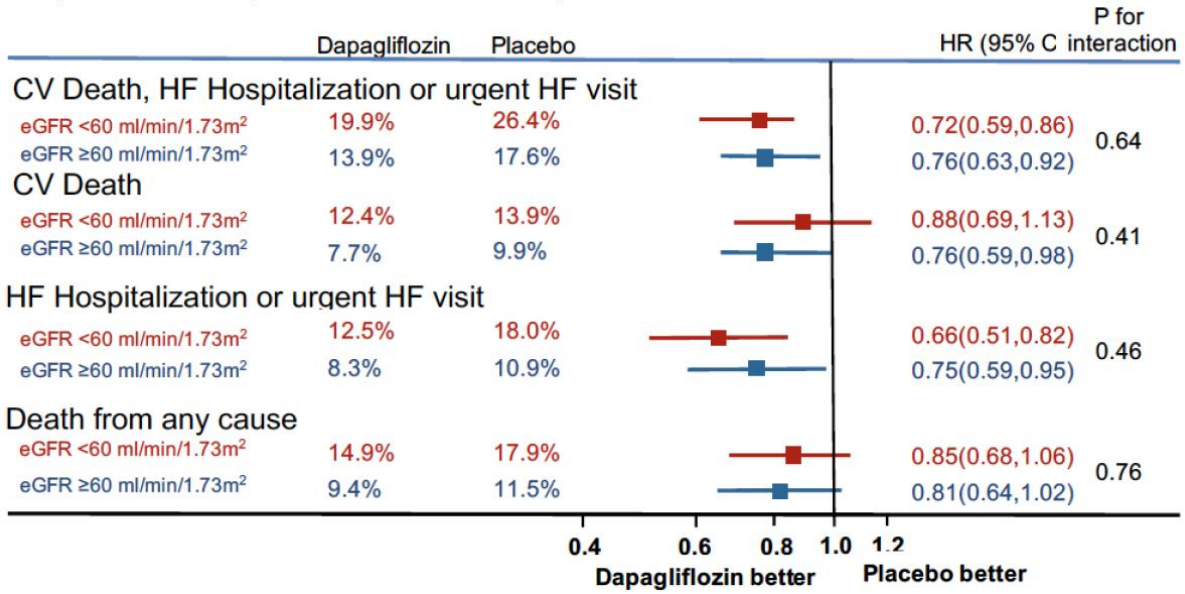
DAPA-HF[5]

The Phase III DAPA-HF RCT (n=4,743) enrolled patients with HFrEF and an eGFR of ≥30 mL/min/1.73m^2, regardless of the presence or absence of comorbid T2D. As outlined above, DAPA-HF enrolled a substantial number of patients with an eGFR ≥60 mL/min/1.73m^2 (n=2,816, 59%) both with and without T2D (n=1,157 patients with eGFR ≥60 mL/min/1.73m^2 and T2M at baseline, n=1,659 patients with eGFR ≥60 mL/min/1.73m^2 without T2M at baseline).

A clear treatment benefit for dapagliflozin was observed among patients with eGFR ≥60 mL/min/1.73m^2 (n=2,816) for the primary outcome of CV death or worsening HF, as well as other outcomes including CV death, hospitalisation for HF or urgent HF visit, or death from any cause (Figure 10). The efficacy of dapagliflozin in preventing the primary outcome of CV death or worsening HF, as well as other outcomes including CV death, hospitalisation for HF or urgent HF visit, or death from any cause was consistent between those with an eGFR of <60 mL/min/1.73m^2 and those with an eGFR ≥60 mL/min/1.73m^2 (Figure 10).[5]

The incidence of the prespecified renal composite outcome did not differ between the treatment groups in the DAPA-HF trial in the total study population (HR: 0.71; 95% CI: 0.44 to 1.16; p=0.17). Among patients with an eGFR ≥60 mL/min/1.73m^2, the rate of the prespecified renal composite outcome was lower in those randomly assigned to dapagliflozin, but the difference was not statistically significant (HR: 0.49; 95% CI: 0.23 to 1.06). There was no effect of eGFR subgroup on the dapagliflozin effect on the renal composite (p-value for interaction=0.19).

Figure 10. Effect of dapagliflozin on the primary and secondary outcomes in DAPA-HF according to eGFR group at baseline (*rate ratio and N provided for total hospitalizations or CV death outcome).



Abbreviations: CI: confidence interval; CV: cardiovascular; eGFR: estimated glomerular filtration rate; HF: heart failure; HR: hazard ratio.
Source: Jhund *et al.*, 2020. Supplementary materials.[5]

Supporting Data

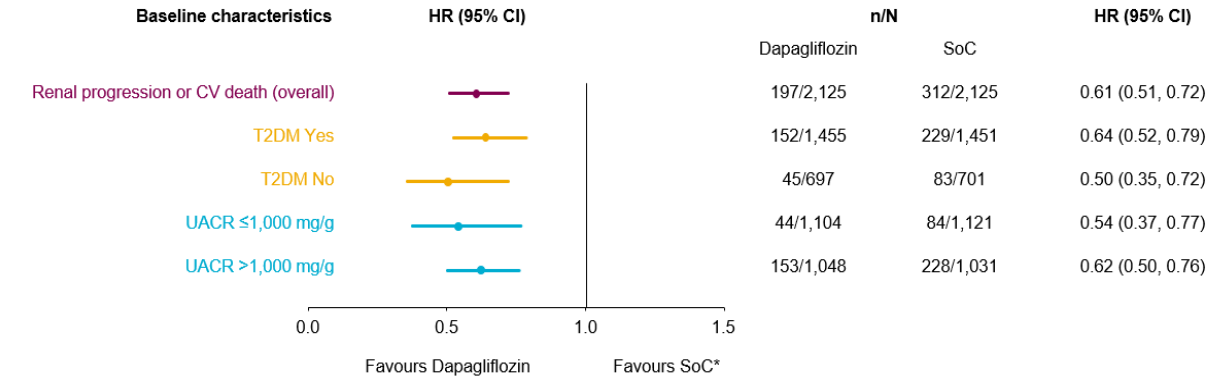
Consistency of Dapagliflozin Treatment Benefit Across uACR categories

Subgroup analyses of DAPA-CKD and DECLARE-TIMI 58 strongly suggest that dapagliflozin's cardiorenal protective benefits are consistent regardless of uACR category and therefore extend to patients with a lower uACR than those enrolled in the DAPA-CKD study.

DAPA-CKD

The treatment benefit of dapagliflozin on the primary outcome (≥50% eGFR decline, ESKD and renal death or CV death) was consistent across pre-specified subgroups based on UACR category (≤1,000 mg/g vs >1,000 mg/g) in DAPA-CKD (Figure 11).

Figure 11. Forest plot of the composite of ≥50% eGFR decline, ESKD and renal death or CV death by T2D status and UACR category in DAPA-CKD



Abbreviations: CI: confidence interval; CV: cardiovascular; ESKD: end stage kidney disease; UACR: urinary albumin-to-creatinine ratio; T2DM: type 2 diabetes mellitus; eGFR: estimated glomerular filtration rate; HR: hazard ratio; SoC: standard of care.
Source: Heerspink *et al.* 2020. [7]

DECLARE-TIMI 58[4]

The treatment effect of dapagliflozin observed in the DECLARE-TIMI 58 trial on the co-primary endpoint of hospitalisation for HF or CV death, and the renal endpoint without CV death (eGFR ≥40%, ESKD, or death from renal causes) was consistent between patients with a uACR <200 mg/g (<22.6 mg/mmol) and ≥200 mg/g (≥22.6 mg/mmol) (**Error! Reference source not found.**). Although the p-value for interaction fell below 0.05 for the cardiorenal endpoint of ≥40% eGFR decline, ESKD, renal death or CV death endpoint, this is likely to be a chance finding as these analyses have not been adjusted for multiple testing. Regardless of the p-value for interaction, a clear treatment benefit was observed for both uACR subgroups, with 95% CIs below one.

[redacted]

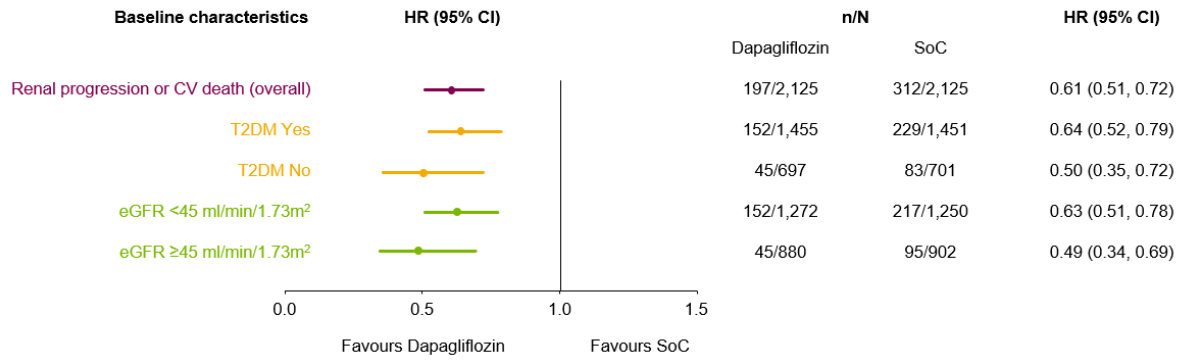
Consistency of Dapagliflozin Treatment Benefit Across eGFR categories

Subgroup analyses of DAPA-CKD and DECLARE-TIMI 58 strongly suggest that dapagliflozin's cardiorenal protective benefits are consistent regardless of eGFR category and therefore extend to patients with a broader eGFR than those enrolled in the DAPA-CKD study.

DAPA-CKD[7]

The treatment benefit of dapagliflozin on the primary outcome (≥50% eGFR decline, ESKD and renal death or CV death) was consistent across pre-specified subgroups based on eGFR category (eGFR <45 mL/min/1.73m^2 vs eGFR ≥45 mL/min/1.73m^2; Figure 12)

Figure 12. Forest plot of the composite of ≥50% eGFR decline, ESKD and renal death or CV death by T2D status and eGFR category in DAPA-CKD



Abbreviations: CI: confidence interval; CV: cardiovascular; ESKD: end stage kidney disease; UACR: urinary albumin-to-creatinine ratio; T2DM: type 2 diabetes mellitus; eGFR: estimated glomerular filtration rate; HR: hazard ratio; SoC: standard of care.
Source: Heerspink *et al.* 2020.[7]

DECLARE-TIMI 58[4]

The treatment benefit of dapagliflozin on the primary outcome (≥50% eGFR decline, ESKD and renal death or CV death) was consistent across pre-specified subgroups based on UACR category (≤1,000 mg/g vs >1,000 mg/g) in DAPA-CKD The treatment effect of dapagliflozin observed in the DECLARE-TIMI 58 trial on the co-primary endpoint of hospitalisation for HF or CV death, and the renal endpoint without CV death (eGFR ≥40%, ESKD, or death from renal causes) was consistent between patients with an eGFR <60 mL/min/1.73m^2 and ≥60–<90 mL/min/1.73m^2 (Figure 13).

Figure 13. Relevant subgroup analyses from the DECLARE-TIMI 58 study by eGFR categories

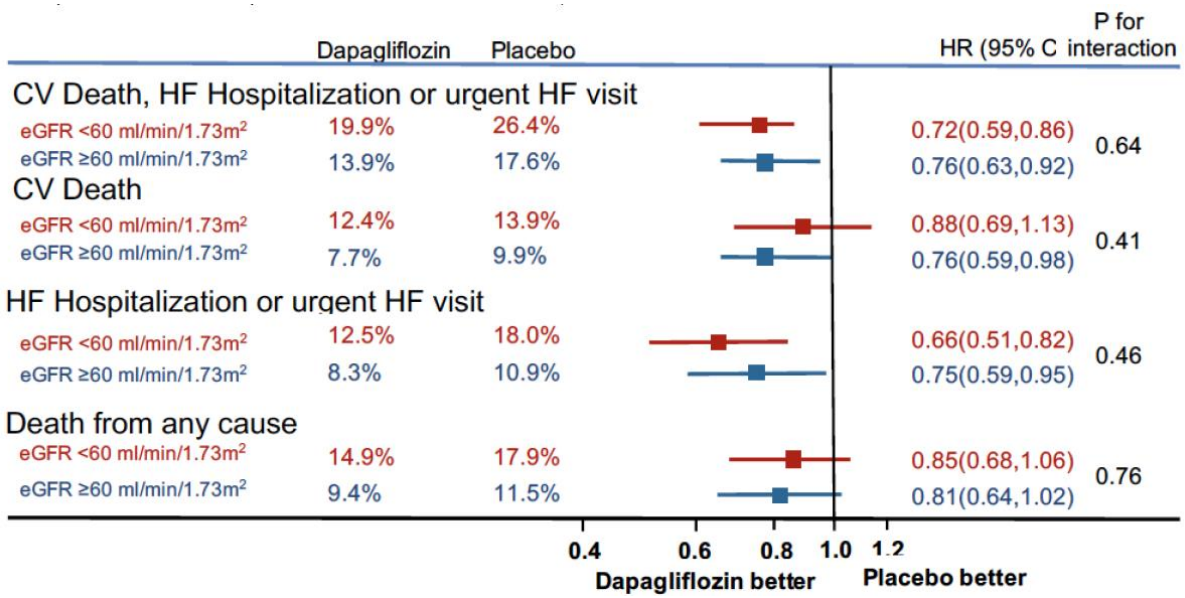
Patient subgroup	Dapagliflozin n/N	Placebo n/N	HR (95% CI)	p-value (interaction)
Co-primary endpoint				
eGFR ≥ 90 ml/min/1.73m²	163/4137	163/4025	0.96 (0.77-1.19)	
eGFR ≥60 to <90 ml/min/1.73m²	199/3838	252/3894	0.79 (0.66-0.95)	0.37
eGFR < 60 ml/min/1.73m²	55/606	81/659	0.78 (0.55-1.09)	
Overall	**417/8581**	**496/8578**	**0.84 (0.74-0.96)**	
Renal endpoint				
eGFR ≥ 90 ml/min/1.73m²	41/4137	79/4025	0.50 (0.34-0.73)	
eGFR ≥60 to <90 ml/min/1.73m²	65/3838	121/3894	0.54 (0.40-0.73)	0.87
eGFR < 60 ml/min/1.73m²	21/606	38/659	0.60 (0.35-1.02)	
Overall	**127/8581**	**238/8578**	**0.53 (0.43-0.66)**	
Cardiorenal endpoint				
eGFR ≥ 90 ml/min/1.73m²	135/4137	164/4025	0.79 (0.63-0.99)	
eGFR ≥60 to <90 ml/min/1.73m²	182/3838	240/3894	0.76 (0.63-0.93)	0.97
eGFR < 60 ml/min/1.73m²	53/606	76/659	0.77 (0.54-1.09)	
Overall	**370/8581**	**480/8578**	**0.77 (0.68-0.89)**	

Footnotes: Co-primary endpoint: hospitalisation for HF or CV death. Renal endpoint: ≥40% sustained eGFR decline, ESKD, renal death. Cardiorenal endpoint: ≥40% sustained eGFR decline, renal death, ESKD, CV death.
Abbreviations: CI: confidence interval; CV: cardiovascular; eGFR: estimated glomerular filtration rate; ESKD: end-stage kidney disease; HF: heart failure; HR: hazard ratio.
Source: Mosenzon *et al.* 2019; Wiviott *et al.* 2018.[8, 9]

DAPA-HF

The efficacy of dapagliflozin in preventing the primary outcome of CV death or worsening HF, as well as other outcomes including CV death, hospitalisation for HF or urgent HF visit, or death from any cause did not differ between those with an eGFR of <60 mL/min/1.73m^2 and those with an eGFR ≥60 mL/min/1.73m^2 (p for interaction=0.64; Figure 14).[5]

Figure 14. Effect of dapagliflozin on the primary and secondary outcomes in DAPA-HF according to eGFR group at baseline (*rate ratio and N provided for total hospitalizations or CV death outcome).



Abbreviations: CI: confidence interval; CV: cardiovascular; eGFR: estimated glomerular filtration rate; HF: heart failure; HR: hazard ratio.
Source: Jhund *et al*., 2020. Supplementary materials.[5]

3. *The CS mentions that clinical opinion supports the alignment of the indication of dapagliflozin with empagliflozin as per the recommendations in TA942. Please clarify all sources of clinical opinions discussing this issue, including any separate clinical advice sought by the company to inform this appraisal.*

As noted in Document B, Section B.1.1, aligning the recommendations of empagliflozin and dapagliflozin as a treatment for CKD would simplify the treatment pathway in both primary and secondary care and remove some of the complexities associated with prescribing empagliflozin and dapagliflozin; by doing so, this would improve access for patients with CKD to effective treatments. This is supported by comments from stakeholders on the draft scope for this review:[10]

- *"I think it would be clearer for prescribers in both primary and secondary care to have the same criteria for both dapagliflozin and empagliflozin use in CKD"* – UK Kidney Association
- *"I think this would simplify things for primary care where much of this prescribing should be happening"* – UK Kidney Association
- *"We agree if dapagliflozin had the same NICE recommendation as empagliflozin, it would avoid unnecessary complexity for prescribers, especially in primary care"* – Kidney Research UK
- *"It is vital that people with CKD who may benefit from SGLT2 inhibitor drugs have prompt access to treatment and we are therefore supportive of pursuing opportunities to remove complexity from the prescribing process"* – Kidney Care UK

In addition, AstraZeneca sought input from UK clinicians experienced in the treatment of CKD to support this review. The clinical experts stated that it was important to align the recommendations to simplify prescribing for primary care clinicians; the current recommendations (which do align with the evidence base, licence or current CKD guidelines) create complexity, which does not support guideline adoption in clinical practice and impacts on outcomes for patients with CKD.[11] The clinicians also supported the existence of a class effect for SGLT2 inhibitors, due to their similar mechanism of action and clinical effect observed in the available data. A summary of the feedback from the clinicians is provided in the reference pack alongside this response.[11]

As discussed further in response to Question 4, the United Kingdom Kidney Association (UKKA) has provided guidance on the use of SGLT2 inhibitors in the treatment of CKD.[12] Importantly, these guidelines do not differentiate between SGLT2 inhibitors, including dapagliflozin and empagliflozin, with the clinical benefits and safety profiles of the molecules being interpreted as a class effect. As they are developed by clinicians, these guidelines represent the current opinions of the CKD clinical community.

Evidence for dapagliflozin vs. empagliflozin

4. *In the absence of direct comparative evidence between dapagliflozin and empagliflozin, please discuss the extent to which dapagliflozin and empagliflozin may be considered biologically similar and have a similar mechanism of action, supported by appropriate evidence.*

Dapagliflozin and empagliflozin are both members of a class of medications called SGLT2 inhibitors. The overall mechanism of SGLT2 inhibitors involves blocking the action of the SGLT2 receptor in the kidneys. Normally, the SGLT2 receptor reabsorbs glucose from the urine back into the bloodstream. By inhibiting this receptor, SGLT2 inhibitors prevent the

reabsorption of glucose, leading to increased urinary glucose excretion and lower blood sugar levels.[13, 14]

In pre-clinical studies, both empagliflozin and dapagliflozin showed similar high selectivity for SGLT2 over SGLT1 versus phlorizin.[15, 16] Using Quantitative Systems Pharmacology Modelling analysis to quantify the effects on SGLT2 inhibitors on renal glucose reabsorption, the ratio of SGLT2:SGLT1 blockade for dapagliflozin 10 mg was 1,200-fold, empagliflozin 25 mg was 1,300-fold and canagliflozin 300 mg was 160-fold, meaning that dapagliflozin and empagliflozin have a stronger preference for binding to SGLT2 receptors and a lower affinity for SGLT1 receptors.[17] The selectivity of SGLT2 inhibitors can have implications for their therapeutic effects and potential side effects, with higher selectivity for SGLT2 over SGLT1 being desirable as it allows for the selective inhibition of glucose reabsorption in the kidneys. This leads to increased urinary glucose excretion and improved glycaemic control, which is beneficial for patients with T2D and/or CKD.

Several RCTs have been conducted to evaluate the efficacy and safety of SGLT2 inhibitors.[9, 18-20] These studies have demonstrated the CV and renal benefits of SGLT2 inhibitors, including reductions in major adverse cardiac events (MACE), HF hospitalisations and kidney disease progression. Several meta-analyses have been conducted to assess the overall efficacy and safety of SGLT2 inhibitors and suggest similarity in terms of the efficacy of empagliflozin and dapagliflozin.[21, 22] Furthermore, these meta-analyses have demonstrated similarities of the safety profiles of these medications. Consistent commonly reported adverse events include urinary tract infections, genital infections and increased urination. These adverse events are consistent with the mechanism of action of SGLT2 inhibitors and are related to the increased urinary glucose excretion. One notable similarity between dapagliflozin and empagliflozin is the low risk of hypoglycaemia. As SGLT2 inhibitors work independently of insulin secretion, they have a minimal risk of causing low blood sugar levels.

The UKKA has provided guidance on the use of SGLT2 inhibitors in the treatment of CKD.[12] According to the guidelines, SGLT2 inhibitors, such as empagliflozin and dapagliflozin, are recommended or suggested for use in patients with CKD with or without T2D depending on eGFR and uACR categories. Most notably for CKD patients with an eGFR ≥20 - <45 mL/min/1.73m^2 and uACR >25 mg/mmol and ≤25 mg/mmol. Importantly, the guidelines do not differentiate between empagliflozin and dapagliflozin, they incorporate and reference all the clinical data for the molecules (CKD outcome, T2D CV outcome and HF outcome trials) presenting the evidence as a class effect specifically highlighting the below class benefits for patients with CKD:

- Efficacy: SGLT2 inhibitors have demonstrated significant benefits in patients with CKD, including a reduction in albuminuria, preservation of kidney function, and a lower risk of kidney failure.
- CV Protection: SGLT2 inhibitors have also been shown to provide CV protection in patients with CKD. They can reduce the risk of major CV events.

In summary, there is no scientific rationale that would suggest the clinical efficacy and safety of empagliflozin differs from dapagliflozin.

5. *Please provide clear and complete evidence comparing the relative efficacy of dapagliflozin and empagliflozin, including evidence gaps and uncertainties, for all subgroups listed in the CS decision problem.*

As noted in Document B, Section B.3.9, an ITC of dapagliflozin versus empagliflozin was not conducted for this review of TA775. An initial feasibility assessment was conducted to evaluate whether it is possible to conduct an ITC using the RCTs for dapagliflozin, empagliflozin, canagliflozin and finerenone, considering methods including MAIC and multi-level network meta-regression (ML-NMR). Following the feasibility assessment, it was identified that due to heterogeneity in the populations enrolled in the DAPA-CKD and EMPA-KIDNEY trials, and lack of available data for the specific subgroups of interest for empagliflozin, it was not feasible to conduct an ITC for dapagliflozin, based on DAPA-CKD, versus empagliflozin, based on EMPA-KIDNEY, in the specific subgroups in this review.

A second investigation into the feasibility of indirectly comparing the treatment effect on cardiorenal outcomes of dapagliflozin versus empagliflozin in the population studied in EMPA-KIDNEY was recently conducted (July 2024). The assessment sought to evaluate the possibility of comparing aggregate and subgroup aggregate baseline characteristics, outcomes and relative outcomes available from EMPA-KIDNEY to outcomes from a matched population of patients prescribed dapagliflozin extracted from the Optum Clinformatics database (hereafter referred to as “Optum”). In order to conduct a comparison between similar populations (in terms of important baseline characteristics), the extracted population from Optum would need to meet the inclusion/exclusion criteria of EMPA-KIDNEY. However, it was not feasible to identify and match key exclusion criteria from the EMPA-KIDNEY study (e.g., scheduled interventions, recent use of investigational medicinal products and history of cancer). This results in a lack of comparable datasets, introducing significant bias and violating the assumptions required for both anchored and unanchored indirect comparison methods. Consequently, it was not feasible to conduct a robust ITC of dapagliflozin versus empagliflozin in the specific subgroups in this review.

However, an ITC in the form of an anchored network meta-analysis (NMA) was previously conducted to inform TA942, which assessed the relative efficacy of dapagliflozin versus empagliflozin in patients with CKD/diabetic kidney disease, with or without comorbidities. The NMA included 13 RCTs.[23] Overall, the results demonstrated that empagliflozin was non-inferior to dapagliflozin for all outcomes. Due to the limitations mentioned previously, this NMA was only conducted for the overlapping populations in the DAPA-CKD and EMPA-KIDNEY trials, so does not assess the relative efficacy of the two SGLT2 inhibitors in the specific subgroups of interest in this review. Although this represents a limitation of this NMA for this targeted review, the results of the NMA contribute to the total evidence of the clinical similarity of dapagliflozin and empagliflozin and formed the basis of a broad recommendation (including in patients without T2D with uACR <22.6 mg/mmol) for empagliflozin from NICE (TA942).[23]

In the absence of an ITC in the specific subgroups in this review, naïve comparisons of the outcomes for dapagliflozin and empagliflozin in the subgroups within this targeted review can be conducted. Published data for empagliflozin are not available for the specific subgroups in this review, however available subgroup analyses can provide insight into the expected efficacy of empagliflozin in the subgroups in this review. The available empagliflozin subgroups that correspond to the subgroups in this review are presented in Table 3, alongside the empagliflozin outcomes for each subgroup, demonstrating the overlap in the available subgroups from EMPA-KIDNEY with the subgroups in this review. As outlined in

response to Questions 1 and 2, efficacy data for dapagliflozin in these subgroups are derived from numerous sources and are available in a variety of endpoints so are not presented alongside the subgroups in Table 3.

Table 3: Subgroups of interest in this review alongside published empagliflozin subgroups

Subgroups in this review		Empagliflozin subgroup	Progression of kidney disease or death from cardiovascular causes; empagliflozin versus placebo (HR [95% CIs])[19]
1	Without T2D, eGFR ≥20–45 mL/min/1.73m^2, **uACR <22.6 mg/mmol**	uACR <30 mg/mmol[a]	1.01 (0.66, 1.55)
2	Without T2D, **eGFR ≥20–25** mL/min/1.73m^2, uACR ≥22.6 mg/mmol	eGFR <30 mL/min/1.73m^2 [b]	0.73 (0.62, 0.86)
4	with T2D, **eGFR ≥20–25** mL/min/1.73m^2, irrespective of uACR		
3	With T2D, **eGFR >75–90** mL/min/1.73m^2, uACR ≥22.6 mg/mmol	eGFR >45 mL/min/1.73m^2 [c]	0.64 (0.44, 0.93)
5	With T2D, **eGFR >75–90** mL/min/1.73m^2, irrespective of uACR		
Overall trial population			0.72 (0.64, 0.82)

Footnotes: [a] Outcomes for empagliflozin for patients with uACR <30 mg/mmol are not reported separately for different levels of eGFR or T2D status. [b] Outcomes for empagliflozin for patients with eGFR <30 mL/min/1.73m^2 are not reported separately for different levels of uACR or T2D status. [c] Outcomes for empagliflozin for patients with eGFR >45 mL/min/1.73m^2 are not reported separately for different levels of uACR or T2D status.
Abbreviations: CI: confidence interval; eGFR: estimated glomerular filtration rate; HR: hazard ratio; T2D: type 2 diabetes; uACR: urine creatine-albumin ratio.
Source: Herrington et al. (2023)[19]

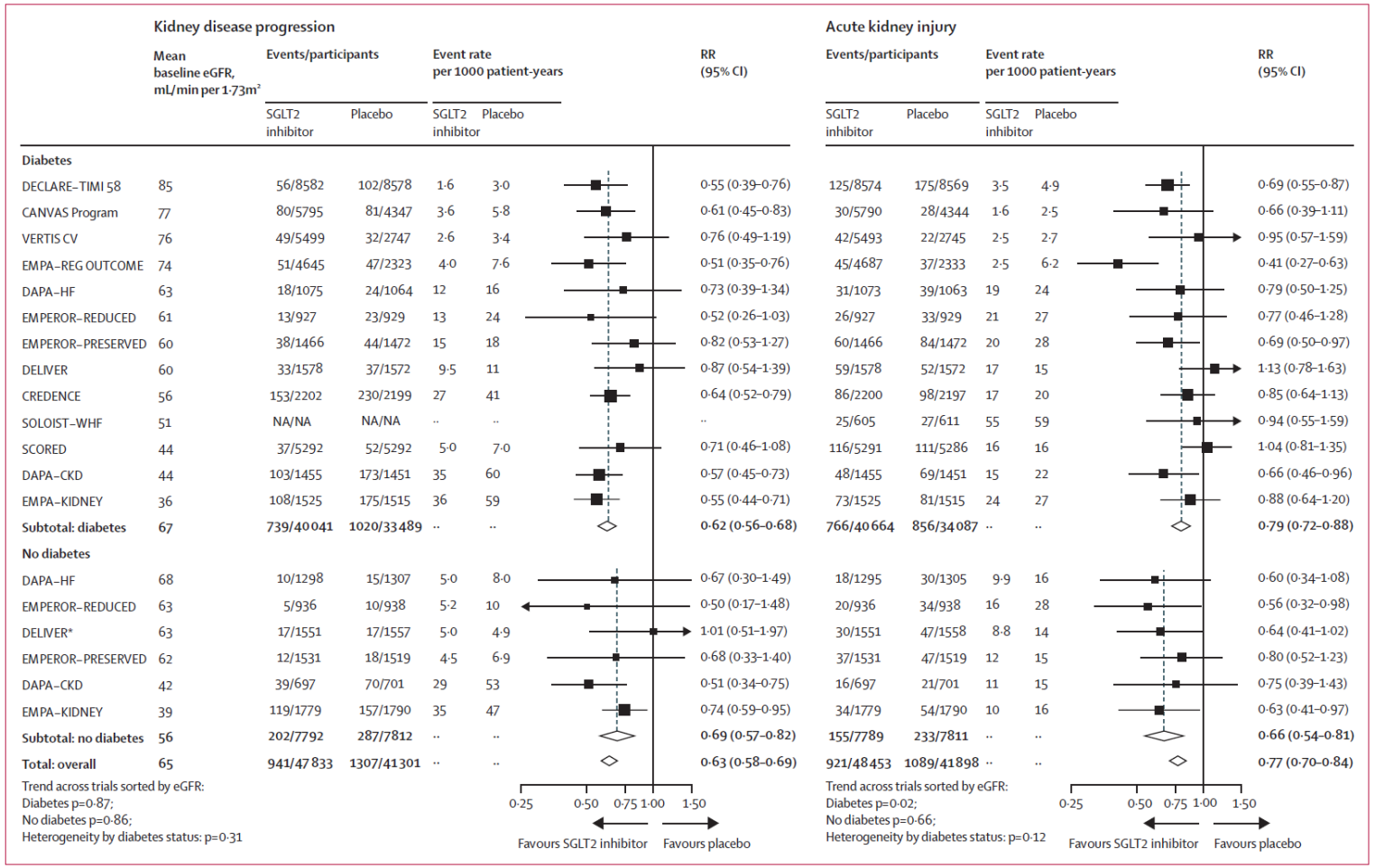
As highlighted in Document B, Section B.3.9.1, subgroup data from EMPA-KIDNEY demonstrate that the HR for patients with low baseline uACR (<30 mg/mmol) was 1.01 (95% CIs: 0.66, 1.55]); this shows a lack of statistically significant treatment benefit of empagliflozin in this population, which differs from the benefit observed in the overall population.[19] In contrast, as discussed in Document B, Section B.3.9.1, post-hoc analyses of DAPA-CKD demonstrate a consistent treatment benefit of dapagliflozin regardless of baseline uACR, which is further supported by RWE from OPTIMISE-CKD and Nakhleh et al., 2024.[1, 3, 24] Other available empagliflozin subgroups for patients with eGFR <30 mL/min/1.73m^2 and >45 mL/min/1.73m^2 demonstrate a broadly consistent treatment benefit, in line with the available evidence for dapagliflozin. It is therefore reasonable to assume that dapagliflozin and empagliflozin are at least clinically equivalent across the subgroups, with the potential for this to be a conservative assumption with regards to the efficacy of dapagliflozin demonstrated across baseline uACR subgroups.

As mentioned in Document B and highlighted in TA942, an independent meta-analysis was conducted which investigated the efficacy of SGLT2 inhibitors with regards to CKD in patients with varying levels of eGFR and uACR as well as with/without T2D, including patients within the subgroups of interest in this review.[22] The meta-analysis was informed by 13 clinical trials that included patients with CKD, including trials in CKD, HF and diabetes. The meta-analysis demonstrated that SGLT2 inhibitors (including dapagliflozin and empagliflozin) are similar in terms of efficacy with regards to CKD, irrespective of T2D status, mean baseline eGFR or uACR, using data from trials across CKD, T2D and HF

(Figure 15). Consistent treatment effect of SGLT2 inhibitors on kidney disease progression were observed in patients with and without T2D and across a broad range of baseline EGFR and uACR values.

Combined with the evidence demonstrating molecular similarity of empagliflozin and dapagliflozin (Question 4), the totality of clinical data for empagliflozin and dapagliflozin demonstrate that they are clinically similar in terms of improving outcomes for patients with CKD, regardless of T2D status, and baseline eGFR and uACR.

Figure 15: Effect of SGLT2 inhibitors on kidney disease outcomes, by diabetes status



Footnotes: Dapagliflozin clinical trials: DECLARE-TIMI 58, DAPA-HF, DELIVER, DAPA-CKD; empagliflozin clinical trials: EMPA-REG OUTCOME, EMPEROR-REDUCED, EMPEROR-PRESERVED, EMPA-KIDNEY. The remaining trials are for other SGLT2 inhibitors. *One participant without diabetes in DELIVER was missing a baseline creatinine measurement and was excluded.
Abbreviations: CI: confidence interval; eGFR: estimated glomerular filtration rate; SGLT2i: SGLT2 inhibitor; RR: relative risk.
Source: Nuffield Department of Population Health Renal Studies Group (2022)[22]

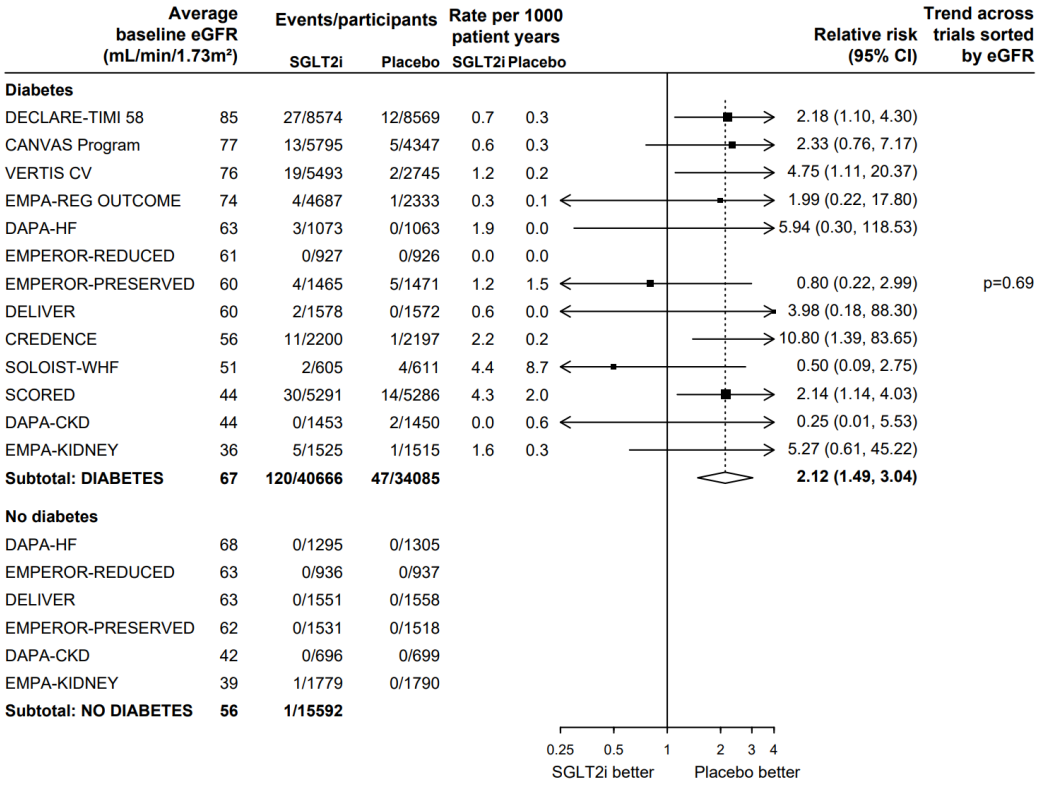
6. *Please provide clear and complete evidence comparing the relative safety of dapagliflozin and empagliflozin, including evidence gaps and uncertainties, for all subgroups listed in the CS decision problem.*

As discussed in response to Question 5 above, it was not feasible to conduct an ITC of dapagliflozin versus empagliflozin in the specific subgroups in this review due to heterogeneity in the trial populations, and this extends to conducting an NMA of safety outcomes.

However, the independent published meta-analysis also investigated the safety of SGLT2 inhibitors and the results demonstrated broadly consistent safety profiles across SGLT2 inhibitors (including dapagliflozin and empagliflozin) in terms of ketoacidosis and lower leg amputation (Figure 16 and Figure 17, from Nuffield Department of Population Health Renal Studies Group [2022] supplementary materials).[22] Broadly, all trials for dapagliflozin and empagliflozin reported low numbers of events of ketoacidosis and lower leg amputation.[22] The meta-analysis also explored additional safety outcomes, however results for this analysis are not separated by type of SGLT2 inhibitor so do not provide insight into the relative safety of dapagliflozin and empagliflozin specifically. This being said, the narrow 95% CIs do suggest consistency in the safety outcomes of all SGLT2 inhibitors included in the meta-analysis.

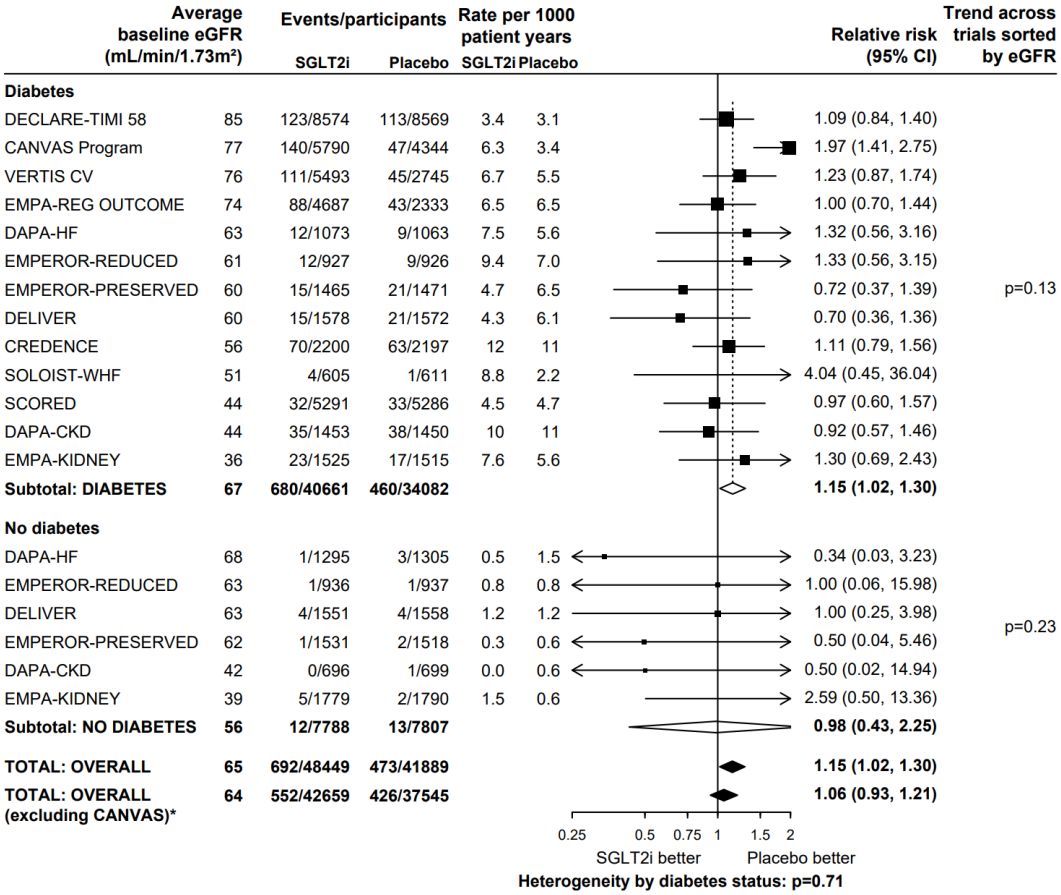
The consistent safety profile of dapagliflozin and empagliflozin was also supported by stakeholder comments in the draft scope for this review, with Kidney Research UK stating that dapagliflozin is expected to be equally "*safe as empagliflozin in the suggested population*".[10]

Figure 16: Effect of SGLT2 inhibitors on ketoacidosis, by diabetes status



Footnotes: Dapagliflozin clinical trials: DECLARE-TIMI 58, DAPA-HF, DELIVER, DAPA-CKD; empagliflozin clinical trials: EMPA-REG OUTCOME, EMPEROR-REDUCED, EMPEROR-PRESERVED, EMPA-KIDNEY. The remaining trials are for other SGLT2 inhibitors.
Abbreviations: CI: confidence interval; eGFR: estimated glomerular filtration rate; SGLT2i: SGLT2 inhibitor.
Source: Nuffield Department of Population Health Renal Studies Group (2022)[22]

Figure 17: Effect of SGLT2 inhibitors on lower limb amputation, by diabetes status



Footnotes: Dapagliflozin clinical trials: DECLARE-TIMI 58, DAPA-HF, DELIVER, DAPA-CKD; empagliflozin clinical trials: EMPA-REG OUTCOME, EMPEROR-REDUCED, EMPEROR-PRESERVED, EMPA-KIDNEY. The remaining trials are for other SGLT2 inhibitors. *The hypothesis that SGLT2 inhibition might increase the risk of lower limb amputation was first raised by results from the CANVAS trial. The subtotal excluding CANVAS therefore reflects the combined results from the independent set of hypothesis-testing trials.
Abbreviations: CI: confidence interval; eGFR: estimated glomerular filtration rate; SGLT2i: SGLT2 inhibitor.
Source: Nuffield Department of Population Health Renal Studies Group (2022)[22]

Supportive evidence of the relative efficacy and safety of dapagliflozin and empagliflozin (e.g. from well-conducted meta-analyses including non-CKD populations) may be used where appropriate.

Additional ITCs have been conducted which demonstrate clinical similarity of dapagliflozin and empagliflozin in other indications (e.g., HF and T2D), supporting at least clinical equivalence of the two SGLT2 inhibitors and existence of a consistent kidney protective effect. For example, ITCs conducted to support the NICE appraisal of empagliflozin in chronic HF with reduced ejection fraction (TA773) demonstrated that empagliflozin is likely to be similar to dapagliflozin, with regards to the risk of dying and likelihood of hospitalisations for HF, forming the basis of a NICE recommendation for empagliflozin.[25]

Additional published ITCs have demonstrated at least clinical equivalence of dapagliflozin to empagliflozin in other indications. An ITC by Shi *et al.* (2022) concluded that dapagliflozin and empagliflozin are comparable with regards to hospitalisation for HF and CV death, with

the HR showing a numerical benefit in favour of dapagliflozin.[26] Dapagliflozin significantly decreased all-cause mortality versus empagliflozin, whilst empagliflozin significantly decreased the risk of exacerbation of HF versus dapagliflozin. A summary of the HR estimates are presented in Table 4.

Table 4: Relative efficacy of empagliflozin versus dapagliflozin – Shi *et al.* (2022)

Outcome	Dapagliflozin versus empagliflozin (HR [95% CIs])	Empagliflozin versus dapagliflozin (HR [95% CIs])
Hospitalisation for HF	0.90 (0.75, 1.10)	NR
Exacerbation of HF	NR	0.70 (0.59, 0.84)
CV death/hospitalisation for HF	0.95 (0.78, 1.17)	NR
CV death	0.87 (0.69, 1.08)	NR
All-cause mortality	0.80 (0.66, 0.98)	NR

Abbreviations: CV: Cardiovascular; HF: heart failure; HR: hazard ratio; NR: not reported.
Source: Shi *et al.* (2022)[26]

Kani *et al.* (2024) conducted an NMA of the effectiveness of SGLT2 inhibitors (including dapagliflozin and empagliflozin) in terms of the composite endpoint of CV death and hospitalisation for HF.[27] Overall, the NMA found that differences in reducing CV and kidney outcomes, as well as safety profiles, between SGLT2 inhibitors were not statistically significant. A summary of the results for empagliflozin versus dapagliflozin are presented in Table 5, demonstrating no statistically significant difference in the treatment effect of the two SGLT2 inhibitors.

Table 5: Relative efficacy of empagliflozin versus dapagliflozin in terms of risk of CV death or hospitalisation for HF – Kani *et al.* (2024)

Population	Empagliflozin versus dapagliflozin – HR for CV death or hospitalisation for HF (95% CIs)
Overall	0.94 (0.85, 1.05)
With T2D	0.92 (0.81, 1.05)
Without T2D	1.02 (0.84, 1.22)

Abbreviations: CV: Cardiovascular; HF: heart failure; HR: hazard ratio.
Source: Kani *et al.* (2024)[27]

Although not conducted in the specific subgroups of interest for this review, there is some overlap in the populations included within these trials focused on other indications and the subgroups in this review, which further validates the similar clinical efficacy of dapagliflozin and empagliflozin in the subgroups of interest in this review.

Evidence identification

7. *Please clarify why a systematic review was not conducted to inform the CS.*

The aim of this submission is to review the current NICE recommendation for dapagliflozin in CKD and align it with the NICE recommendation for empagliflozin (in TA942). The methods used to identify evidence for dapagliflozin and empagliflozin were selected based on these aims.

As outlined in Section B.3.1 of Document B, a systematic literature review (SLR) was not conducted to inform this review. Instead, the evidence base was informed by the key clinical studies presented in the original appraisal for dapagliflozin in CKD (TA775) and the appraisal of empagliflozin in CKD (TA942). These studies were previously identified via SLRs that were conducted to support TA775 and TA942, respectively. Data from RWE studies for dapagliflozin that have become available since TA742 and TA942 were used to further inform this review. As outlined in Section B.3.1 of Document B, data from these RWE studies were published in April 2024, so would not have been identified in an SLR conducted to inform this review due to the timelines.[1, 3, 24]

As noted in the NICE Document B template for a cost-comparison submission, an SLR for clinical evidence is not required, and search strategies to identify new comparator data should instead start from the date of the literature searches in the NICE appraisal of the comparator. As the appraisal of empagliflozin in CKD (TA942) was conducted recently (published December 2023), it was not deemed necessary to conduct systemic searches to identify any new data for empagliflozin that may have been published in the six months between publication of TA942 and submission of this review.

8. *Please clarify which methods were used to identify the evidence for dapagliflozin and empagliflozin presented in the CS. Where appropriate, please provide a list of studies considered for inclusion in the CS but ultimately excluded with justifications.*

As noted in response to Question 7 above, the methods used to identify evidence for dapagliflozin and empagliflozin were selected based on the aims of the review, with the included studies for dapagliflozin and empagliflozin being based on those used to inform TA775 and TA942, further supplemented by recently published RWE on dapagliflozin.

The uncertainties raised in TA775 can be best addressed via post-hoc analyses of the relevant dapagliflozin clinical trials (DAPA-CKD, DAPA-HF, DECLARE-TIMI 58), as well as the two recently published RWE studies for dapagliflozin. As noted in response to Question 7 above, an SLR would not have identified the recently published RWE studies for dapagliflozin due to the publication date (May 2024) and submission deadline for this review (June 2024). Regardless, these RWE studies were included to aid the appraisal of dapagliflozin in the subgroups in the decision problem. AstraZeneca are not aware of any further published data for dapagliflozin in indications of interest that have been excluded from this review. As EMPA-KIDNEY was the only source of clinical data for empagliflozin in TA942, this was assumed to be the only relevant clinical data for empagliflozin to inform this targeted review.

Aligning the recommendation of dapagliflozin with that of empagliflozin would ideally be addressed by data on the relative efficacy of dapagliflozin versus empagliflozin in the relevant subgroups (i.e., via ITCs). However, due to challenges and limitations associated

with conducting an ITC in populations which do not overlap between DAPA-CKD and EMPA-KIDNEY, it is not feasible to conduct ITCs in the subgroups in the decision problem for this review. Since ITCs and NMAs have been published previously investigating the efficacy of dapagliflozin and empagliflozin in relevant indications, AstraZeneca made best use of the evidence which has previously been accepted by NICE and formed the basis of multiple recommendations for both SGLT2 inhibitors.

9. *The CS states that there are no ongoing studies of dapagliflozin relevant to this appraisal (CS Document B, Section B.3.12). Please support this statement with evidence as appropriate.*

As the marketing authorisation holder for dapagliflozin, AstraZeneca are not aware of any ongoing studies for dapagliflozin. AstraZeneca can therefore confirm that there are no ongoing studies for dapagliflozin of relevance to this review. All details of the timelines of the relevant clinical trials of dapagliflozin (DAPA-CKD, DECLARE-TIMI 58 and DAPA-HF) are presented in Section B.3.3 of Document B. This is supported by the records on clinicaltrials.gov, which state that the relevant trials are now complete.[28-30]

Health economics evidence

10. Please present a formal cost comparison, including:
   a. overview of all relevant aspects of resource use and associated costs of dapagliflozin and the comparator, such as acquisition costs, administration costs, and monitoring costs.

As clinical equivalency is demonstrated in the response to Question 5 and 6, a cost comparison analysis is conducted evaluating the difference in costs treating CKD patients with dapagliflozin and empagliflozin. Drug acquisition, administration, adverse event (AE) and resource use costs are discussed in the following sections.

Drug Acquisition and Administration Costs

The model includes the acquisition costs for dapagliflozin and empagliflozin. Both dapagliflozin and empagliflozin are administered 10 mg once daily orally to patients with CKD.[13, 14] The list prices for the two treatments are both £36.59 per 28-dose pack with no confidential commercial arrangements.[31, 32] As both treatments are administered orally, they are assumed to not incur any administration costs.[13, 14]

The discontinuation rate of dapagliflozin was derived from the DAPA-CKD trial, with a constant rate of discontinuation applied to all patients receiving treatment with dapagliflozin in each modelled cycle.[18] This annual probability of discontinuation was converted to a monthly probability in the model before being applied to the monthly cycles. Discontinuation rate of empagliflozin is assumed to be the same as dapagliflozin. This is supported by the scientific similarity (demonstrated in the response to Question 2) and clinical efficacy equivalency (demonstrated in the response to Question 4 and 5) of dapagliflozin and empagliflozin. The adverse event profile is also comparable between the two treatments in patients with CKD (demonstrated in the response to Question 6). Therefore, there is no logical or scientific reason indicating a difference in discontinuation rate. The same assumption of equivalency is made for the adherence in dapagliflozin and empagliflozin for the same rationale.

However, in patients with CKD with T2D, there is potential for empagliflozin to result in a higher cost than dapagliflozin to the NHS. This was discussed in detail in Section B.4.6 in the Review of TA775 Document B. The empagliflozin summary of product characteristics (SmPC) suggests adding on combination therapy with other medicinal products for the treatment of diabetes and an increase in dosage to 25 mg in tolerating patients who have an eGFR ≥60 mL/min/1.73 m^2 and need tighter glycaemic control.[14] Therefore, these patients might require potential primary care visit for empagliflozin dosing adjustment. Moreover, the SmPC indicates that when eGFR drops below 60 mL/min/1.73 m2, patients will need to be down-titrated to the 10 mg dose.[14] Costs associated with up- and down-titration can impact the overall cost-comparison between empagliflozin and dapagliflozin.

On the other hand, dapagliflozin provides consistent and simple posology across the whole CKD population irrespective of T2D status (demonstrated in the response to Question 2), with the exception of patients with severe hepatic impairment who are initiated at 5 mg before increasing dose to 10 mg if tolerated, thereby alleviating pressure from an already burdened primary care system through the elimination of additional testing, patient visits, and clinician time.[13] This difference in potential primary care needs between dapagliflozin

and empagliflozin is not included in the cost comparison model due to a lack of accurate real-world data, therefore, the cost comparison outcomes are considered conservative.

Table 6. Drug Cost Inputs

Input	Dapagliflozin Value	Source	Empagliflozin Value	Source
Acquisition costs	10 mg once daily	DAPA-CKD[18]	10 mg once daily	EMPA-KIDNEY[19]
Administration costs	£0	Assumption	£0	Assumption
Drug acquisition costs	£36.59 per pack, pack size 28	BNF[32]	£36.59 per pack, pack size 28	BNF[31]
Monthly probability of discontinuation	0.47%	DAPA-CKD[18]	0.47%	Assumption; assumed the same as dapagliflozin

Abbreviations: BNF: British National Formulary

Adverse Events

The modelled probabilities of AEs were informed by the most common serious AEs reported in the DAPA-CKD trial and by the genital infections and urinary tract infections (UTIs) reported in DECLARE-TIMI 58 trial.[18, 33] Genital infection and UTI occurrences were not routinely collected in the DAPA-CKD trial, as genital infections and UTIs were not an AE of special interest. However, the incidences of genital infection and UTI were nevertheless included in the analysis for the proportion of patients with comorbid T2DM at baseline, based on the incidences of these AEs observed in the dapagliflozin and placebo arms of the CV outcomes trial of dapagliflozin in T2DM patients (DECLARE-TIMI 58).[33]

The annual probability of AEs modelled is summarised in Table 7. These annual probabilities were converted to monthly probabilities in the model before being applied to the monthly model cycles. Several meta-analyses have shown similarities of the safety profile across SGLT2 inhibitors with negligible confidence intervals. [21, 22] The consistency in safety profiles between dapagliflozin and empagliflozin was also supported by stakeholder comments in the draft scope of this review. Detailed information is demonstrated in the response to Question 6. Therefore, the cost comparison assumes the same AE rates for dapagliflozin and empagliflozin.

Table 7. AE Rates

Adverse Event	Dapagliflozin Mean Annual Probability	Source	Empagliflozin Mean Annual Probability	Source
Volume depletion	0.031	DAPA-CKD[18]	0.031	Assumed the same as dapagliflozin due to similar mechanism of action, efficacy and safety
Major hypoglycaemic event	0.003		0.003	
Bone fractures	0.020		0.020	
DKA	0.000		0.000	

Adverse Event	Dapagliflozin Mean Annual Probability	Source	Empagliflozin Mean Annual Probability	Source
Amputation	0.009	Calculated based on the event incidence rate in DECLARE-TIMI 58 and proportion of patients with comorbid T2DM in the base case[33]	0.009	profiles (Questions 4, 5 and 6)
Genital infections	[redacted]		[redacted]	
UTI	[redacted]		[redacted]	

Abbreviations: DKA: diabetic ketoacidosis; UTI: urinary tract infection

The per-event costs applied for AEs in the base case cost comparison analysis are summarised in Table 8. All costs were inflated to 2022/2023 values.

The costs of treating volume depletion, UTI, and genital infection were represented by the cost of a GP visit, as it was assumed the majority of these AEs could be treated by oral rehydration therapy, antibiotics, and topical antifungals, respectively. This was sourced from the latest PSSRU Unit Costs of Health and Social Care 2023.[34]

The cost of hypoglycaemic events was informed by Hammer *et al.* (2009), which surveyed the healthcare resource used by patients with T1D and T2D who had experienced a severe hypoglycaemic event.[35] In UK patients with T2D, the estimated average cost per serious hypoglycaemic event was €537. This value was converted to pounds using a conversion rate of £1.00 = €1.473 provided in the paper. The value was inflated from 2007 to 2022/2023 cost year.

The cost of bone fractures was sourced from calculating the weighted average NHS national reference cost 2022/23 total HRG, for fractures in various parts of the body (HE11, HE21, HE41, HE31, HE51, and HE71).[36]

The cost of a diabetic ketoacidosis (DKA) event was estimated from Dhatariya *et al.* (2017), a costing study based on a national survey of UK hospitals on aspects of their care during acute hospital admissions of DKA.[37] The total cost per DKA estimated by Dhatariya *et al.* (2017) included costs for diagnostic and laboratory assessments, nurse and physician contacts, drug usage during the acute phase of DKA admission, and daily ward costs following resolution of DKA.[37]

The cost of amputation was informed by Alva *et al.* (2015), which accounted for inpatient care costs and outpatient care costs associated with amputation in the UKPDS T2DM study.[38] The study found amputation to be associated with inpatient and outpatient care costs of £9,546 and £2,699, respectively. The inpatient and outpatient care costs were summed to inform the cost of amputation in the cost comparison analysis.[38]

Table 8. AE Costs

Adverse Events	2022/2023 Cost	Source	Assumption
Volume depletion	£49.00	PSSRU 2023[34]	Assume one GP visit
Major hypoglycaemic events	£468.96	Hammer *et al.* 2009[35]	Severe hypoglycaemic events
Bone fractures	£2,023.00	NHS Reference Costs 2022/23[36]	Total HRG, weighted average of HE11, HE21, HE41, HE31, HE51 and HE71
DKA	£2,072.29	Dhatariya *et al.* 2017[37]	Dhatariya et al. 2017
Amputation	£12,506.38	Alva *et al.* 2015[38]	Inpatient care cost and outpatient care cost
Genital infections	£49.00	PSSRU 2023[34]	Assume one GP visit
UTI	£49.00	PSSRU 2023[34]	Assume one GP visit

Abbreviations: AE: adverse events; DKA: diabetic ketoacidosis; UTI: urinary tract infection; GP: general practitioner; HRG: Healthcare Resource Groups.

Resource Use

Dapagliflozin and empagliflozin are considered to have no difference in service provision or management due to their similar mechanism of action, efficacy and safety profile demonstrated in the responses to Question 1, 4, 5 and 6. Therefore, there is no logical rationale to believe the management resource use would be different between the two treatments. This assumption was accepted for decision making in the cost comparison conducted for TA942, and formed the basis of the NICE recommendation for empagliflozin.[23] Due to the lack of published accurate data on the frequency of resource use and the clinical equivalence between dapagliflozin and empagliflozin, the current cost comparison analysis does not include resource use costs.

To conclude, the clinical effectiveness of dapagliflozin and empagliflozin is comparable (as shown in the response to Question 4 and 5) for the treatment of adult patients with CKD. A cost comparison model was developed to examine the difference in cost impact between the two treatments over a 5-year time horizon from a UK National Health Service (NHS) perspective. Costs are equivalent for the administration of both treatments. However, dapagliflozin could incur a lower cost due to the up titration of empagliflozin in patients with tolerance. AE costs are included in the model while resource use costs are excluded due to a lack of data. Results of the analysis are shown in Table 9, demonstrating no meaningful difference in costs between the treatments. This conclusion aligns with the cost comparison analysis in TA942.[23]

Table 9: Cost Comparison Results

Technology	Drug Acquisition Costs	Administration Costs	AE Costs	Total Costs
Dapagliflozin	£2,083.50	£0	[redacted]	[redacted]
Empagliflozin	£2,083.50	£0		
Net	£0	£0	£0	£0

Abbreviations: AE: adverse event.

b. *all assumptions that are needed to correctly reflect the clinical practice, such as treatment discontinuation rates, potential dose adjustments due to a loss of efficacy, adherence, adverse events, and time horizon.*

- Treatment effects are assumed to be the same between the two treatments.
- Empagliflozin is assumed to have the same adverse event rates as dapagliflozin.
- Empagliflozin is assumed to have the same discontinuation rates and adherence as dapagliflozin.
- Empagliflozin is assumed to have the same resource use frequency as dapagliflozin, this is not included in the cost comparison model.
- Treatment administration costs are assumed to be zero for empagliflozin and dapagliflozin.
- Time horizon is 5 years.

c. *clear reasoning and justification where costs are considered equivalent and indicate where the resource use and the associated costs may differ between the treatments.*

An overview of the cost-related assumptions in the model are presented in Table 10.

Table 10. Cost Assumptions

Parameter assumed equivalent	Justification
Drug acquisition costs	Dapagliflozin and empagliflozin have the same list price and are both administrated once daily orally. The discontinuation rate and adherence of the two treatments are considered the same, demonstrated in the response to question 10.a. This assumption was accepted in TA942.[23] However, this is a conservative assumption as the up-titration in patients with T2D might result in a higher costs of empagliflozin on the NHS (Question 10a).
Drug administration costs	Dapagliflozin and empagliflozin are both administrated orally therefore are assumed to incur no administration costs.
Adverse event costs	Several meta-analyses have shown similarities of the safety profile across SGLT2 inhibitors (see the response to Question 6).[21, 22] The assumption of similar safety profiles between the two treatments are accepted in TA942.[23]
Resource use costs	Same resource use is assumed based on the clinical equivalence between empagliflozin and dapagliflozin. This assumption was accepted in TA942.[23]

Abbreviations: T2D: type 2 diabetes; NHS: National Health Service; SGLT2: sodium-glucose co-transporter-2.

d. *Please indicate the evidence sources for resource use, costs, and all the other assumptions made in the cost comparison. Where resource use relates to health outcomes (e.g., adverse events, patient adherence), please provide supporting trial data.*

An overview of the model input sources is presented in Table 11.

Table 11. Model input sources and assumptions

Model Input	**Sources**
Drug acquisition costs	BNF 2024[31, 32]
Dosing	Dapa CKD, EMPA-Kidney trial[18, 19]
Adverse event costs	TA775, cited from PSSRU, Hammer et al 2009, NHS Reference Costs 2022/23[36], Dhatariya et al 2017, Alva et al 2015
Adverse event rates	Dapa CKD; calculated based on the event incidence rate in DECLARE-TIMI 58 and proportion of patients with comorbid T2D in the base case[18]
Assumptions	**Evidence**
Dapagliflozin is considered to have a consistent treatment effect independent of uACR, eGFR and T2D status.	Evidence from DAPA–CKD, DAPA–HF, DECLARE–TIMI 58, OPTIMISE CKD and Nakhleh et al., 2024 provides evidence demonstrating that dapagliflozin is associated with similar kidney protective effects and cardiorenal risk reduction among patients with CKD irrespective of T2D status, uACR category or eGFR category (see the response to Question 1).[1-6]
Treatment effects are assumed to be the same between dapagliflozin and empagliflozin.	Dapagliflozin and empagliflozin have similar mechanism of action as demonstrated in the response to Question 1. The clinical effectiveness of dapagliflozin is comparable to empagliflozin supported by several ICTs, NMAs and clinical opinions as demonstrated in the response to Question 4 and Question 5. This has been accepted for decision making TA942. [23]
Empagliflozin is assumed to have the same adverse event rates as dapagliflozin.	The similar mechanism of action of empagliflozin and dapagliflozin (Question 2), indicates no rational to believe the discontinuation rate and adherence should differ between the two treatments. The adverse event profile is also comparable.[10, 22] Several meta-analyses have shown similarities of the safety profile across SGLT2 inhibitors with narrow confidence intervals (Question 6).[21, 22] This assumption was accepted in TA942.[23]
Empagliflozin is assumed to have the same discontinuation and adherence rates as dapagliflozin.	Similar mechanism of action (Question 2) and clinical efficacy equivalency (Question 4 and 5) of dapagliflozin and empagliflozin indicates no rational to believe the discontinuation rate and adherence should differ between the two treatments. The adverse event profile is also comparable between the two treatments in patients with CKD (Question 6).
Treatment administration costs are assumed to be zero for empagliflozin and dapagliflozin.	The mode of administration for empagliflozin and dapagliflozin, once daily oral tablet, does not incur any additional administration cost.[13, 14]
Empagliflozin is assumed to have the same resource use frequency as	Same resource use is assumed based on the clinical equivalence and similar mechanism of action of

dapagliflozin, this is not included in the cost comparison model.	empagliflozin and dapagliflozin (Question 1, 5 and 6). This assumption was also accepted in TA942.[23]

Abbreviations: BNF: British National Formulary; PSSRU: Personal Social Services Research Unit; T2DM: type 2 diabetes mellitus; SGLT2: Sodium-glucose co-transporter-2.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Dapagliflozin for the treatment of adults with chronic kidney disease – Review of TA775 [ID6411]

Summary of Information for Patients (SIP)

June 2024

File name	Version	Contains confidential information	Date
ID6411_Dapaglifolzin_CKD_TA775 review_SIP	Final	No	19/06/2024

Summary of Information for Patients (SIP):

The pharmaceutical company perspective

What is the SIP?

The Summary of Information for Patients (SIP) is written by the company who is seeking approval from NICE for their treatment to be sold to the NHS for use in England. It is a plain English summary of their submission written for patients participating in the evaluation. It is not independently checked, although members of the public involvement team at NICE will have read it to double-check for marketing and promotional content before it is sent to you.

The **Summary of Information for Patients** template has been adapted for use at NICE from the Health Technology Assessment International – Patient & Citizens Involvement Group (HTAi PCIG). Information about the development is available in an open-access IJTAHC journal article

SECTION 1: Submission summary

1a) Name of the medicine (generic and brand name):

Dapagliflozin (Forxiga®)

1b) Population this treatment will be used by. Please outline the main patient population that is being appraised by NICE:

Dapagliflozin is already recommended by the **National Institute of Health and Care Excellence (NICE),** following a **technology appraisal (TA)** called TA775, for treating **chronic kidney disease (CKD)** in adults who have an **estimated glomerular filtration rate (eGFR)** of 25 ml/min/1.73 m^2 to 75 ml/min/1.73 m^2 at the start of treatment and:(1)

- Have **type 2 diabetes (T2D)**, or
- Have a **urine albumin-to-creatinine ratio (uACR)** of 22.6 mg/mmol or more.

Dapagliflozin is a **sodium-glucose co-transporter-2 (SGLT2) inhibitor** which has been shown to have similar effectiveness and safety to an alternative SGLT2 inhibitor, called **empagliflozin.**(2) Despite being considered to have similar effectiveness to dapagliflozin, empagliflozin was recommended by NICE for CKD in TA942 in an expanded population of adults with an eGFR rate of:

- 20 ml/min/1.73 m^2 to less than 45 ml/min/1.73 m^2, or
- 45 ml/min/1.73 m^2 to 90 ml/min/1.73 m^2 and either:
  - T2D, or
  - a uACR of 22.6 mg/mmol or more.

The purpose of this submission is to review the current NICE recommendation for dapagliflozin in CKD and align it with the NICE recommendation for empagliflozin in CKD. Therefore, this targeted review includes the subgroups of patients which are currently recommended in TA942 but not in TA775. These are:

1. Adults with CKD, without T2D, and with:
   a. eGFR ≥20–45 mL/min/1.73m^2 and a uACR <22.6 mg/mmol (200 mg/g); or
   b. eGFR ≥20–25 mL/min/1.73m^2 and a uACR ≥22.6 mg/mmol (≥200 mg/g); or
   c. eGFR >75–90 mL/min/1.73m^2 and a uACR ≥22.6 mg/mmol (≥200 mg/g).
2. Adults with CKD, with T2D, and with:
   a. eGFR ≥20–25 mL/min/1.73m^2; or
   b. eGFR >75–90 mL/min/1.73m^2.

Further details about the condition and disease staging are provided in **Section 2a** of this document, with a table summarising the different subgroups of adult patients with CKD considered within this submission provided in **Section 2c.**

Please note: Further explanations for the words and phrases highlighted in **blue bold text** are provided in the glossary (**Section 4b**). Cross references to other sections are highlighted in **purple bold text**.

1c) Authorisation: Please provide marketing authorisation information, date of approval and link to the regulatory agency approval. If the marketing authorisation is pending, please state this, and reference the section of the company submission with the anticipated dates for approval.

This submission is covered by the **marketing authorisation** of dapagliflozin from the **Medicines and Healthcare products Regulatory Agency (MHRA)**, which is indicated for the treatment of:(3)

- Adults and children aged 10 years and above with insufficiently controlled T2D as an adjunct to diet and exercise, either as a monotherapy when metformin is considered inappropriate due to intolerance or in addition to other medicinal products for the treatment of T2D;
- Adults with symptomatic chronic **heart failure (HF)**;
- Adults with CKD.

Dapagliflozin received marking authorisation for the treatment of adult patients with CKD in August 2021: https://www.medicines.org.uk/emc/product/7607/smpc

1d) Disclosures. Please be transparent about any existing collaborations (or broader conflicts of interest) between the pharmaceutical company and patient groups relevant to the medicine. Please outline the reason and purpose for the engagement/activity and any financial support provided:

AstraZeneca UK Limited engages with the following patient advocacy groups relevant to this medicine, with the aims of strengthening patient insights and responding to requests for information:

- Diabetes UK
- Kidney care UK
- Kidney Research UK
- National Kidney Federation
- Pumping Marvellous Foundation

Funding provided to UK patient groups is published annually on the AstraZeneca UK's website, which can be accessed here: https://www.astrazeneca.co.uk/partnerships/working-with-patient-groups.

SECTION 2: Current landscape

2a) The condition – clinical presentation and impact

Please provide a few sentences to describe the condition that is being assessed by NICE and the number of people who are currently living with this condition in England.

Please outline in general terms how the condition affects the quality of life of patients and their families/caregivers. Please highlight any mortality/morbidity data relating to the condition if available. If the company is making a case for the impact of the treatment on carers this should be clearly stated and explained.

What is chronic kidney disease (CKD)?

CKD is a long-term condition where the kidneys do not work as well as they should.(4) The kidneys are responsible for filtering the blood to remove waste products and excess water, which are converted into urine and excreted.(5) In CKD, progressive damage triggers harmful changes which cause kidney function to decline over time, eventually leading to **end-stage kidney disease** (ESKD) in some patients, at which point the kidneys no longer function sufficiently to maintain health and **homeostasis**.(6)

CKD is usually caused by other conditions that put a strain on the kidneys, including:(4)

- **Hypertension** – over time, this can put strain on the small blood vessels in the kidneys and stop the kidneys working properly;
- **Diabetes** – too much glucose in your blood can damage the tiny filters in the kidneys;
- High **cholesterol** – this can cause a build-up of fatty deposits in the blood vessels supplying your kidneys, which can make it harder for them to work properly;
- Kidney infections;
- **Glomerulonephritis** – kidney inflammation.

In addition to contributing to the development of CKD, conditions such as T2D, hypertension and **cardiovascular disease** (CVD; including HF) can also develop as a result of reduced kidney function.(7, 8) T2D and CVD, therefore, commonly co-occur with CKD both as a cause and as a result of CKD.

What are the different stages of CKD?

CKD is categorised based how damaged your kidneys are, with higher eGFR and uACR stages indicating more severe kidney disease. The eGFR is categorised from stage from 1 of 5:(4)

- Stage 1 (G1) – a normal eGFR above 90ml/min, but other tests have detected signs of kidney damage
- Stage 2 (G2) – a slightly reduced eGFR of 60 to 89ml/min, with other signs of kidney damage
- Stage 3a (G3a) – an eGFR of 45 to 59ml/min
- Stage 3b (G3b) – an eGFR of 30 to 44ml/min
- Stage 4 (G4) – an eGFR of 15 to 29ml/min
- Stage 5 (G5) – an eGFR below 15ml/min, meaning the kidneys have lost almost all of their function

Whereas uACR is categorised from stage 1 to 3:(4)

- A1 – an uACR of less than 3mg/mmol
- A2 – an uACR of 3 to 30mg/mmol
- A3 – an uACR of more than 30mg/mmol

ESKD, the most severe stage of CKD, is defined as eGFR consistently <15 mL/min/1.73m^2.(9) Increased uACR and decreased eGFR are independently associated with an increased risk of adverse outcomes, and these parameters are, therefore, used to guide decisions for monitoring, treatment and referral to specialist care.(9, 10)

How common is CKD?

CKD is a common condition often associated with getting older.(4) An estimated 7.19 million people in the UK had CKD (all stages) in 2023, which corresponded to 12.8% of the population aged 16 years or older. By disease stage (and excluding **transplantation** and **dialysis** patients), this included 3.9 million people (55%) with CKD stage 1-2 and 3.25 million people (45%) with CKD stage 3-5 in the UK.(11)

What is the impact of CKD?

Life expectancy

CKD can get worse over time and eventually the kidneys may stop working altogether, but this is uncommon. Many people with CKD are able to live long lives with the condition.(4) However, older adults over the age of 70 years, who are on dialysis, have an average life expectancy which is about half of that of people with a kidney transplant, and about three times less than people of the same age in the general population. This difference in average life expectancy increases as age decreases.(12)

Symptoms of CKD and their physical impact

People with CKD do not usually have symptoms during the early stages of the disease. It may only be diagnosed if you have a blood or urine test for another reason and the results show a possible problem with your kidneys.(4) Symptoms such as weight loss and poor appetite, swollen ankles, feet or hands, shortness of breath, tiredness, feeling sick and itchy skin can develop as the disease progresses.(9, 13)

Patients with CKD experience worsening kidney function over time, which can be observed as declining eGFR, and this may eventually lead to ESKD where some patients will require dialysis or a kidney **transplant** (collectively termed renal replacement therapy).(6)

CKD is also associated with a substantial clinical burden outside of adverse **renal** outcomes, encompassing an increased risk of **cardiovascular** (CV) events, CV and all-cause mortality, and also **morbidity** resulting from complications such as **anaemia**. Despite the asymptomatic nature of early-stage CKD, even patients with earlier stages of CKD have a significantly increased risk of CV events, ESKD and premature mortality compared to the general population. However, later stages of CKD and higher **albuminuria** categories are associated with a particularly elevated risk compared with earlier stages.(14)

Impact on quality of life

In research, the physical and mental health of patients are referred to as **health-related quality of life (HRQoL).** The HRQoL of patients are typically measured through patient questionnaires, and their scores are compared to those of the general population to assess the impact of disease. CKD has a considerable impact on the HRQoL of patients, comprising physical, emotional, and social wellbeing, which increases as the disease progresses. An analysis of data from the 2010 Health Survey for England indicated that patients with stage 4/5 CKD reported significantly reduced HRQoL scores for mobility, usual activity and pain/discomfort compared to those with normal kidney function and stage 1 CKD.(15)

The requirement for dialysis for patients with ESKD can be distressing, and further reduces HRQoL, as patients may have to attend lengthy appointments three times a week and adhere to strict dietary and fluid restrictions.(16, 17) One study reported that patients with ESKD experienced greater decreases in HRQoL compared with the general population and compared with patients with other chronic diseases such as arthritis and cancer.(18)

Impact on families and carers

CKD and the requirement for dialysis can also affect the families and caregivers of patients, who are often responsible for providing transport to appointments and administering treatment including home dialysis, which can reduce their own HRQoL. For example, a 2019 **systematic literature review** (SLR) which identified 61 studies, of which two were in a UK population, found that the quality of life for caregivers of patients with CKD receiving dialysis was poorer compared to the general population, and was largely comparable to carers of patients with other chronic conditions, such as cancer and frailty in old age.(19)

2b) Diagnosis of the condition (in relation to the medicine being evaluated)

Please briefly explain how the condition is currently diagnosed and how this impacts patients. Are there any additional diagnostic tests required with the new treatment?

How is CKD diagnosed?

The main test for CKD is a blood test. The test measures the levels of a waste product called **creatinine** in your blood.(4)

- A doctor uses your blood test results, plus your age, size, and gender to calculate how many millilitres of waste your kidneys should be able to filter in a minute.
- This calculation is known as your eGFR.
- Healthy kidneys should be able to filter more than 90ml/min. You may have CKD if your rate is lower than this.

A urine test is also done to:(4)

- Check the levels of substances called **albumin** and creatinine in your urine – known as the uACR.
- Check for blood or protein in your urine.

Alongside your eGFR, urine tests can help give a more accurate picture of how well your kidneys are working.(4)

There are no additional diagnostic tests required to receive treatment with dapagliflozin, and dapagliflozin is already used widely within clinical practice for patients with CKD, if people have an eGFR of 25 ml/min/1.73 m^2 to 75 ml/min/1.73 m^2 at the start of treatment and:(1)

- have T2D or
- have a uACR of 22.6 mg/mmol or more.

2c) Current treatment options:

The purpose of this section is to set the scene on how the condition is currently managed:

- What is the treatment pathway for this condition and where in this pathway the medicine is likely to be used? Please use diagrams to accompany text where possible. Please give emphasis to the specific setting and condition being considered by NICE in this review. For example, by referencing current treatment guidelines. It may be relevant to show the treatments people may have before and after the treatment under consideration in this SIP.
- Please also consider:
  - if there are multiple treatment options, and data suggest that some are more commonly used than others in the setting and condition being considered in this SIP, please report these data.
  - are there any drug–drug interactions and/or contraindications that commonly cause challenges for patient populations? If so, please explain what these are.

What current treatment guidelines are used for the management of CKD within the National Health Service (NHS)?

The management of CKD in the NHS is currently informed by the clinical guideline for CKD (called NG203) and T2D (called NG28), published by the NICE.(9, 20) These guidelines provide recommendations to doctors on what treatments should be prescribed for patients with CKD.(9, 20)

What is the current treatment pathway for CKD?

There is no cure for CKD, but treatment can help relieve symptoms and stop it from getting worse. The current standard of care (Soc) for the management of CKD in England encompasses a variety of treatment strategies, including:(4, 21-24)

- Lifestyle changes, such as quitting smoking and eating a healthy balanced diet;
- Medicines to help control many of the problems that cause the condition and the complications that can happen as a result of it:
  - **Angiotensin converting enzyme (ACE) inhibitors** to help control high **blood pressure**;
  - An SGLT2 inhibitor, such as dapagliflozin or empagliflozin, to help control T2D, HF or a high uACR;
  - Statins to help control high cholesterol.
- Management of additional complications such as anaemia or bone problems.

Since the appraisal of dapagliflozin in CKD in TA775,(1) SGLT2 inhibitors have become routinely recommended for the treatment of patients with CKD, with and without T2D, in addition to optimised SoC. However, current NICE guidelines for the management of CKD (NG203) only recommend SGLT2 inhibitors in selected CKD patients who meet uACR thresholds and/or have T2D, despite the availability of evidence demonstrating **efficacy** of SGLT2 inhibitors across the uACR spectrum, irrespective of diabetes status.

Table 1 summarises the currently recommended SGLT2 inhibitor treatments within the NHS for CKD in addition to SoC, by diabetes status and eGFR range.

Table 1. Recommended SGLT2 inhibitor treatments for CKD in addition to SoC by eGFR and uACR

	uACR (mg/mmol)			
	With T2D		Without T2D	
eGFR range (mL/min/1.73 m²)	≥22.6	<22.6	≥22.6	<22.6
20–25	Empagliflozin	Empagliflozin	Empagliflozin	Empagliflozin
25–<45	Dapagliflozin Empagliflozin	Dapagliflozin Empagliflozin	Dapagliflozin Empagliflozin	Empagliflozin
≥45–75	Dapagliflozin Empagliflozin	Dapagliflozin Empagliflozin	Dapagliflozin Empagliflozin	None recommended
>75–90	Empagliflozin	Empagliflozin	Empagliflozin	None recommended

Abbreviations: CKD: chronic kidney disease; eGFR: glomerular filtration rate; SoC: standard of care; SGLT2: sodium-glucose co-transporter-2; T2D: type 2 diabetes; uACR: urine albumin-creatinine ratio.
Source: NG203, TA775 and TA942.(1, 2, 9)

Where in the current treatment pathway would dapagliflozin be used?

As summarised in Table 2, the positioning of dapagliflozin in the existing care pathway would be in addition to optimised SoC and as an alternative to empagliflozin.

This review will enable dapagliflozin to become an alternative to empagliflozin for the treatment of patients with CKD, with an eGFR ≥20 and <45 mL/min/1.73m² with or without T2D, and patients with CKD with an eGFR ≥45 and <90 mL/min/1.73m² and either a uACR ≥22.6 mg/mmol or T2D, thereby providing both patients and physicians with choice of medications based on best available evidence to optimise treatment plans.

A recommendation for dapagliflozin within this setting will enable continuity of care and increase clinician and patient treatment choice in a difficult to treat area to optimise treatment plans based on the best available evidence. Ultimately, this will improve treatment outcomes and delay the progression of patients to ESKD and renal replacement therapy.

Table 2. Proposed positioning of dapagliflozin

	uACR (mg/mmol)			
	With T2D		Without T2D	
eGFR range (mL/min/1.73 m²)	≥22.6	<22.6	≥22.6	<22.6
20–25	**Dapagliflozin** Empagliflozin	**Dapagliflozin** Empagliflozin	**Dapagliflozin** Empagliflozin	**Dapagliflozin** Empagliflozin
25–<45	Dapagliflozin Empagliflozin	Dapagliflozin Empagliflozin	Dapagliflozin Empagliflozin	**Dapagliflozin** Empagliflozin
≥45–75	Dapagliflozin Empagliflozin	Dapagliflozin Empagliflozin	Dapagliflozin Empagliflozin	None recommended
>75–90	**Dapagliflozin** Empagliflozin	**Dapagliflozin** Empagliflozin	**Dapagliflozin** Empagliflozin	None recommended

Footnote: Green border indicates the patient group in which dapagliflozin can be recommended in this review to align with the recommendation for empagliflozin in TA942.
Abbreviations: CKD: chronic kidney disease; eGFR: glomerular filtration rate; SoC: standard of care; T2D: type 2 diabetes; uACR: urine albumin-creatinine ratio.

2d) Patient-based evidence (PBE) about living with the condition

Context:

- **Patient-based evidence (PBE)** is when patients input into scientific research, specifically to provide experiences of their symptoms, needs, perceptions, quality of life issues or experiences of the medicine they are currently taking. PBE might also include carer burden and outputs from patient preference studies, when conducted in order to show what matters most to patients and carers and where their greatest needs are. Such research can inform the selection of patient-relevant endpoints in clinical trials.

In this section, please provide a summary of any PBE that has been collected or published to demonstrate what is understood about **patient needs and disease experiences**. Please include the methods used for collecting this evidence. Any such evidence included in the SIP should be formally referenced wherever possible and references included.

CKD including non-T2D CKD has a considerable impact on the HRQoL of patients, including physical, emotional, and social wellbeing, which increases as the disease progresses, as highlighted in **Section 2a.**

A study conducted in the UK, US and Australia included adult patients with any stage of CKD and caregivers to identify patient and caregiver prioritises for outcomes important for research in CKD.(25) Across 10 focus groups, 67 participants (54 patients and 13 caregivers) identified and ranked the outcomes, and the reasons for their choices was discussed. The top five outcomes ranked by participants in the UK were kidney function, ESKD, mortality, blood pressure, and fatigue.(25)

The key themes that explained participants' choices and prioritisation of outcomes were discussed. Patients were fearful of needing dialysis: *"It's kind of a scary thing because when you have a kidney disease, you know that if your kidneys aren't functioning you're going to die. You just know that you're going to go to dialysis and you're going to die" (Female, UK, CKD).* Patients also reported feelings of despair in being confronted with death: *"But when you're in early stage, you would want to know. That was the first question, am I going to die?" (Female, UK, transplant).*(25)

Additionally, caregivers emphasised the impact CKD can have on life activities and goals: *"Fatigue was her number 1 thing. She was going to school full time, I don't know how she managed that. She'd go to school and come home and sleep the whole day" (Female, US, caregiver).* The emotional impact of CKD on patients was also highlighted*: "Just in terms of with any kind of disease and particularly since we're here discussing this there is a mental and emotional impact, finding out you have this, stages of grief and then there's things that you go through" (Female, Australia, caregiver).*(25)

SECTION 3: The treatment

3a) How does the new treatment work?

What are the important features of this treatment?

Please outline as clearly as possible important details that you consider relevant to patients relating to the mechanism of action and how the medicine interacts with the body

Where possible, please describe how you feel the medicine is innovative or novel, and how this might be important to patients and their communities.

If there are relevant documents which have been produced to support your regulatory submission such as a summary of product characteristics or patient information leaflet, please provide a link to these.

Overview of dapagliflozin

The summary of product characteristics (SmPC) for dapagliflozin (Forxiga®) can be found here:(3)
https://www.medicines.org.uk/emc/product/7607/smpc

A patient information leaflet for dapagliflozin is available here:(26)
https://www.medicines.org.uk/emc/product/7607/pil#gref.

What is dapagliflozin and how does it work?

Dapagliflozin contains the active substance dapagliflozin. It belongs to a group of medicines called "sodium glucose co-transporter-2 (SGLT2) inhibitors". They work by blocking the SGLT2 protein in your kidney. By blocking this protein, blood sugar (glucose), salt (sodium) and water are removed from your body via the urine.(26)

When you have CKD, your kidneys may gradually lose their function. This means they would not be able to clean and filter your blood the way they should. Loss of kidney function can lead to serious medical problems and need for hospital care. Dapagliflozin helps protect your kidneys from losing their function, which can help some patients to live longer.(26)

3b) Combinations with other medicines

Is the medicine intended to be used in combination with any other medicines?

- Yes / No

If yes, please explain why and how the medicines work together. Please outline the mechanism of action of those other medicines so it is clear to patients why they are used together.

If yes, please also provide information on the availability of the other medicine(s) as well as the main side effects.

If this submission is for a combination treatment, please ensure the sections on efficacy (3e), quality of life (3f) and safety/side effects (3g) focus on data that relate to the combination, rather than the individual treatments.

There are no requirements for dapagliflozin to be given alongside any other specific medicines.(3) However, as described above, it is expected that dapagliflozin will be given in addition to optimised SoC.

3c) Administration and dosing

How and where is the treatment given or taken? Please include the dose, how often the treatment should be given/taken, and how long the treatment should be given/taken for.

How will this administration method or dosing potentially affect patients and caregivers? How does this differ to existing treatments?

How much dapagliflozin to take:(26)

- The recommended dose of dapagliflozin is one 10 mg tablet each day.
- Your doctor may start you on a 5 mg dose if you have a liver problem.
- Your doctor will prescribe the strength that is right for you.

Taking dapagliflozin:(26)

- Swallow the tablet whole with half a glass of water.
- You can take your tablet with or without food.
- You can take the tablet at any time of the day. However, try to take it at the same time each day. This will help you to remember to take it.

3d) Current clinical trials

Please provide a list of completed or ongoing clinical trials for the treatment. Please provide a brief top-level summary for each trial, such as title/name, location, population, patient group size, comparators, key inclusion and exclusion criteria and completion dates etc. Please provide references to further information about the trials or publications from the trials.

DAPA-CKD was the key **clinical trial** investigating how well dapagliflozin works in patients with CKD, which was previously assessed by NICE in TA775. However, since TA775, additional real-world evidence (RWE) has been generated for dapagliflozin in CKD, including OPTIMISE-CKD and a **retrospective** study by Nakhleh *et al.,* 2024. A summary of the relevant evidence demonstrating the effectiveness of dapagliflozin in CKD, irrespective of uACR levels and diabetes status, is provided below.

DAPA-CKD(27)

DAPA-CKD (NCT03036150) was a double-blind, randomised controlled trial (RCT), which means that the treatment each patient received in the trial was decided randomly, and both the patient and care provider were blinded to the treatment being given. The trial studied how well dapagliflozin, in addition to SoC, works (its efficacy) in treating a broad range of patients with CKD, including those with and without **comorbid** T2D. DAPA-CKD was an international trial and included 4,304 patients in total from around the world. In the trial, 2,152 patients were given dapagliflozin in addition to SoC, and 2,152 patients were given **placebo** in addition to SoC.

Adults with or without T2D who had an eGFR of 25–75 mL/minute/1.73 m^2 and a uACR of 22.6–565 mg/mmol (200–5,000 mg/g) were eligible to be included in the trial. Key exclusion criteria were a documented diagnosis of type 1 diabetes, **polycystic kidney disease, lupus nephritis, or antineutrophil cytoplasmic antibody‑associated vasculitis**.

The primary endpoint (goal) of the study was a combined endpoint, which measured the time to occurrence of any of the following events:

- ≥50% sustained decline in eGFR from baseline
- Reaching ESKD
- CV death
- Renal death

The main publication detailing the DAPA-CKD trial can be found here: https://www.nejm.org/doi/full/10.1056/NEJMoa2024816

OPTIMISE-CKD

OPTIMISE-CKD was an **observational study** programme which included 28,795 patients newly treated with dapagliflozin for CKD with or without T2D in the United States (US), and 20,407 patients with CKD in the US and Japan. The goal was to describe dapagliflozin treatment for CKD in routine clinical practice. Different analyses of the data collected during this study were conducted, including those by Svensson *et al*., 2024 and Tangri *et al*., 2024.

Svensson et al., 2024(28)

The first observational study as part of the OPTMISE-CKD programme included data from the US to compare kidney and **cardiorenal protection** in patients without T2D across uACR levels after initiation of dapagliflozin 10 mg in addition to SoC for the treatment of CKD.

Adult patients with CKD without T2D were included in the primary analysis, whereas patients with T2D were included in the supportive analysis. Patients with prior use of an SGLT2 inhibitor, CKD stage 5 or type 1 or **gestational diabetes** were excluded.

Baseline uACR was grouped as normal/mildly elevated (0–29 mg/g), low (30–200 mg/g) and high (>200 mg/g). In total, 1480 patients had low (n=796) and high (n=684) uACR.

28,795 new users of dapagliflozin 10 mg were identified:

- In those without T2D, 3,029 (27%) had a uACR reading, of which 796 (26%) had low, 684 (23%) had high and 1,549 (51%) had normal/mildly elevated uACR.
- In those with T2D, 7,776 (45%) has a uACR reading, of which 2,411 had low (31%), 1,983 (26%) had high and 3,382 (43%) had normal/mildly elevated uACR.

The study measured eGFR outcomes and clinical outcomes, including in-patient hospitalisations, a diagnosis of CKD, HF and all-cause mortality. Outcomes were compared for patients with T2D versus without T2D, and across uACR subgroups.

The main publication detailing the study by Svensson et al., 2024 can be found here: https://academic.oup.com/ckj/advance-article/doi/10.1093/ckj/sfae100/7640869

Tangri et al., 2024(29)

A second observational study from OPTMISE-CKD included data from the US and Japan, with two objectives:

1) To describe the real-world utilisation of dapagliflozin 10 mg following its approval for the CKD indication in the US and Japan, and
2) To assess the real-world effectiveness of initiating versus not initiating dapagliflozin 10 mg on kidney function decline in patients with uACR <200 mg/g.

For the first objective, data was included from all adult patients with CKD if they initiated or were eligible for dapagliflozin 10 mg during the study period. For the second objective, adult patients were required to meet a CKD definition on or within 2 years before the index date, specifically: uACR ≥30 mg/g, **urine protein creatinine ratio** (**uPCR)** ≥150 mg/g, CKD diagnosis code and two eGFR measurements ≥90 days apart, both <60 mL/min/1.73 m^2. The index date of dapagliflozin initiators was defined as the date of the first dapagliflozin 10 mg prescription. The detailed exclusion criteria is listed in the publication, link provided below.

For the assessment of objective one, 20,407 dapagliflozin 10 mg initiators were included in the analysis.

For objective two, 3,029 dapagliflozin 10 mg initiators with uACR <200 mg/g were included. Additionally, 13,813 comparators who did not initiate dapagliflozin 10 mg were randomly sampled from 444,000 potential comparator patients.

- Each dapagliflozin initiator was matched 1:1 with a potential comparator patient who had not initiated treatment on the same date and had the closest **matching propensity score**. This resulted in 2,972 dapagliflozin 10 mg initiators being matched with a comparator patient.

The primary study outcome was eGFR slope (declining eGFR over-time) between index and the end of follow-up.

The main publication detailing the study by Tangri et al., 2024 can be found here: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10879247/

Nakhleh et al., 2024(30)

The study by Nakhleh et al., 2024 was an observational study in Israel to evaluate the real-world effectiveness of SGLT2 inhibitors on the progression of CKD in patients without diabetes, with and without albuminuria.

Patients were included if they were aged >18 years, had a baseline eGFR of 25–60 mL/min/1.73 m^2, and received an SGLT2 inhibitor (empagliflozin or dapagliflozin) between September 2020 and November 2022. Patients were excluded if they had type 1 or 2 diabetes, were pregnant or had no baseline or follow-up slopes (individuals who did not have a minimum of 2 eGFR evaluations, with at least 180 days between them in each period). In total, 354 participants were included in the analysis.

The efficacy of dapagliflozin was measured according to change in eGFR slope (declining eGFR over-time) from baseline to follow-up.

The main publication detailing the study by Nakhleh et al., 2024 can be found here: https://dom-pubs.pericles-prod.literatumonline.com/doi/10.1111/dom.15623

Supporting RCT data outside of the DAPA-CKD trial

The efficacy of dapagliflozin in the broader population of patients with CKD, regardless of uACR and eGFR category, is further supported by RCTs called DECLARE-TIMI 58 and DAPA-HF. While the DAPA-CKD trial enrolled patients with an eGFR of 25–75 mL/min/1.73 m^2 and a uACR of 200–5,000 mg/g (22.6–565 mg/mmol), the extensive clinical trial program for dapagliflozin in T2D and heart failure with a reduced **ejection fraction** (**HFrEF)** covers patients with a range of renal functions and provides data supporting the efficacy of dapagliflozin in patients who were not eligible for inclusion in DAPA-CKD with respect to uACR and eGFR.

DECLARE-TIMI 58(31, 32)

DECLARE-TIMI 58 (NCT01730534) was a double-blind RCT to study how well dapagliflozin, in addition to SoC, works (its efficacy) in treating patients with T2D with either established CVD or CV risk factors. DECALIRE-TIMI 58 was an international trial and included 17,160 patients in total from around the world. In the trial, 8,582 patients were given dapagliflozin in addition to SoC, and 8,578 patients were given placebo in addition to SoC. As the trial enrolled a proportion of patients with comorbid CKD, it is, therefore, of relevance to this appraisal.

Patients with T2D and either established **atherosclerotic cardiovascular disease (ASCVD;** age ≥40 years and either **ischaemic heart disease**, **cerebrovascular disease**, or **peripheral arterial disease**), or multiple risk factors for ASCVD (age ≥55 years for men or ≥60 years for women plus at least one of **dyslipidaemia**, hypertension, or current tobacco use) were eligible to be enrolled.

The primary safety outcome was a composite of major adverse cardiovascular events (MACE), defined as CV death**,** a heart attack, or **ischemic stroke**. The primary efficacy outcomes were MACE and a composite of CV death or hospitalisation for HF.

The main publication detailing the DECLARE-TIMI 58 trial can be found here:
https://www.nejm.org/doi/full/10.1056/NEJMoa1812389

DAPA-HF(33, 34)

DAPA-HF (NCT03036124) was a double-blind RCT to study how well dapagliflozin, in addition to SoC, works (its efficacy) on the incidence of worsening HF or CV death in patients with chronic HF with reduced **ejection fraction.** DAPA-HF was an international trial and included 4,744 patients in total from around the world. In the trial, 2,373 patients were given dapagliflozin in addition to SoC, and 2,371 patients were given placebo in addition to SoC. As the trial enrolled a proportion of patients with comorbid CKD, it is, therefore, of relevance to this appraisal.

Patients were included in the trial if they were aged at least 18 years, had an ejection fraction of 40% or less, and had New York Heart Association (NYHA) class II, III, or IV symptoms. Exclusion criteria included recent treatment with or unacceptable side effects associated with an SGLT2 inhibitor, type 1 diabetes, symptoms of **hypotension** or a **systolic blood pressure** of less than 95 mm Hg, and an eGFR below 30 ml per minute per 1.73 m^2 (or rapidly declining renal function).

The primary outcome of DAPA-HF was the composite of worsening HF (HF hospitalisation or urgent visit for HF requiring intravenous therapy) or CV death, whichever occurred first.

The main publication detailing the DAPA-HF trial can be found here:
https://www.nejm.org/doi/full/10.1056/NEJMoa1911303

3e) Efficacy

Efficacy is the measure of how well a treatment works in treating a specific condition.

In this section, please summarise all data that demonstrate how effective the treatment is compared with current treatments at treating the condition outlined in section 2a. Are any of the outcomes more important to patients than others and why? Are there any limitations to the data which may affect how to interpret the results? Please do not include academic or commercial in confidence information but where necessary reference the section of the company submission where this can be found.

Evidence previously assessed in TA775 - DAPA-CKD(27)

The DAPA-CKD trial was considered as part of TA775 (the initial appraisal of dapagliflozin for treating CKD) and provided strong clinical evidence that patients with CKD with an eGFR of 25–75 mL/min/1.73m^2 and a uACR of 22.6–565 mg/mmol (200-5,000 mg/g) would receive a significant benefit from treatment with dapagliflozin. Overall, the results of the DAPA-CKD study demonstrate that dapagliflozin is an effective and well tolerated treatment across a wide range of patients, including those with and without comorbid T2D and comorbid CVD. By delaying CKD progression, reducing the risk of chronic dialysis and reducing all-cause

mortality compared with SoC, dapagliflozin can reduce the burden of CKD to the NHS and improve outcomes for patients with CKD.

The DAPA-CKD trial met its primary efficacy endpoint (goal). **Relative risk (RR)** is used in clinical trials to measure the ratio of the probability of an event occurring in the exposed group versus the probability of the event occurring in the non-exposed group. In DAPA-CKD, patients who received treatment with dapagliflozin had a significantly reduced RR of a composite outcome of sustained decline in eGFR ≥50%, ESKD or death from renal or CV causes by 39%, versus patients receiving placebo. Fewer patients in the dapagliflozin group experienced significant kidney decline than those in the placebo group, and they were also less likely to reach ESKD. Importantly, a 34% reduction in the RR of chronic dialysis was observed with dapagliflozin compared with placebo.

Additional evidence generated for dapagliflozin since TA775

As discussed in **Section 1b and Section 2c**, the purpose of this submission is to review the current NICE recommendation which was made in TA775 for dapagliflozin in CKD. The additional RWE which has been generated for dapagliflozin in CKD since TA775 is presented below, to support dapagliflozin becoming an alternative to empagliflozin for the treatment of patients with CKD, with an eGFR ≥20 and <45 mL/min/1.73m^2 with or without T2D, and patients with CKD with an eGFR ≥45 and <90 mL/min/1.73m^2 and either a uACR ≥22.6 mg/mmol or T2D.

A patients eGFR can be used in clinical studies to assess how well the kidneys are filtering, measured using millilitres of cleansed blood per minute per body surface area (a measurement that reads mL/min/1.73m^2). In clinical studies, the eGFR slope is the mean change in eGFR over a pre-specified time period, where the effect of a treatment is expressed as the mean difference between the eGFR slope in the groups of patients being compared in the study (e.g., the treatment group and the placebo group).(35) The eGFR slope is used as a **surrogate endpoint** to predict CKD progression.(36)

Consistent treatment effect of dapagliflozin in patients with non-T2D and uACR <22.6 mg/mmol (<200 mg/g)

OPTIMISE-CKD

- **Svensson et al., 2024(28)**
    - Both moderately increased and moderately to severely increased uACR groups (3–22.6 mg/mmol [30–200 mg/g] and >22.6 mg/mmol [>200 mg/g] respectively; described as low uACR and high uACR in the study) were reported to have an eGFR decrease of 3 mL/min/1.73 m^2 after starting on dapagliflozin (patients without T2D). The change over time in eGFR was consistent for both groups.
    - Patients with normal/mildly elevated uACR (0–3 mg/mmol [0–29 mg/g]) showed similar eGFR slopes compared to those with low uACR (3–22.6 mg/mmol [30–200 mg/g]).
    - Similar hospitalisation risk for cardiorenal complications were observed during follow-up in the low and high uACR groups. In addition, patients with normal/mildly elevated uACR (0–3 mg/mmol [0–29 mg/g]) showed similar cardiorenal and mortality risk development compared to those with low and high uACR.
- **Tangri et al., 2024(29)**
    - Among dapagliflozin initiators with uACR <200 mg/g, the median eGFR slope was 1.07 mL/min/1.73m^2 per year better than in patients who did not initiate treatment.
    - The benefit of dapagliflozin initiation was observed across the whole eGFR slope distribution among patients with uACR <200 mg/g. Specifically, the difference was 1.28 mL/min/1.73 m^2 per year in favour of dapagliflozin initiation in patients with non-T2D CKD.

This evidence highlights dapagliflozin's broad applicability in the management of CKD, particularly in patients with normal to moderately increased uACR levels, reinforcing its potential to protect against CKD progression without the constraint of albuminuria severity.(28, 29)

Nakhleh *et al.*, 2024(30)

- The study demonstrated that SGLT2 inhibitors significantly slowed the annual decline in eGFR from -5.6 mL/min/1.73 m² to -1.7 mL/min/1.73 m^2 across the albuminuria range in those without T2D and an eGFR between 25–60 mL/min/1.73m2, 41.2% of whom had normal to mildly increased albuminuria (uACR <3 mg/mmol) at baseline.
- Lower levels of uACR were also associated with greater attenuation of eGFR slope after SGLT2 inhibitor administration:
  - uACR <30 mg/g (<3 mg/mmol) experienced an 86.0% reduction;
  - uACR of 30–300 mg/g (3–30 mg/mmol) experienced an 69.0% reduction;
  - uACR >300 mg/g (>30 mg/mmol) experienced an 29.3% reduction.

DAPA-CKD(37)

- A post-hoc analysis of the DAPA-CKD trial aimed to assess whether the kidney protective benefits of dapagliflozin, as demonstrated in the DAPA-CKD trial, extend to participants without T2D and with lower levels of albuminuria. While the trial inclusion criteria was patients with a uACR of 22.6 mg/mmol (200 mg/g) to 565 mg/mmol (5,000 mg/g), the study included 136 patients with uACR 3 to <30 mg/mmol, of whom 24 had uACR 3 to <22.6 mg/mmol at baseline.
- By week 2, dapagliflozin compared with placebo changed eGFR from baseline with similar effects in participants without T2D and with uACR <30 mg/mmol (−2.4 mL/min/1.73m^2) or ≥30mg/mmol (−2.0 mL/min/1.73m^2).
- Outcomes from this analysis were consistent with those observed in the DAPA-CKD trial and, therefore, further validate the effectiveness of dapagliflozin in patients with a uACR <30 mg/mmol as demonstrated in RWE.

DAPA-HF(38)

- Subgroup analysis of the DAPA-HF trial also supports the consistency of the dapagliflozin treatment effect across patients with and without T2D. The trial included patients with HFrEF across a wide range of uACR, including patients with uACR<22.6 mg/mmol, and demonstrated a significant reduction in the risk of the primary outcome of worsening HF or CV death independently of diabetes status.

Consistent treatment effect of dapagliflozin in patients with eGFR of ≥20-25 or >75-90 mL/min/1.73 m^2

OTIMISE-CKD

OPTIMISE-CKD demonstrated the consistent benefit of dapagliflozin initiation across the whole eGFR slope distribution among patients with a uACR <200mg/g (22.6 mg/mmol), thereby establishing the benefit of dapagliflozin in patients with eGFR of ≥20-25 mL/min/1.73 m^2.(28, 29)

DECLARE-TIMI 58 and DAPA-HF

- Post-hoc analyses from DECLARE-TIMI 58 and DAPA-HF also provide evidence of the consistent treatment effect of dapagliflozin in patients with an eGFR ≥20 mL/min/1.73 m^2 and ≥75 mL/min/1.73 m^2, and ≥75–90 mL/min/1.73m^2, respectively.(31, 32, 34)
- Not only did DECLARE-TIMI 58 achieve significant treatment outcomes in patients with T2D and uACR <22.6 mg/mmol, the study also demonstrated a statistically significant improvement in the composite renal-specific outcome in patients with an eGFR of 60–<90 mL/min/1.73 m^2.(31)
- Similarly in DAPA-HF, dapagliflozin was associated with significant reductions in the primary endpoint of worsening HF or CV death, which enrolled patients across a wide range of uACR categories.(33) The efficacy of dapagliflozin in preventing the primary outcome of CV death or worsening HF did not differ between those with an eGFR of <60 mL/min/1.73 m², and individuals with an eGFR ≥60 mL/min/1.73 m^2. Additionally, between day 14 and day 720, the change in eGFR in the dapagliflozin group was about

one-third of that in the placebo group. The same pattern was observed in patients with and without T2D at baseline and in patients with an eGFR <60 or ≥60 mL/min/1.73 m^2.(34)

3f) Quality of life impact of the medicine and patient preference information

What is the clinical evidence for a potential impact of this medicine on the quality of life of patients and their families/caregivers? What quality of life instrument was used? If the EuroQol-5D (EQ-5D) was used does it sufficiently capture quality of life for this condition? Are there other disease specific quality of life measures that should also be considered as supplementary information?

Please outline in plain language any quality of life related data such as **patient reported outcomes (PROs).**

Please include any **patient preference information (PPI)** relating to the drug profile, for instance research to understand willingness to accept the risk of side effects given the added benefit of treatment. Please include all references as required.

The real-world evidence informing this submission did not assess the HRQoL of patients. However, the impact of dapagliflozin on HRQoL of patients with CKD has been previously reported in the DAPA-CKD trial, which was described in detail in TA775.

3g) Safety of the medicine and side effects

When NICE appraises a treatment, it will pay close attention to the balance of the benefits of the treatment in relation to its potential risks and any side effects. Therefore, please outline the main side effects (as opposed to a complete list) of this treatment and include details of a benefit/risk assessment where possible. This will support patient reviewers to consider the potential overall benefits and side effects that the medicine can offer.

Based on available data, please outline the most common side effects, how frequently they happen compared with standard treatment, how they could potentially be managed and how many people had treatment adjustments or stopped treatment. Where it will add value or context for patient readers, please include references to the Summary of Product Characteristics from regulatory agencies etc.

Like all medicines, dapagliflozin can cause side effects, although not everybody gets them. The following side effects are listed in the patient information leaflet for dapagliflozin as they have been reported in patients taking dapagliflozin previously, though many of them are very rare.(26)

Patients should contact a doctor or the nearest hospital straight away if they have any of the following side effects:(26)

Angioedema, seen very rarely (may affect up to 1 in 10,000 people).
These are signs of angioedema:

- Swelling of the face, tongue or throat
- Difficulties swallowing
- Hives and breathing problems

Diabetic ketoacidosis - this is a rare condition that can arise in patients with T2D (may affect up to 1 in 1,000 people)
These are the signs of diabetic ketoacidosis:

- Increased levels of “ketone bodies” in the urine or blood
- Feeling sick or being sick
- Stomach pain
- Excessive thirst
- Fast and deep breathing
- Confusion
- Unusual sleepiness or tiredness
- A sweet smell to the breath, a sweet or metallic taste in the mouth or a different odour to the urine or sweat
- Rapid weight loss.

Necrotising fasciitis of the perineum or Fournier's gangrene, a serious soft tissue infection of the genitals or the area between the genitals and the anus, seen very rarely.

Patients should stop taking dapagliflozin and see a doctor as soon as possible if they notice any of the following serious side effects:(26)

Urinary tract infection, seen commonly (may affect up to 1 in 10 people).
These are signs of a severe infection of the urinary tract:

- Fever and/or chills
- Burning sensation when passing water (urinating)
- Pain in the back or side.

Patients should contact their doctor as soon as possible if they have any of the following side effects:(26)

Low blood sugar levels (hypoglycaemia), seen very commonly (may affect more than 1 in 10 people) in patients with diabetes taking this medicine with a sulphonylurea or insulin.
These are the signs of low blood sugar:

- Shaking, sweating, feeling very anxious, fast heartbeat
- Feeling hungry, headache, change in vision
- A change in mood or feeling confused.

Other side effects when taking dapagliflozin:(26)
Common

- Genital infection (thrush) of the penis or vagina (signs may include irritation, itching, unusual discharge or odour)
- Back pain
- Passing more water (urine) than usual or needing to pass water more often
- Changes in the amount of cholesterol or fats in the blood (shown in tests)
- Increases in the amount of red blood cells in the blood (shown in tests)
- Decreases in creatinine renal clearance (shown in tests) in the beginning of treatment
- Dizziness
- Rash

Uncommon (may affect up to 1 in 100 people)

- Loss of too much fluid from the body (dehydration, signs may include very dry or sticky mouth, passing little or no urine or fast heartbeat)
- Thirst
- Constipation
- Awakening from sleep at night to pass urine
- Dry mouth
- Weight decreased
- Increases in creatinine (shown in laboratory blood tests) in the beginning of treatment
- Increases in urea (shown in laboratory blood tests)

Very rare

- Inflammation of the kidneys (tubulointerstitial nephritis)

3h) Summary of key benefits of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key benefits of the treatment for patients, caregivers and their communities when compared with current treatments.
- Please include benefits related to the mode of action, effectiveness, safety and mode of administration

This review will enable dapagliflozin to become an alternative treatment option to empagliflozin for patients with CKD, with an eGFR ≥20 and <45 mL/min/1.73m^2 with or without T2D, and patients with CKD

with an eGFR ≥45 and <90 mL/min/1.73m^2 and either a uACR ≥22.6 mg/mmol or T2D, thereby providing both patients and physicians with choice of medications based on best available evidence to optimise treatment plans.

A recommendation for dapagliflozin within this setting will enable continuity of care and increase clinician and patient treatment choice in a difficult to treat area to optimise treatment plans based on the best available evidence. Ultimately, this will improve treatment outcomes and delay the progression of patients to ESKD and renal replacement therapy.

3i) Summary of key disadvantages of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key disadvantages of the treatment for patients, caregivers and their communities when compared with current treatments. Which disadvantages are most important to patients and carers?
- Please include disadvantages related to the mode of action, effectiveness, side effects and mode of administration
- What is the impact of any disadvantages highlighted compared with current treatments

Side effects

Like all medicines, dapagliflozin can cause side effects, although not everybody gets them. The main side effects that patients taking dapagliflozin should look out for are listed above in **Section 3g.**

Administration

Dapagliflozin is to be prescribed in addition to SoC. This means that patients may already be taking other medicines onto which dapagliflozin would be added if prescribed. However, as described above, dapagliflozin is an oral treatment (tablet) that can be taken by patients in the comfort of their own home, therefore administration should present a minor inconvenience to patients' lives.

3i) Value and economic considerations

Introduction for patients:

Health services want to get the most value from their budget and therefore need to decide whether a new treatment provides good value compared with other treatments. To do this they consider the costs of treating patients and how patients' health will improve, from feeling better and/or living longer, compared with the treatments already in use. The drug manufacturer provides this information, often presented using a health economic model.

In completing your input to the NICE appraisal process for the medicine, you may wish to reflect on:

- The extent to which you agree/disagree with the value arguments presented below (e.g., whether you feel these are the relevant health outcomes, addressing the unmet needs and issues faced by patients; were any improvements that would be important to you missed out, not tested or not proven?)
- If you feel the benefits or side effects of the medicine, including how and when it is given or taken, would have positive or negative financial implications for patients or their families (e.g., travel costs, time-off work)?
- How the condition, taking the new treatment compared with current treatments affects your quality of life.

Dapagliflozin and empagliflozin are expected to have no differences in cost or resource use. The acquisition costs of dapagliflozin and empagliflozin are equivalent at £36.59 per pack, with no confidential commercial arrangements and the same method and frequency of administration.(39, 40) There is no difference in patient monitoring or follow-up, adverse events or patient adherence.

3j) Innovation

NICE considers how innovative a new treatment is when making its recommendations. If the company considers the new treatment to be innovative please explain how it represents a 'step change' in treatment and/ or effectiveness compared with current treatments. Are there any QALY benefits that have not been captured in the economic model that also need to be considered (see section 3f)
Dapagliflozin has clinical comparability to empagliflozin and is anticipated to be used as an alternative treatment option.

3k) Equalities

Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here
The use of dapagliflozin in the subgroups outlined above is not expected to raise any issues related to equality given its clinical comparability to empagliflozin.

SECTION 4: Further information, glossary and references

4a) Further information

Feedback suggests that patients would appreciate links to other information sources and tools that can help them easily locate relevant background information and facilitate their effective contribution to the NICE assessment process. Therefore, please provide links to any relevant online information that would be useful, for example, published clinical trial data, factual web content, educational materials etc. Where possible, please provide open access materials or provide copies that patients can access.
Useful resources: • The DAPA-CKD publication: https://www.nejm.org/doi/full/10.1056/NEJMoa2024816 • The main publication by Svensson et al., 2024: https://academic.oup.com/ckj/advance-article/doi/10.1093/ckj/sfae100/7640869 • The main publication by Tangri et al., 2024: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10879247/ • The main publication by Nakhleh et al., 2024: https://dom-pubs.pericles-prod.literatumonline.com/doi/10.1111/dom.15623 • The DECLARE-TIMI 58 publication: https://www.nejm.org/doi/full/10.1056/NEJMoa1812389 • The DAPA-HF publication: *https://www.nejm.org/doi/full/10.1056/NEJMoa1911303* • Dapagliflozin SmPC: https://www.medicines.org.uk/emc/product/7607/smpc#gref • Dapagliflozin PIL: https://www.medicines.org.uk/emc/files/pil.7607.pdf • NHS CKD overview: https://www.nhs.uk/conditions/kidney-disease/ • Kidney Care UK CKD overview: https://kidneycareuk.org/kidney-disease-information/kidney-conditions/ckd-chronic-kidney-disease/ **Further information on NICE and the role of patients:** • Public Involvement at NICE Public involvement | NICE and the public | NICE Communities | About | NICE • NICE's guides and templates for patient involvement in HTAs Guides to developing our guidance | Help us develop guidance | Support for voluntary and community sector (VCS) organisations | Public involvement | NICE and the public | NICE Communities | About | NICE

- EUPATI guidance on patient involvement in NICE: https://www.eupati.eu/guidance-patient-involvement/
- EFPIA – Working together with patient groups: https://www.efpia.eu/media/288492/working-together-with-patient-groups-23102017.pdf
- National Health Council Value Initiative. https://nationalhealthcouncil.org/issue/value/
- INAHTA: http://www.inahta.org/
- European Observatory on Health Systems and Policies. Health technology assessment - an introduction to objectives, role of evidence, and structure in Europe: http://www.inahta.org/wp-content/themes/inahta/img/AboutHTA_Policy_brief_on_HTA_Introduction_to_Objectives_Role_of_Evidence_Structure_in_Europe.pdf

4b) Glossary of terms

This glossary explains terms highlighted in **blue bold text** in this summary of information for patients. At times, an explanation for a term might mean you need to read other terms to understand the original terms.

- **Angiotensin converting enzyme (ACE) inhibitors:** A type of medicine that lowers your blood pressure.
- **Antineutrophil cytoplasmic antibody–associated vasculitis:** A heterogeneous group of rare autoimmune conditions that causes an inflammation of blood vessels with various manifestations.
- **Albumin**: Your liver makes albumin. Albumin carries substances such as hormones, medicines, and enzymes throughout your body.
- **Albuminuria:** When there is too much albumin in your urine. This is a sign of kidney disease.
- **Anaemia**: A lack of red blood cells.
- **Asymptomatic**: Producing or showing no symptoms.
- **Atherosclerotic cardiovascular disease (ASCVD):** Includes a variety of diseases causes by plaque build-up in artery walls.
- **Blood pressure:** The force exerted in the arteries by blood as it goes around the body. Having high blood pressure increases a patient's risk of heart attack and stroke.
- **Cardiorenal protection:** Protection from any acute or chronic problem in the heart or kidneys.
- **Cardiovascular (CV):** The term cardiovascular relates to the heart and blood vessels.
- **Cardiovascular disease (CVD):** A general term that describes a disease of the heart or blood vessels.
- **Cerebrovascular disease:** A term for conditions that affect blood flow to your brain.
- **Cholesterol:** A waxy, fat-like substance made in the liver, and found in the blood and in all cells of the body.
- **Chronic:** Chronic means long-term.
- **Chronic kidney disease (CKD):** A long-term condition where a patient's kidneys do not work as well as they should.
- **Clinical trial/clinical study:** A type of research study that tests how well new medical approaches work in people. These studies test new methods of screening, prevention, diagnosis or treatment of a disease. Also called a clinical study.

- **Comorbid:** Simultaneous presence of two or more medical conditions in a patient.
- **Creatinine**: A waste product that comes from the digestion of dietary protein and the normal breakdown of muscle tissue.
- **Dapagliflozin:** The medicine under review for this submission. Dapagliflozin belongs to a group of medicines called "**sodium-glucose co-transporter 2 (SGLT2) inhibitors**". They work by targeting the kidneys and blocking a protein called the SGLT2 protein. Blocking this protein helps to increase the amount of blood sugar (glucose), salt (sodium) and water that are removed from the body via the urine.
- **Diabetes:** A condition that causes the level of sugar (glucose) in the blood to become too high.
- **Dialysis:** A procedure to remove waste products and excess fluid from the blood when the kidneys stop working properly. It often involves diverting blood to a machine to be cleaned.
- **Dyslipidaemia:** Results in abnormal levels of lipids (fats) in the blood that can increase the risk of **cardiovascular diseases (CVD).**
- **Ejection fraction:** The amount of blood - given as a percentage - pumped out of a ventricle during each heartbeat. The ejection fraction evaluates how well the heart is pumping. Normal ejection fractions range from 55% to 65%.
- **Empagliflozin**: Empagliflozin belongs to a group of medicines called "**sodium-glucose co-transporter 2 (SGLT2) inhibitors**". They work by targeting the kidneys and blocking a protein called the SGLT2 protein. Blocking this protein helps to increase the amount of blood sugar (glucose), salt (sodium) and water that are removed from the body via the urine.
- **Efficacy:** The ability of a drug to produce the desired beneficial effect on your disease or illness in a **clinical trial.**
- **End-stage kidney disease (ESKD):** When your eGFR is less than 15ml/min. It means your kidneys have stopped working or are close to stopping.
- **Estimated glomerular filtration rate (eGFR):** Assesses how well the kidneys are filtering, using a simple blood test which measures your **creatinine** levels.
- **Gestational diabetes:** A condition characterised by an elevated level of glucose in the blood during pregnancy.
- **Glomerulonephritis:** Inflammation and damage to the filtering part of the kidneys.
- **Heart failure (HF):** A condition where a patient's heart can't pump blood around the body as well as it should, causing the body to retain salts and fluids.
- **Health-related quality of life (HRQoL**): The overall enjoyment of life. Many **clinical trials** assess the effects of a disease and its treatment on the quality of life of patients. These studies measure aspects of a patient's sense of well-being and their ability to carry out activities of daily living.
- **Hypertension:** When the pressure in your blood vessels is too high.
- **Hypotension:** When the pressure in your blood vessels is too low.
- **Homeostasis:** The regulation of internal conditions inside cells or organisms, to create the optimum conditions for biological function.
- **Insulin resistance:** When your body's cells don't respond properly to the insulin that your body makes or the insulin you inject as a medication. Because your body cannot use the insulin as it should your blood sugar levels can increase.

- **Ischemic heart disease:** Heart problems caused by narrowed heart arteries. When arteries are narrowed, less blood and oxygen reach the heart muscle.
- **Ischemic stroke:** Happens when a blockage cuts off the blood supply to part of your brain, killing brain cells. Damage to brain cells can affect how the body works. It can also change how you think and feel.
- **Kidney transplant:** A kidney transplant is a treatment option for many patients who **ESKD**. During a kidney transplant, a kidney is removed from one person (the donor) and given to another person (the recipient). Kidneys can be donated from living donors or from those who have died (deceased donors).
- **Lupus nephritis:** Lupus is an "autoimmune" disease, meaning your immune system (your body's defence system), which usually protects the body from disease, turns against the body. This causes harm to organs and tissues, like your kidneys. Lupus nephritis results in inflammation (swelling or scarring) of the small blood vessels that filter wastes in your kidney (glomeruli).
- **Marketing authorisation:** The legal approval by a **regulatory body** that allows a medicine to be given to patients in a particular country.
- **Medicines and Healthcare products Regulatory Agency (MRHA):** The **regulatory body** that evaluates, approves and supervises medicines throughout the UK.
- **Morbidity**: The condition of suffering from a disease or medical condition.
- **National Institute for Health and Care Excellence (NICE):** The body in England that decides whether to approve new medicines for funding on the NHS based on whether they can be demonstrated to be value for money.
- **Observational study:** Research studies in which researchers collect information from participants or look at data that was already collected.
- **Peripheral arterial disease:** A common condition where a build-up of fatty deposits in the arteries restricts blood supply to leg muscles.
- **Placebo:** An inactive substance or other intervention that looks the same as, and is given the same way as, an active drug or treatment being tested.
- **Polycystic kidney disease:** Causes numerous cysts to grow in the kidneys. These cysts are filled with fluid. If too many cysts grow or if they get too big, the kidneys can become damaged. These cysts can slowly replace much of the kidneys, reducing kidney function and leading to kidney failure.
- **Propensity score matching:** A way researchers can use statistical techniques to construct an artificial control group by matching each treated unit with a non-treated unit of similar characteristics. Using these matches, the researcher can estimate the impact of an intervention.
- **Regulatory bodies:** Legal bodies that review the quality, safety and **efficacy** of medicines and medical technologies.
- **Relative risk (RR):** Used in clinical trials to measure the ratio of the probability of an event occurring in the exposed group versus the probability of the event occurring in the non-exposed group.
- **Renal**: Relating to the kidneys.
- **Reimbursement:** Funding on the NHS.
- **Retrospective:** A retrospective study uses existing data that have been recorded for reasons other than research.

- **SGLT2 inhibitor:** A type of medicine that works by targeting the kidneys and blocking a protein called the SGLT2 protein. Blocking this protein helps to increase the amount of blood sugar (glucose), salt (sodium) and water that are removed from the body via the urine.
- **Surrogate endpoint**: A clinical trial endpoint used as a substitute for a direct measure of how a patient feels, functions, or survives. A surrogate endpoint does not measure the clinical benefit of primary interest in and of itself, but rather is expected to predict that clinical benefit.
- **Systematic literature review (SLR):** A review which uses explicit and systematic methods to identify, appraise and summarise the literature according to predetermined criteria.
- **Systolic blood pressure:** The force at which your heart pumps blood around your body.
- **Technology appraisal:** In technology appraisal guidance, **NICE** makes recommendations on the use of new and existing medicines and other treatments within the NHS. For more information, please refer here: https://www.nice.org.uk/About/What-we-do/Our-Programmes/NICE-guidance/NICE-technology-appraisal-guidance
- **Transplantation/transplant:** A medical procedure in which an organ is removed from one body and placed in the body of a recipient, to replace a damaged or missing organ.
- **Type 1 diabetes:** A condition that causes the level of sugar (glucose) in the blood to become too high. Patients with type 1 diabetes are unable to make a hormone called insulin, which controls blood glucose.
- **Type 2 diabetes (T2D):** A condition that causes the level of sugar (glucose) in the blood to become too high. Patients with type 2 diabetes may not be able to make enough of a hormone called insulin, which controls blood glucose, or the insulin it makes not working properly — known as **insulin resistance**.
- **urine albumin-creatinine ratio (uACR):** A measure of the amount of two different substances in your urine – creatinine and albumin (an important protein normally found in the blood that serves many roles in the body). Healthy kidneys stop most of your albumin from getting through their filters and entering the urine. There should be very little or no albumin in your urine. If your kidneys are damaged, albumin can "leak" through their filters and into your urine.
- **urine protein creatinine ratio (uPCR):** A urine test which measures the levels of protein and **creatinine** in your urine.

4c) References

Please provide a list of all references in the Vancouver style, numbered and ordered strictly in accordance with their numbering in the text:

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Dapagliflozin for treating chronic kidney disease [ID6411]

Clarification questions

August 2024

File name	Version	Contains confidential information	Date
ID6411_Dapagliflozin_CKD_TA775 review_clarification-questions [CON]	Final	Yes	21.08.2024

Notes for company

Highlighting in the template

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Section A: Clarification on effectiveness data

Decision problem

A1. Priority question: The final scope issued by NICE for this review (CS, Document B, Table 1) defines a population of people with CKD which aligns with the population recommended for Empagliflozin in TA942. Please clarify why the five CKD subgroups defined in the company decision problem address only the sub-populations of the current NICE scope where Empagliflozin is recommended and Dapagliflozin is not, omitting the sub-populations from the current NICE scope where both Dapagliflozin and Empagliflozin are recommended; i.e. people with T2D and eGFR range between 25 and 75 mL/min/1.73 m2 irrespective of uACR and people without T2D, between 25 and 75 mL/min/1.73 m2 and uACR ≥22.6 mg/mmol as outlined in CS, Document B, Table 5.

As noted in Document B (Section B.1.1), the Company Submission (CS) Addendum and agreed with the National Institute for Health and Care Excellence (NICE) prior to this review, the aim of this submission is to review the current NICE recommendation for dapagliflozin in chronic kidney disease (CKD; TA775) and ***align it with the NICE recommendation for empagliflozin as a treatment for CKD*** (TA942).[1, 2] This submission is not intended to re-

evaluate the subgroups in which dapagliflozin and empagliflozin are currently recommended and have already been evaluated by NICE.

In light of the body of evidence demonstrating the similar efficacy and safety of these treatments (i.e., indicating a class effect), aligning the recommendations will optimise access for patients by creating a consistent approach in the treatment of CKD across patient subgroups. As discussed in the CS Addendum (Question 3), stakeholder comments on the draft scope for this review and feedback from UK clinical experts sought by AstraZeneca supported the clinical importance of aligning the dapagliflozin and empagliflozin recommendations (which currently do not align with the evidence base, licences or current CKD guidelines).[3] Aligning the recommendations would simplify the treatment pathway in both primary and secondary care and remove some of the complexities associated with prescribing empagliflozin and dapagliflozin; by doing so, this would improve access for patients with CKD to effective treatments.

NICE recommended dapagliflozin in March 2022 as an option for the treatment of CKD in adults with an estimated glomerular filtration rate (eGFR) of 25 to 75 ml/min/1.73m^2 and:[1]

- Type 2 diabetes (T2D) *or*
- A urine albumin-creatinine ratio (uACR) of 22.6 mg/mmol or more

NICE subsequently recommended empagliflozin in December 2023 ***in a broader population***, as an option for the treatment of CKD in adults with:[2]

- An eGFR of 20 to less than 45 ml/min/1.73m^2 *or*
- An eGFR of 45 to 90 ml/min/1.73m^2 *and either:*
    - A uACR of 22.6 mg/mmol or more
    - T2D

As such, the aim of this review is to expand the existing dapagliflozin recommendation to the broader empagliflozin recommendation. The subgroups in this review are therefore based on the subgroups of patients that are recommended for empagliflozin but not recommended for dapagliflozin, rather than being clinically significant or different CKD subgroups. In clinical practice, these subgroups would be managed and treated in the same way as the rest of the NICE reimbursed CKD populations. Many of the subgroups included in this review represent very high risk patients (based on the KDIGO framework), so improving access to treatments and outcomes for these patients should be prioritised.[4]

Based on this, the subgroups of interest in this review are recommended for empagliflozin but not currently recommended for dapagliflozin are as follows:

Adults with CKD without T2D

- **Subgroup 1**: Adults with CKD without T2D and with an eGFR ≥20–45 mL/min/1.73m^2 and uACR <22.6 mg/mmol (200 mg/g)
- **Subgroup 2**: Adults with CKD without T2D and with an eGFR ≥20–25 mL/min/1.73m^2 and a uACR ≥22.6 mg/mmol (≥200 mg/g)
- **Subgroup 3**: Adults with CKD without T2D and an eGFR >75–90 mL/min/1.73m^2 and a uACR ≥22.6 mg/mmol (≥200 mg/g)

Adults with CKD with T2D

- **Subgroup 4:** Adults with CKD, with T2D, and with an eGFR ≥20–25 mL/min/1.73m^2 (irrespective of uACR)
- **Subgroup 5:** Adults with CKD, with T2D, and with an eGFR >75–90 mL/min/1.73m^2 (irrespective of uACR)

A2. Priority question: Health related quality of life and adverse events of treatment are outcomes defined in the NICE scope (CS, Document B, Table 1)

a. Please clarify whether any health-related quality of life evidence was available from any of the studies of Dapagliflozin.

b. Please clarify whether adverse events of treatment were available from any of the studies of Dapagliflozin.

Where available, please summarise this evidence aligned to the five CKD subgroups defined within the company decision problem

Health-related quality of life (HRQoL) or adverse event (AE) data for dapagliflozin have not be collected in the observational studies, including OPTIMISE-CKD or Nakhleh *et al.* (2024) and are therefore not available.

In the randomised controlled trials (RCTs) of dapagliflozin (DAPA-CKD, DAPA-HF and DECLARE-TIMI 58) that provide additional supportive evidence for this review, HRQoL and AE endpoints were collected for dapagliflozin. However, analyses of these endpoints are not available for the specific subgroups of interest in this review, but they are inherently included within the overall trial populations.

HRQoL

As outlined in the original appraisal for dapagliflozin in CKD (TA775), change from baseline Kidney Disease Quality of Life-36 (KDQOL-36) and EuroQoL-5 dimensions-5 levels (EQ-5D-5L) were analysed in DAPA-CKD.[1] These data presented in response to Clarification Question A15 in TA775 and evaluated as part of TA775, are re-presented below to aid the External Assessment Group's (EAG's) review.

HRQoL data are only presented from DAPA-CKD as HRQoL endpoints specific to diseases other than CKD (i.e., diabetes and heart failure [HF]) were used in the other dapagliflozin RCTs. Regardless, dapagliflozin has demonstrated a consistent impact on HRQoL across indications.

The consistent HRQoL impact observed for dapagliflozin is in line with that for empagliflozin. Although EMPA-KIDNEY planned to collect KDQOL-36 data, no data are publicly available so it is not possible to conduct a direct comparison of dapagliflozin and empagliflozin in terms of KDQOL-36. However, in TA942, the Company conducted a qualitative comparison of HRQoL data for empagliflozin and dapagliflozin from HF trials with left ventricular ejection fraction (LVEF) >40% and concluded that the HRQoL data were consistent for both

treatments.[5] Based on the acceptance of a cost comparison analysis in TA942, the HRQoL data for dapagliflozin were deemed comparable to that of empagliflozin in patients with CKD.[5]

KDQOL-36 results from DAPA-CKD

The KDQOL-36 absolute scores and mean change from baseline for each subscale are presented in Table 1 below. There were [redacted] in KDQOL-36 scores between the dapagliflozin and placebo groups at baseline and [redacted] (based on Mapes et al. 2004[6] and Samsa et al. 1999[7]), compared to baseline at 12, 24 and 36 months.[8] [redacted]

A separate published analysis of KDQOL-36 results from DAPA-CKD are available from Heerspink *et al.* (2024), which demonstrates broadly consistent results to those presented in Table 1; notably, based on the analysis by Heerspink *et al.* (2024), patients receiving treatment with dapagliflozin were significantly less likely to experience a clinically meaningful (≥5 units) decline in physical health composite compared with placebo (HR: 0.90 [95% confidence intervals [CIs]: 0.81, 0.9]).[9]

Table 1: Analysis of KDQOL-36 scores by subscale – DAPA-CKD

Subscale/ treatment group	Absolute values		Repeated measures analysis						
			Change from baseline				Difference between dapagliflozin and placebo		
			Dapagliflozin		Placebo				
	Dapagliflozin (N=2,013), Mean (SD)	Placebo (N=2,019), Mean (SD)	LS Mean (SE)	95% CI	LS Mean (SE)	95% CI	LS Mean Difference (SE)	95% CI	p-value
Symptom/problem									
Baseline	[redacted]	[redacted]	-	-	-	-	-	-	-
12 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
24 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
36 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Effects of kidney disease									
Baseline	[redacted]	[redacted]	-	-	-	-	-	-	-
12 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
24 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
36 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Burden of kidney disease									
Baseline	[redacted]	[redacted]	-	-	-	-	-	-	-
12 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
24 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
36 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Subscale/ treatment group	Absolute values		Repeated measures analysis						
			Change from baseline				Difference between dapagliflozin and placebo		
	Dapagliflozin (N=2,013), Mean (SD)	Placebo (N=2,019), Mean (SD)	Dapagliflozin		Placebo		LS Mean Difference (SE)	95% CI	p-value
			LS Mean (SE)	95% CI	LS Mean (SE)	95% CI			
SF-12 Physical health composite									
Baseline	[redacted]	[redacted]	-	-	-	-	-	-	-
12 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
24 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
36 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SF-12 Mental health composite									
Baseline	[redacted]	[redacted]	-	-	-	-	-	-	-
12 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
24 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
36 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The repeated measures model includes terms for randomised treatment group, baseline scores, visit and visit by treatment group interaction.
Abbreviations: CI: confidence interval; LS: least squares; SD: standard deviation; SE: standard error; SF-12:12-Item Short Form Survey.
Source: AstraZeneca Data on File 2020: DAPA-CKD Clinical Study Report.[8]

EQ-5D results from DAPA-CKD

The mean baseline EQ-5D-5L utility score was [redacted] in both the dapagliflozin and placebo arms. The difference in mean change from baseline in EQ-5D-5L utility scores between dapagliflozin and placebo at 4, 8, 12, 24 and 36 months is presented in Table 2.

Table 2: Difference in change from baseline EQ-5D-5L utility scores between dapagliflozin and placebo treatment arms

Characteristic and timepoint	Difference in LS mean change from baseline between dapagliflozin 10 mg and placebo		
	LS Mean difference (SE)	95% CI	p-value
4 months	[redacted]	[redacted]	[redacted]
8 months	[redacted]	[redacted]	[redacted]
12 months	[redacted]	[redacted]	[redacted]
24 months	[redacted]	[redacted]	[redacted]
36 months	[redacted]	[redacted]	[redacted]

The EQ-5D-5L health states were converted to utility scores using the UK-specific value set. Utility scores range in the interval [-0.594,1] where 1 corresponds to the full health (the health state 11111) and -0.594 corresponds to the worst health (the health state 55555).
Abbreviations: CI: confidence interval; LS: least squares; SE: standard error.
Source: AstraZeneca Data on File 2020: DAPA-CKD Clinical Study Report.[8]

Safety

Safety data from DAPA-CKD and DAPA-HF were previously presented in prior appraisals of dapagliflozin (TA775 and TA679).[1, 10] To aid the EAG's review and in the absence of data specific to the subgroups, AE data from the whole trial populations of the RCTs supporting this review (DAPA-CKD, DAPA-HF and DECLARE-TIMI 58) are presented in Table 5 for dapagliflozin and placebo; for comparative purposes, AE data from EMPA-KIDNEY are also presented. Furthermore, AEs reported in the Summary of Product Characteristics (SmPC) for dapagliflozin, based on placebo-controlled trials and post-marketing experience across all licensed indications, are presented in Table 3. This shows the totality of the dapagliflozin safety profile across all licensed indications and is similar to the safety profile of empagliflozin (Clarification Question B3).

Subgroup analyses of the safety data for dapagliflozin from DAPA-HF are available for baseline eGFR subgroups, presented in Table 4. These subgroup analyses demonstrate a consistent safety profile of dapagliflozin across the baseline eGFR subgroups.[11] The consistent safety profile of dapagliflozin across CKD subgroups is also supported by the Medicines and Healthcare products Regulatory Agency (MHRA) license for dapagliflozin which is for all adults with CKD, rather than differentiating by baseline eGFR or uACR, supporting the consistent effect of dapagliflozin across CKD subpopulations.[12] Furthermore, dapagliflozin was deemed safe for initiation in adults with CKD with an eGFR of >15 ml/min/1.73m^2, without a need to discontinue treatment once eGFR falls below 15 ml/min/1.73m^2.[12]

Overall, dapagliflozin demonstrates a consistent safety profile across the RCTs; as noted in the SmPC for dapagliflozin, the overall safety profile of dapagliflozin observed in DAPA-CKD, DAPA-HF and DECLARE-TIMI 58 was consistent with the known safety profile of

dapagliflozin.[12] This is further supported by an independent meta-analysis of sodium-glucose cotransporter-2 (SGLT2) inhibitors which demonstrated a consistent safety profile of SGLT2 inhibitors as a class across indications, in terms of ketoacidosis and lower leg amputation (Figure 1 and Figure 2).[13]

Table 3: Adverse events reported in SmPC for dapagliflozin, based on placebo-controlled clinical studies and post-marketing experience across all licensed indications

System organ class	Very common	Common*	Uncommon**	Rare	Very rare
Infections and infestations		Vulvovaginitis, balanitis and related genital infections; Urinary tract infections	Fungal infection		Necrotising fasciitis of the perineum (Fournier's gangrene)
Metabolism and nutrition disorders	Hypoglycaemia (when used with SU or insulin)		Volume depletion; Thirst	Diabetic ketoacidosis (when used in T2D)	
Nervous system disorders		Dizziness			
Gastrointestinal disorders			Constipation; Dry mouth		
Skin and subcutaneous disorders		Rash			Angioedema
Musculoskeletal and connective tissue disorders		Back pain			
Renal and urinary disorders		Dysuria; Polyuria	Nocturia		Tubulointerstitial nephritis
Reproductive system and breast disorders			Vulvovaginal pruritis; Pruritis genital		
Investigations		Haematocrit increased; Creatinine renal clearance decreased during initial treatment Dyslipidaemia	Blood creatinine increased during initial treatment; Blood urea increased; Weight decreased		

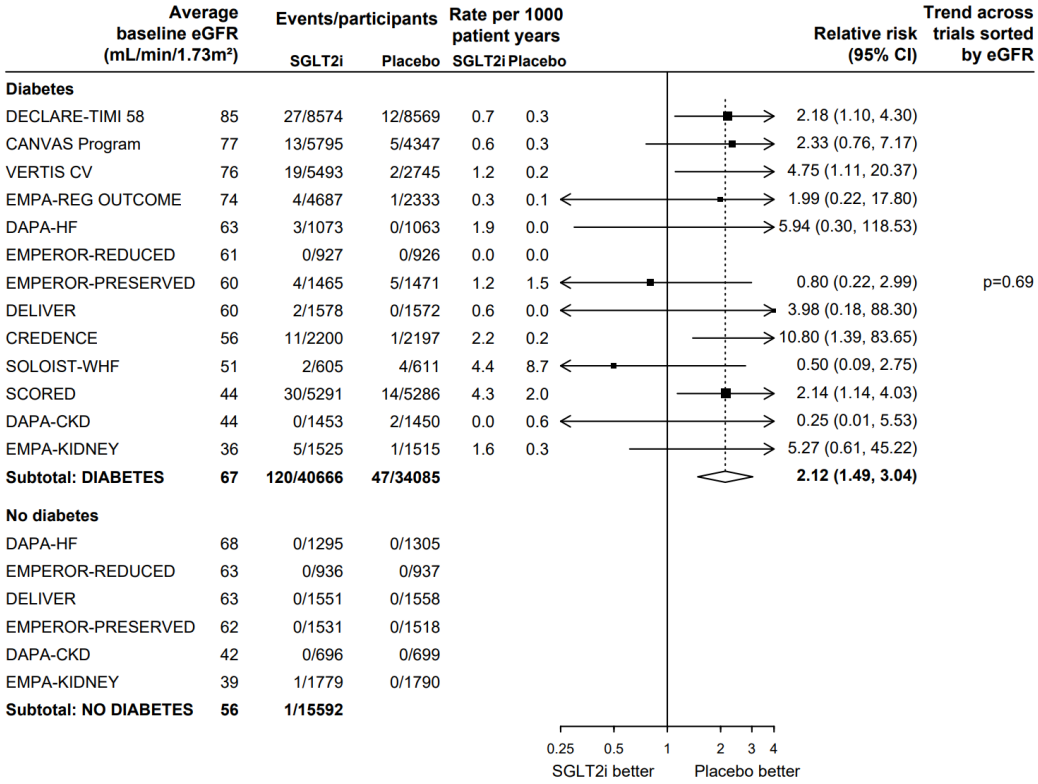
Further information on selected AEs is presented in the SmPC for dapagliflozin. * Reported in ≥2% of patients and ≥1% more and at least 3 more patients treated with dapagliflozin 10 mg compared with placebo. ** reported by the investigator as possible related, probably related or related to study treatment and reported in ≥0.2% of patients and ≥0.1% more and at least 3 more patients treated with dapagliflozin 10 mg compared with placebo.
Abbreviations: SmPC: Summary of Product Characteristics; T2D: type 2 diabetes.
Source: SmPC (dapagliflozin)[12]

Table 4: Safety of dapagliflozin across baseline eGFR subgroups – DAPA-HF

	eGFR <60 ml/min/1.73 m²			eGFR ≥60 ml/min/1.73 m²		
AEs, n (%)	Dapagliflozin n=960	Placebo n=962	*P* value	Dapagliflozin n=1407	Placebo n=1,405	*P* value
Volume depletion	97 (10.1)	86 (8.9)	0.39	81 (5.8)	76 (5.4)	0.74
Renal events	97 (10.1)	115 (12.0)	0.22	56 (4.0)	55 (3.9)	1
Amputation	8 (0.8)	9 (0.9)	1	5 (0.4)	3 (0.2)	0.73
Major hypoglycaemia	3 (0.3)	0 (0.0)	0.12	1 (0.1)	4 (0.3)	0.22
Fracture	28 (2.9)	25 (2.6)	0.68	21 (1.5)	25 (1.8)	0.56
Permanent treatment discontinuation	121 (12.6)	130 (13.5)	0.59	128 (9.1)	128 (9.1)	1
Any serious AE	417 (43.4)	482 (50.1)	0.003	478 (34.0)	512 (36.4)	0.18

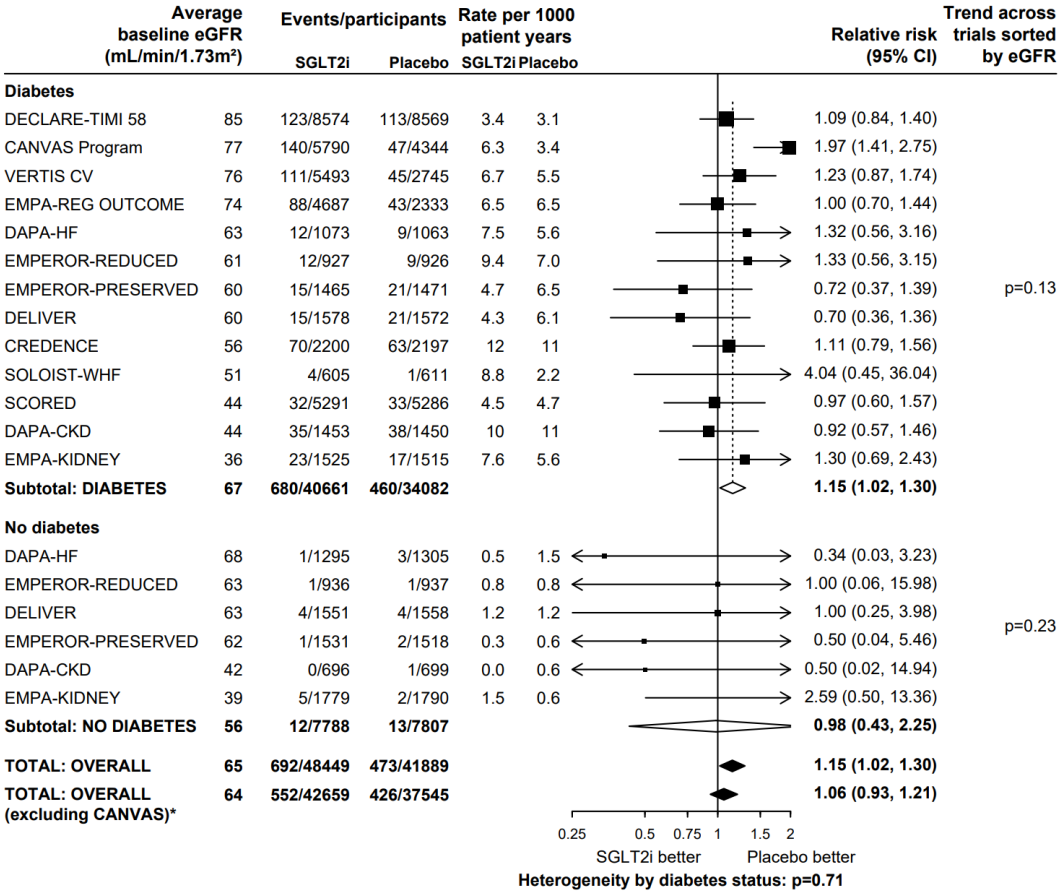
Abbreviations: AE: adverse event; eGFR: estimated glomerular filtration rate
Source: Jhund *et al.* (2021)[11]

Figure 1: Effect of SGLT2 inhibitors on ketoacidosis, by diabetes status



Dapagliflozin clinical trials: DECLARE-TIMI 58, DAPA-HF, DELIVER, DAPA-CKD; empagliflozin clinical trials: EMPA-REG OUTCOME, EMPEROR-REDUCED, EMPEROR-PRESERVED, EMPA-KIDNEY. The remaining trials are for other SGLT2 inhibitors.
Abbreviations: CI: confidence interval; eGFR: estimated glomerular filtration rate; SGLT2i: SGLT2 inhibitor.
Source: Nuffield Department of Population Health Renal Studies Group (2022)[13]

Figure 2: Effect of SGLT2 inhibitors on lower limb amputation, by diabetes status



Dapagliflozin clinical trials: DECLARE-TIMI 58, DAPA-HF, DELIVER, DAPA-CKD; empagliflozin clinical trials: EMPA-REG OUTCOME, EMPEROR-REDUCED, EMPEROR-PRESERVED, EMPA-KIDNEY. The remaining trials are for other SGLT2 inhibitors. *The hypothesis that SGLT2 inhibition might increase the risk of lower limb amputation was first raised by results from the CANVAS trial. The subtotal excluding CANVAS therefore reflects the combined results from the independent set of hypothesis-testing trials.
Abbreviations: CI: confidence interval; eGFR: estimated glomerular filtration rate; SGLT2i: SGLT2 inhibitor.
Source: Nuffield Department of Population Health Renal Studies Group (2022)[13]

Table 5: Safety outcomes for dapagliflozin in DAPA-CKD, DAPA-HF and DECLARE-TIMI 58, and empagliflozin in EMPA-KIDNEY

	DAPA-CKD		DAPA-HF		DECLARE-TIMI 58		EMPA-KIDNEY	
	Dapagliflozin (n=2,149)	Placebo (n=2,149)	Dapagliflozin (n=2,368)	Placebo (n=2,368)	Dapagliflozin (n=8,574)	Placebo (n=8,569)	Empagliflozin (n=3,304)	Placebo (n=3,305)
Discontinuation due to AE	118 (5.5)	123 (5.7)	111 (4.7)	116 (4.0)	693 (8.1)	592 (6.9)	232 (7.0)	315 (9.5)
Any serious AE	633 (29.5)	729 (33.9)	846 (35.7)	951 (40.2)	2,925 (34.1)	3,100 (36.2)	NR	NR
AEs of interest								
Volume depletion	127 (5.9)	90 (4.2)	178 (7.5)	162 (6.8)	213 (2.5)	207 (2.4)	98 (3.0)	90 (2.7)
Renal AE	155 (7.2)	188 (8.7)	153 (6.5)	170 (7.2)	NR	NR	NR	NR
Fracture	85 (4.0)	69 (3.2)	49 (2.1)	50 (2.1)	457 (5.3)	440 (5.1)	133 (4.0)	123 (3.7)
Amputation	35 (1.6)	39 (1.8)	13 (0.5)	12 (0.5)	123 (1.4)	113 (1.3)	28 (0.8)	19 (0.6)
Major hypoglycaemia	14 (0.7)	28 (1.3)	4 (0.2)	4 (0.2)	58 (0.7)	83 (1.0)	77 (2.3)	77 (2.3)
Diabetic ketoacidosis	0 (0.0)	2 (<0.1)	3 (0.1)	0 (0.0)	27 (0.3)	12 (0.1)	6 (0.2)	1 (<0.1)
Fournier's gangrene	NR	NR	0 (0.0)	1 (<0.1)	NR	NR	NR	NR
Acute kidney injury	NR	NR	NR	NR	125 (1.5)	175 (2.0)	107 (3.2)[a]	135 (4.1)[a]
Genital infection	NR	NR	NR	NR	76 (0.9)	9 (0.1)	1 (<0.1)[b]	1 (<0.1)[b]
UTI	NR	NR	NR	NR	127 (1.5)	133 (1.6)	52 (1.6)[c]	54 (1.6)[c]
Bladder cancer	NR	NR	NR	NR	45 (0.5)	45 (0.5)	NR	NR
Breast cancer	NR	NR	NR	NR	35 (0.4)	35 (0.4)	NR	NR
Hypersensitivity	NR	NR	NR	NR	32 (0.4)	36 (0.4)	NR	NR
Hepatic event	NR	NR	NR	NR	82 (1.0)	87 (1.0)	NR	NR

a Reported as 'serious acute kidney injury'. [b] Reported as 'serious genital infection'. [c] Reported as 'serious urinary tract infection'.
Abbreviations: AE: adverse event; NR: not reported; UTI: urinary tract infection.
Source: Heerspink *et al.* (2020),[14] McMurray *et al.* (2019),[15] NICE TA679,[10] Wiviott et al. (2019)[16], NICE TA942,[5] EMPA-KIDNEY Collaborative Group (2023)[17]

Conclusion

As presented above, dapagliflozin demonstrates a consistent safety profile and HRQoL impact across indications and patient populations based on the relevant RCTs. Although HRQoL and safety subgroup analyses are not available for the specific subgroups within this review, these RCTs overlap with the subgroups providing relevant evidence. There is no scientific rationale to believe that the safety profile or HRQoL impact of dapagliflozin would differ in the subgroups included within this review versus other patient populations for which it has already been assessed. This is also supported by the MHRA licence for dapagliflozin which is for all adults with CKD, rather than differentiating by baseline eGFR or uACR, supporting the consistent effect and safety of dapagliflozin across CKD subpopulations.[12] As such, the HRQoL and AE data for dapagliflozin in the whole trial populations can be considered generalisable to all patients with CKD receiving dapagliflozin, including the specific subgroups of interest in this review.

In addition, based on the acceptance of a cost comparison analysis in TA942, the HRQoL and AE data for dapagliflozin were deemed comparable to that of empagliflozin in patients with CKD.[5]

Selection of Dapagliflozin studies

A3. Priority question: The systematic review conducted as part of the CS for TA775 included the following studies of dapagliflozin:

a. Kohan DE, Fioretto P, Tang W, et al. Long-term study of patients with type 2 diabetes and moderate renal impairment shows that dapagliflozin reduces weight and blood pressure but does not improve glycemic control. Kidney Int 2014;85:962-71.

b. Fioretto P, Del Prato S, Buse JB, et al. Efficacy and safety of dapagliflozin in patients with type 2 diabetes and moderate renal impairment (chronic kidney disease stage 3A): The DERIVE Study. Diabetes Obes Metab 2018;20:2532-2540.

c. Pollock C, Stefánsson B, Reyner D, et al. Albuminuria-lowering effect of dapagliflozin alone and in combination with saxagliptin and effect of dapagliflozin and saxagliptin on glycaemic control in patients with type 2

diabetes and chronic kidney disease (DELIGHT): a randomised, double-blind, placebo-controlled trial. Lancet Diabetes Endocrinol 2019;7:429-441.

Furthermore, the systematic review conducted as part of the CS for TA942 included the following references to studies of dapagliflozin:

d. Study MB102029. Kohan DE, Fioretto P, Tang W, List JF. Long-term study of patients with type 2 diabetes and moderate renal impairment shows that dapagliflozin reduces weight and blood pressure but does not improve glycemic control. Kidney international. 2014;85(4):962-71.

e. Dekkers CC, Wheeler DC, Sjöström CD, Stefansson BV, Cain V, Heerspink HJ. Effects of the sodium–glucose co-transporter 2 inhibitor dapagliflozin in patients with type 2 diabetes and Stages 3b–4 chronic kidney disease. Nephrology dialysis transplantation. 2018 Nov 1;33(11):2005-11.

Please clarify whether these studies were considered for inclusion in this CS. Please either justify the exclusion of these references from this CS or if deemed relevant, please provide a summary of the design and results of these studies as per other evidence presented.

SLR conducted to inform TA775

As noted by the EAG, the systematic literature review (SLR) conducted to inform TA775 included studies by Kohan *et al.* (2014), Fioretto *et al.* (2018) and Pollock *et al.* (2019). However, these were presented as supportive evidence only, with DAPA-CKD providing the primary evidence for dapagliflozin, due to limitations with the studies including small populations exclusively involving patients with T2D and comorbid CKD.

Importantly, these studies do not provide any evidence for dapagliflozin in the subgroups of interest in this review as the populations included within the trials do not overlap with the subgroups of interest. All trials included patients with T2D so subgroups 4 and 5 would be the only relevant subgroups. However, the eGFR eligibility criteria of these trials (as presented in Table 7 of Document B of TA775) does not allow patients within subgroup 4 (eGFR ≥20–25 mL/min/1.73m^2) or subgroup 5 (>75–90 mL/min/1.73m^2) to be included within the trials.[1]

The populations included within these studies are presented in Table 6, with the relevant characteristic excluding these studies from providing evidence for this review marked in ***bold and italics***.

Table 6: Populations included within trials used as supportive evidence in TA775

Study	DERIVE	DELIGHT	Kohan *et al.* (2014)
Population	• Adults (17–75 years) with T2D for >12 months, inadequate glycaemic control and CKD stage 3a • ***eGFR 45 to 59 ml/min/1.73m²*** • Stable glucose-lowering treatment regimen	• Adults (17–75 years) with T2D for >12 months • ***eGFR 25 to 75 ml/min/1.73m²*** • uACR 3.4 to 395.5 mg/mmol • Stable glucose-lowering and anti-hypertensive treatments for ≥12 weeks before randomisation	• Adults (17–75 years) with T2D and inadequate glycaemic control • ***eGFR 30 to 59 ml/min/1.73m²*** • Stable antidiabetic regimen

Abbreviations: CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; T2D: type 2 diabetes; uACR: urine albumin-creatinine ratio.
Source: NICE. TA775[1]

SLR conducted to inform TA942

As noted by the EAG, the SLR conducted to inform TA942 identified one additional study providing supportive evidence for dapagliflozin, Dekkers *et al.* (2018), whilst also identifying Kohan *et al.* (2014).

As discussed above, and noted in Table 20 of Document B of TA942, the inclusion criteria of Kohan *et al.* (2014) exclude this study from providing relevant evidence for any of the subgroups of interest in this review as it only included patients with T2D with eGFR 30 to 59 ml/min/1.73m^2.[2]

Dekkers *et al.* (2018) included patients with T2D with eGFR 12 to 45 ml/min/1.73m^2.[18] As such, the population included within this study does overlap with subgroup 4 within this review. However, Dekkers *et al.* (2018) is a pooled analysis of 11 phase III RCTs of dapagliflozin (5 mg or 10 mg) in combination with other T2D medications, including metformin, insulin and thiazolidinediones.[18] Neither the dapagliflozin dose nor the combination treatments represent standard of care for patients with CKD so this study was deemed unsuitable to provide supportive evidence for dapagliflozin in the populations of interest in this review.

Dapagliflozin clinical effectiveness evidence

A4. Priority question: Please clarify whether the company has access to the individual participant data for each of the studies of Dapagliflozin (OPTIMIZE-CKD, Nakhleh et al 2024, DECLARE-TIMI 58, DAPA-HF, DAPA-CKD).

For any studies where IPD is available to the company, please explain why direct effect estimates for each of the specific CKD subgroups addressed in

the review (CS addendum p3-4 and Table 1) have not been calculated for the outcomes listed in the Decision Problem (CS, Document B, Table 1).

Direct effect estimates of dapagliflozin in the specific subgroups in this review are not available from the real-world evidence (RWE) studies or the RCTs of dapagliflozin. The subgroups in this review combine criteria for T2D status, baseline eGFR and baseline uACR. This results in low numbers of patients being identified so any direct effect estimates are uncertain and not statistically powered to detect differences in treatment effect.

To ensure sufficient patient numbers to assess the real-world effectiveness of dapagliflozin across uACR categories, the analyses conducted using OPTIMISE-CKD presented in this review included patients across all baseline eGFR levels. Baseline eGFR was separately taken into account when comparing eGFR slopes, as presented in Figure 2 of the CS Addendum.

[redacted]

[redacted]

Figure 3: [redacted]

In summary, the criteria of the specific subgroups in this review result in too few patient numbers to produce robust effect estimates; any direct effect estimates would not have sufficient power to detect statistical differences in treatment effect and would not provide any meaningful evidence to inform decision-making.

Moreover, due to the absence of publicly available subgroup analyses for empagliflozin that align with the subgroups in this review, it is not possible to conduct any comparison versus empagliflozin within these subgroups, so these data do not provide new evidence to assess the clinical equivalence of dapagliflozin and empagliflozin. However, as discussed extensively in the CS Addendum, the totality of evidence presented demonstrates the consistency of the treatment effect of dapagliflozin across the subgroups in this review, and the clinical equivalence of dapagliflozin and empagliflozin across CKD populations. Based on the available data and mechanism of action of the two SGLT2 inhibitors, there is no scientific rationale to suggest the clinical efficacy and safety of empagliflozin differs from that of dapagliflozin. This is further supported by the broad licenses granted for both treatments and UK Kidney Association clinical guidelines which treat SGLT2 inhibitors as a treatment class.[12, 19, 20]

A5. The EAG understands that the sub-population of the DECLARE-TIMI trial with CKD presented in this submission are defined as in Table 1 (Source: data-on-file REF-231259 – DECLARE subgroup analysis)

Table 1: eGFR and uACR inclusion criteria of the DECLARE-TIMI trial

	eGFR ≤60 mL/min/1.73 m^2	eGFR >60 mL/min/1.73 m^2
uACR <30mg/g	INCLUDED	EXCLUDED
uACR ≥30mg/g	INCLUDED	INCLUDED

Please confirm whether this is correct or please provide the eGFR and uACR inclusion criteria used to define the CKD population in the DECLARE-TIMI trial.

The inclusion and exclusion criteria for the CKD subpopulation of DECLARE-TIMI 58 presented in the above table are correct.

Patients with uACR <30 mg/g and eGFR >60 ml/min/1.73m^2 were excluded from the CKD subpopulation as this is not defined as CKD per the KDIGO criteria, unless there is a structural abnormality.[4]

A6. Please clarify whether baseline characteristics of the CKD sub-populations of the DECLARE-TIMI and DAPA-HF trials presented in the CS are available.

If available, please present baseline characteristics in a similar format to CS, Document B, Table 11.

Baseline characteristics from the overall trial populations of DAPA-HF and DECLARE-TIMI 58 were presented in previous NICE submissions for dapagliflozin (TA679 and TA775) and were deemed generalisable to UK clinical practice.[1, 10]

DAPA-HF

As part of an analysis investigating the efficacy and safety of dapagliflozin in patients with HF with reduced ejection fraction (HFrEF) according to baseline kidney function, baseline characteristics from DAPA-HF are available for two subgroups of patients by baseline eGFR (<60 and ≥60 ml/min/1.73m^2).[11] Although not strictly providing baseline characteristics of all patients with CKD in DAPA-HF, the eGFR cut-offs used for these subgroups represent clinically important subgroups in terms of treatment of CKD in UK clinical practice, in line with KDIGO guidelines.[4]

These baseline characteristics are presented in Table 7. Overall, the baseline characteristics of patients included within each subgroup were similar. Patients with a lower eGFR were older, included more women and more patients had an ischemic cause of heart failure versus those with higher eGFR.[11]

Table 7: Baseline characteristics by baseline eGFR subgroups in DAPA-HF

Baseline characteristic	eGFR <60 ml/min/1.73m^2 (n=1,926)	eGFR ≥60 ml/min/1.73m^2 (n=2,816)
Baseline eGFR, ml/min/1.73m^2	47.0 ± 8.0	78.7 ± 13.5
Age, years	70.9 ± 9.0	63.2 ± 11.0
Female sex, N (%)	534 (27.7)	575 (20.4)
Geographic region, N (%)		
Asia/Pacific	365 (19.0)	731 (26.0)
Europe	891 (46.3)	1,263 (44.9)
Norther America	305 (15.8)	370 (13.1)
South America	365 (19.0)	452 (16.1)
New York Heart Association class		
II	1,267 (65.8)	1,934 (68.7)
III	645 (33.5)	853 (30.3)

Baseline characteristic	eGFR <60 ml/min/1.73m^2 (n=1,926)	eGFR ≥60 ml/min/1.73m^2 (n=2,816)
IV	14 (0.7)	29 (1.0)
Heart rate, bpm	70.7 ± 11.6	72.0 ± 11.7
Baseline systolic blood pressure, mmHg	121.7 ± 16.2	121.9 ± 16.4
Baseline ejection fraction, %	31.3 ± 6.6	30.9 ± 6.9
Baseline N-terminal pro-B-type natriuretic peptide, pg/mL, median (interquartile range)	1,823.8 (1,060.2–3,326.2)	1261.1 (769.9–2,207.7)
Body mass index, kg/m^2	28.4 ± 5.8	28.0 ± 6.0
Main cause of heart failure		
Ischemic	1,174 (61.0)	1,498 (53.2)
Nonischaemic	605 (31.4)	1,082 (38.4)
Unknown	147 (7.6)	236 (8.4)
T2D status at baseline		
Yes	982 (51.0)	1,157 (41.1)
Patients with T2D at baseline		
Haemoglobin A1c, %	6.6 ± 1.4	6.4 ± 1.3
Biguanide	406 (21.1)	624 (22.2)
Sulfonylurea	198 (10.3)	242 (8.6)
Dipeptidyl peptidase 4 inhibitor	164 (8.5)	146 (5.2)
Glucagon-like peptide 1-receptor agonist	15 (0.8)	6 (0.2)
Insulin	304 (15.8)	236 (8.4)

Abbreviations: CRT: cardiac resynchronisation therapy; eGFR: estimated glomerular filtration rate; T2D: type 2 diabetes
Source: Jhund et al. (2021)[11]

DECLARE-TIMI 58

In addition, an analysis of the impact of dapagliflozin on renal outcomes in DECLARE-TIMI 58 is published by Mosenzon *et al.* (2019) which presents baseline characteristics for three subgroups of patients by baseline eGFR (<60, 60 to <90 and ≥90 ml/min/1.73m^2).[21] These are presented in Table 8. Overall, the baseline characteristics of patients included within each subgroup were similar. Patients with lower eGFR at baseline were older, had been diagnosed with T2D for longer and were more likely to have a history of heart failure and cardiovascular (CV) risk factors.[21] This is broadly consistent with the trends observed in DAPA-HF.

Table 8: Baseline characteristics by baseline eGFR subgroups in DECLARE-TIMI 58

Baseline characteristic	eGFR ≥90 ml/min/1.73m^2 (n=8,162)	eGFR 60 to <90 ml/min/1.73m^2 (n=7,732)	eGFR <60 ml/min/1.73m^2 (n=1,265)
Female sex, N (%)	5,057 (62.0%)	4,866 (62.9%)	814 (64.3%)
Median age, years (SD)	3,105 (38.0%)	2,866 (37.1%)	451 (35.7%)
Age ≥75 years, n (%)	61.2 (6.1)	66.2 (6.5)	67.3 (6.6)
Body mass index, kg/m^2	95 (1.2%)	818 (10.6%)	183 (14.5%)
Race, n (%)			
White	6,251 (76.6%)	6,313 (81.6%)	1,088 (86.0%)
Non-white	1,911 (23.4%)	1,419 (18.4%)	177 (14.0%)
Medical history			

Baseline characteristic	eGFR ≥90 ml/min/1.73m^2 (n=8,162)	eGFR 60 to <90 ml/min/1.73m^2 (n=7,732)	eGFR <60 ml/min/1.73m^2 (n=1,265)
Duration of T2D	10.9 (7.2)	12.5 (8.0)	14.5 (8.9)
Established atherosclerotic CV disease, n (%)	3,193 (39.1%)	3,138 (40.6%)	643 (50.8%)
History of congestive heart failure, n (%)	688 (8.4%)	809 (10.5%)	227 (17.9%)
History of dyslipidaemia, n (%)	6,370 (78.0%)	6,327 (81.8%)	1,098 (86.8%)
History of hypertension, n (%)	7,133 (87.4%)	7,088 (91.7%)	1,205 (95.3%)
Laboratory and clinical measurements			
HbA1c, n (%)	8.5 (1.2)	8.1 (1.1)	8.2 (1.2)
HbA1c, mmol/mol	68.9 (13.6)	65.3 (12.5)	66.5 (12.9)
eGFR, ml/min/1.73m^2	98.3 (6.5)	77.0 (8.5)	51.4 (7.2)
uACR group, mg/g			
N[a]	8,026	7,582	1,234
<30	5,691 (70.9%)	5,267 (69.5%)	686 (55.6%)
30–300	1,887 (23.5%)	1,761 (23.2%)	381 (30.9%)
>300	448 (5.6%)	554 (7.3%)	167 (13.5%)
Blood pressure, mmHg			
Systolic	134.9 (15.0)	135.3 (15.6)	133.5 (16.6)
Diastolic	78.9 (8.8)	77.5 (9.2)	75.3 (9.4)
Lipids, mg/dL			
LDL cholesterol	90.3 (35.9)	85.4 (34.5)	83.5 (36.4)
HDL cholesterol	47.4 (13.1)	47.4 (13.0)	44.2 (12.0)
Triglycerides	179.4 (141.8)	173.9 (121.7)	197.4 (155.3)

[a] Baseline uACR was not measured for all patients so N values are smaller for uACR groups than for the overall population.
Abbreviations: eGFR: estimated glomerular filtration rate; T2D: type 2 diabetes; uACR: urine albumin-creatinine ratio
Source: Mosenzon et al. (2019)[21]

A7. Subgroup analyses of the DAPA-CKD trial reported in Heerspink (2020) showed variation in the hazard ratio (HR) estimates between subgroups for the composite primary outcome of the trial, including by baseline eGFR, T2DM, uACR and systolic blood pressure. Please provide results of heterogeneity tests for these subgroups and discuss the clinical relevance of these subgroup results.

Results of the heterogeneity tests of the subgroup analyses were previously presented in Document B of TA775.[1] However, to aid the EAG's review, the results of the subgroup analyses of the composite primary endpoint (≥50% eGFR decline, end stage renal disease and renal or CV death) including the interaction p-value are re-presented in Table 9.

The interaction p-values were conducted as explorative testing without a defined significance limit. All subgroup analyses show a nominal non-significant interaction, except systolic blood pressure at baseline; however, this is explained by dapagliflozin showing a treatment benefit in both systolic blood pressure subgroups, with the ≤130 mmHg subgroup showing a more pronounced benefit than the >130 mmHg subgroup which still shows a substantial treatment benefit. Furthermore, this p-value for interaction should be interpreted in the context of

multiple testing across many different subgroups, which increases the likelihood of a chance finding.

Table 9: Time to first event of the composite endpoint of ≥50% eGFR decline, ESRD and renal or CV death by subgroups

Characteristic	Dapagliflozin (n=2,152); n (%)	Placebo (n=2,152); n (%)	HR (95% CIs)	Interaction p-value
Age (years)				
≤65	122 (9.8)	191 (15.4)	0.64 (0.51, 0.80)	[redacted]
>65	75 (8.3)	121 (13.3)	0.58 (0.43, 0.77)	
Sex				
Male	126 (8.7)	209 (14.6)	0.57 (0.46, 0.72)	[redacted]
Female	71 (10.0)	103 (14.4)	0.65 (0.48, 0.88)	
Race				
White	110 (9.8)	174 (14.9)	0.62 (0.49, 0.79)	[redacted]
Black or African American	7 (6.7)	14 (16.1)	0.33 (0.13, 0.81)	
Asian	53 (7.1)	77 (10.7)	0.66 (0.46, 0.93)	
Other	27 (15.4)	47 (26.0)	0.54 (0.33, 0.86)	
Geographic region				
Asia	50 (7.2)	69 (10.6)	0.70 (0.48, 1.00)	[redacted]
Europe	57 (9.3)	89 (14.3)	0.60 (0.43, 0.85)	
North America	35 (8.7)	69 (16.7)	0.51 (0.34, 0.76)	
Latin/South America	55 (12.2)	85 (18.4)	0.61 (0.43, 0.86)	
T2D at baseline[a]				
Yes	152 (10.4)	229 (15.8)	0.64 (0.52, 0.79)	[redacted]
No	45 (6.5)	83 (11.8)	0.50 (0.35, 0.72)	
uACR (mg/g) at baseline				
≤1000	44 (4.0)	84 (7.5)	0.54 (0.37, 0.77)	[redacted]
>1000	153 (14.6)	228 (22.1)	0.62 (0.50, 0.76)	
eGFR (ml/min/1.73m^2) at baseline[b]				
<45	152 (11.9)	217 (17.4)	0.63 (0.51, 0.78)	[redacted]
≥45	45 (5.1)	95 (10.5)	0.49 (0.34, 0.69)	
eGFR (ml/min/1.73m^2) at baseline[b]				
<30	59 (20.1)	87 (26.3)	0.73 (0.53, 1.02)	[redacted]
≥30	138 (7.4)	225 (12.4)	0.58 (0.47, 0.71)	
Systolic blood pressure (mmHg) at baseline				
≤130	46 (5.8)	96 (12.8)	0.44 (0.31, 0.63)	[redacted]
>130	151 (11.1)	216 (15.4)	0.68 (0.56, 0.84)	

HR, CI and p-value are calculated from Cox proportional hazards model stratified by randomisation stratification of T2D status and uACR, adjusting for baseline eGFR, with factors for treatment group, subgroup, and the interaction between treatment group and the subgroup variable. [a] Defined as history of T2DM or HbA1c ≥ 6.5% at both visit 1 and visit 2. [b] This analysis does not adjust for baseline eGFR.
Abbreviations: ESRD: end stage renal disease; CV: cardiovascular;HR: hazard ratio; CI: confidence interval; T2D: Type 2 diabetes; uACR: urine albumin creatinine ratio; eGRF: estimated glomerular filtration rate.
Source: DAPA-CKD CSR

A8. The results of the Nakhleh (2024) study presented in CS, Document B, Section 3.6.3 and CS addendum, p8 and p13-14 are not reported separately by SGLT2 inhibitor received (dapagliflozin or empagliflozin). Please provide further justification of how these results provide supportive evidence for the efficacy of dapagliflozin and, if applicable, how these results provide supportive evidence of the clinical similarity of dapagliflozin and empagliflozin.

As noted above, the data presented in Nakhleh *et al.* (2023) are not presented separately for dapagliflozin and empagliflozin but are instead reported for SGLT2 inhibitors as a class of treatments.[22] However, as noted in the CS Addendum, the majority of patients in Nakhleh *et al.* (2024) received dapagliflozin (75.4%) versus empagliflozin (24.6%).[22] Therefore, data from Nakhleh *et al.* (2024) can be broadly considered generalisable to dapagliflozin and supports the consistent treatment effect of dapagliflozin across eGFR and uACR subgroups. This is supported by the publication acknowledging the consistency of the RWE with the study results of DAPA-CKD.[22]

As a proportion of patients did receive empagliflozin, these results can also support the clinical similarity of dapagliflozin and empagliflozin as the 95% confidence intervals [CIs] around the point estimates provide an indication of the variation in treatment effect observed across all patients, including variation observed between dapagliflozin and empagliflozin. For example, difference in mean eGFR slope before and after SGLT2 inhibitor administration was 3.91 (95% CIs: 2.81, 5.02) mL/min/1.73m^2 per year.[22] The narrow 95% CIs around the point estimate support that there is minimal variation in the treatment effect of the two SGLT2 inhibitors, providing evidence of the clinical similarity of the treatments. This is also supported by the consistency of the findings from this RWE study with the results of both EMPA-KIDNEY and DAPA-CKD, therefore providing additional evidence to further reduce any uncertainty in this review.

A9. Priority question: The company interpretation of the evidence provided within the CS Document B Section 3.6 and the CS addendum (response to Question 2) to demonstrate consistent efficacy of dapagliflozin regardless of eGFR category, uACR category and presence of T2D. Please provide discussion, supported by evidence where applicable, relating to the presence or absence of any interaction between defining criteria of the CKD subgroups (i.e. eGFR, uACR and T2D).

The subgroup analyses of the primary composite endpoint are presented in response to Clarification Question A7, these demonstrate a nominally non-significant interaction for all subgroups, except systolic blood pressure at baseline which still shows a benefit of dapagliflozin across the subgroups. Analyses looking at the interaction of multiple variables, and additive effect of these variables, in the dapagliflozin RCTs are not available; it is not standard practice in RCTs to include analyses of the additive interaction of variables.

This review presents a variety of evidence from real-world and clinical trial settings which explore the treatment effect of dapagliflozin in patients with and without T2D and across eGFR and uACR subgroups. Although analyses looking at the interaction of multiple variables are not available, the totality of presented evidence demonstrate the consistent treatment effect of dapagliflozin across all patient characteristics across RCTs. This is further supported by an additional analysis from Waijer *et al.* (2022) which demonstrates a consistent treatment benefit, in terms of kidney and CV outcomes, of dapagliflozin across KDIGO categories.[23] The same consistent effect across KDIGO categories was observed when analysing patients with and without T2D. Although there may be an additive effect of variables on the efficacy of dapagliflozin, the evidence presented demonstrates the consistent treatment effect of dapagliflozin across CKD patients so this should not be a source of uncertainty in this review.

The clinical relevance of considering eGFR and uACR categories separately is also supported by the KDIGO framework. Although the framework does combine uACR and eGFR, a change in either variable independently impacts classification of disease, as presented in Figure 4. For example, for a patient with eGFR of 45–59 ml/min/1.73m^2, variation in their uACR level can result in their disease being categorised as either 1) increased risk, 2) high risk or 3) very high risk.[4]

Comparison with Empagliflozin

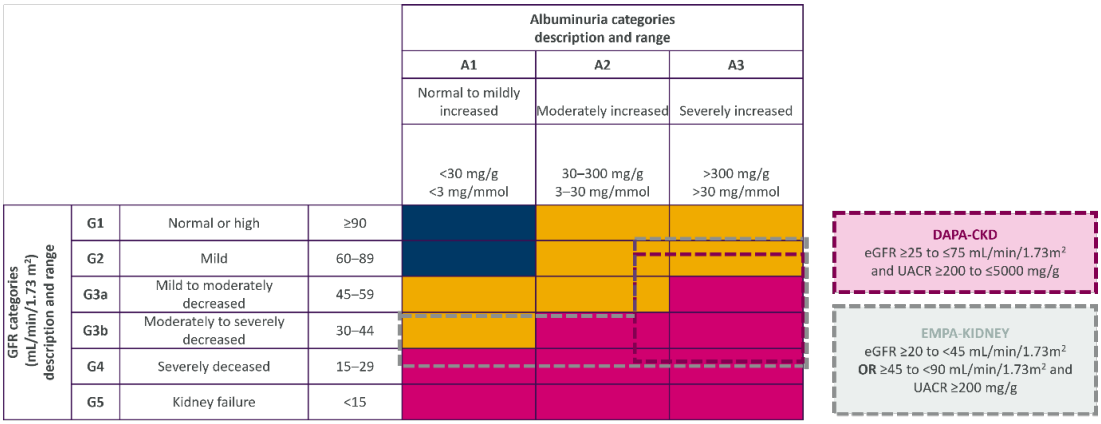
A10. Priority question: Please provide a summary of the eligibility criteria, trial and patient baseline characteristics from the EMPA-Kidney trial and a discussion of the specific areas of heterogeneity between this trial and the studies of Dapagliflozin which have precluded the execution of an indirect treatment comparison (CS, Document B, pp 87-88 and CS addendum, p27)

Feasibility assessments for ITCs of dapagliflozin versus empagliflozin

ITC of dapagliflozin based on DAPA-CKD and empagliflozin based on EMPA-KIDNEY

As outlined in Document B, an ITC in the overlapping populations of DAPA-CKD and EMPA-KIDNEY was conducted to support the appraisal of empagliflozin in CKD (TA942). This ITC demonstrated that empagliflozin was not inferior to dapagliflozin and formed the basis of the broad NICE recommendation for empagliflozin.[2] As this ITC has already been conducted, an ITC in these overlapping populations was not re-conducted to support this review. A diagram showing the overlapping populations of DAPA-CKD and EMPA-KIDNEY (i.e., the populations of relevance to this ITC) is presented in Figure 4.

Figure 4: KDIGO grid of albuminuria categories and GFR categories with study overlap between DAPA-CKD and EMPA-KIDNEY



Abbreviations: eGFR: estimated glomerular filtration rate; uACR: urine albumin-creatinine ratio.

Due to the eligibility criteria of DAPA-CKD, the trial only includes a small sample of patients that fall within subgroup 1 (adults with CKD without T2D, an eGFR ≥20–45 mL/min/1.73m^2 and uACR <22.6 mg/mmol), with no patients falling within the remaining subgroups being included within the trial. The inclusion criteria of the empagliflozin studies showed overlap with the subgroups defined in this review, however baseline characteristics and outcomes were not publicly available for these subgroups. As such, it was not possible to facilitate an ITC of empagliflozin versus dapagliflozin in these subgroups. Individual patient-level data (IPD) from EMPA-KIDNEY are also not available, hence it was not feasible to derive these data or match the DAPA-CKD trial population. As such, it was not possible to conduct a robust ITC of dapagliflozin based on DAPA-CKD alone versus empagliflozin to inform the subgroups in this review.

ITC of dapagliflozin based on OPTIMISE-CKD and empagliflozin based on EMPA-KIDNEY

As outlined in the CS Addendum (Question 5), a second feasibility assessment was conducted in July 2024 to assess the possibility of comparing the treatment effect of dapagliflozin versus empagliflozin in the EMPA-KIDNEY population, using real-world data from a matched population of patients prescribed dapagliflozin from the Optum Clinformatics database (hereafter referred to as 'Optum'). It was not feasible to identify and match key exclusion criteria from the EMPA-KIDNEY study (e.g., scheduled interventions, recent use of investigational medicinal products and history of cancer) in the Optum database. This results in a lack of comparable datasets, introducing significant bias and violating the assumptions required for both anchored and unanchored indirect comparison methods. Consequently, it was not feasible to conduct a robust ITC of dapagliflozin versus empagliflozin in the specific subgroups in this review.

EMPA-KIDNEY – Patient baseline characteristics and trial design

The published patient baseline characteristics of patients randomised to receive empagliflozin and placebo in EMPA-KIDNEY are presented in Table 10. A summary of the EMPA-KIDNEY trial, including trial design and eligibility criteria, is provided in Table 11.

Table 10: Baseline characteristics of patients randomised to receive empagliflozin and placebo in EMPA-KIDNEY

Baseline characteristic	Empagliflozin	Placebo
Number of patients, N	3,304	3,305
Age (years), mean (SD)	63.9 (13.9)	63.8 (13.9)
Female sex, N (%)	1,097 (33.2)	1,095 (33.1)
Race, N (%)		
White	1,939 (58.7)	1,920 (58.1)
Black	128 (3.9)	134 (4.1)
Asian	1,194 (36.1)	1,199 (36.3)
Multiple	14 (0.4)	7 (0.2)
Other	29 (0.9)	45 (1.4)
Body mass index (kg/m^2), mean (SD)	29.7 (6.7)	29.8 (6.8)
Blood pressure (mm Hg)		
Systolic	136.4 (18.1)	136.7 (18.4)
Diastolic	78.1 (11.7)	78.1 (11.9)
History of DM, N (%)		
Yes	1,525 (46.2)	1,515 (45.8)
DM type, N (%)		
Type 1	34 (2.2)	34 (2.2)
Type 2	1,470 (96.4)	1,466 (96.8)
Other or unknown	21 (1.4)	15 (1.0)
History of cardiovascular disease, N (%)		
Yes	861 (26.1)	904 (27.4)
eGFR		
Mean – mL/min/1.73m^2 (SD)	37.4 (14.5)	37.3 (14.4)
Distribution, N (%)		
<30 mL/min/1.73m^2	1,131 (34.2)	1,151 (34.8)
30 to <45 mL/min/1.73m^2	1,467 (44.4)	1,461 (44.2)
≥45 mL/min/1.73m^2	706 (21.4)	693 (21.0)
uACR		
Geometric mean (95% CI)	219 (205-234)	226 (211-242)
Median (IQR)	331 (46-1061)	327 (54-1074)
Distribution, N (%)		
<30	665 (20.1)	663 (20.1)
30 to 300 (inclusive)	927 (28.1)	937 (28.4)
>300	1,712 (51.8)	1,705 (51.6)
Median NT-proBNP (IQR) – ng/litre	162 (70-421)	159 (68-417)
Baseline medications, N (%)		
Renin-angiotensin system inhibitor	2,831 (85.7)	2,797 (84.6)
Any diuretic	1,362 (41.2)	1,453 (44.0)
Any lipid-lowering medication	2,190 (66.3)	2,188 (66.2)
Cause of kidney disease, N (%)		
Diabetic kidney disease	1,032 (31.2)	1,025 (31.0)
Hypertensive or renovascular disease	706 (21.4)	739 (22.4)
Glomerular disease	853 (25.8)	816 (24.7)
Other	387 (11.7)	421 (12.7)
Unknown	326 (9.9)	304 (9.2)

Abbreviations: DM: diabetes mellitus; eGFR: estimated glomerular filtration rate; SD: standard deviation; uACR: urine albumin-creatinine ratio.
Source: NICE. TA942.[2]

Table 11: Overview of trial design and inclusion/exclusion criteria for EMPA-KIDNEY

Trial name	EMPA-KIDNEY
Study design	Phase III, randomised, double-blind, placebo-controlled trial with parallel assignment
Population	Patients with evidence of CKD at risk of kidney disease progression, with or without diagnosed diabetes mellitus
Intervention and comparator	• Empagliflozin per oral 10mg OD in addition to SoC[a] • Placebo plus SoC[a]
Inclusion criteria	• Males and females aged ≥18 years, or 'full age' as required by local regulation (e.g., 20 years in Japan) • Evidence of CKD at risk of kidney disease progression, defined on the basis of local laboratory results recorded ≥3 months before and at the time of the screening visit, and required that: CKD-EPI eGFR ≥20 and <45 mL/min/1.73m^2 ; or CKD-EPI eGFR ≥45 and <90 mL/min/1.73m^2 with uACR ≥200 mg/g (22.6 mg/mmol) (A2-A3) (or protein: creatinine ratio ≥300 mg/g [30 mg/mmol]) • A local investigator judging that the participants neither required empagliflozin (or any other SGLT2 or dual SGLT1/2 inhibitor), nor that such treatment was inappropriate • Patients treated with clinically appropriate doses of a RAS inhibitor with either ACE inhibitors or ARB, unless treatment was either not tolerated or indicated
Exclusion criteria	• Receiving a SGLT2 or dual SGLT1/2 inhibitor at the time of study or, receiving dual RAS-inhibition (two of ACE inhibitors, ARB, or DRI treatment) • T2DM and prior atherosclerotic cardiovascular disease† with an eGFR>60 mL/min/1.73m2 at screening • T1DM‡ • Undergoing maintenance dialysis, functioning kidney transplant, or scheduled living donor transplant* • Polycystic kidney disease or Previous or scheduled bariatric surgery or ketoacidosis in the past 5 years • Symptomatic hypotension*, or systolic blood pressure <90 or >180 mmHg, or ALT or AST >3x ULN at screening • Hypersensitivity to empagliflozin or another SGLT2 inhibitor • Intravenous immunosuppression therapy in the previous 3 months; or anyone currently on >45 mg prednisolone (or equivalent)* • Use of an investigational medicinal product in the 30 days prior to screening visit • Poorly compliant with clinic visits or prescribed medication* • Medical history that might limit individual's ability to take trial treatments for the duration of the study (e.g., severe respiratory disease; history of cancer or evidence of spread within last 4 years, other than non-melanoma skin cancer; or recent history of alcohol or substance misuse)* • Current pregnancy, lactation, or women of childbearing potential, unless using highly effective contraception

	• Additionally, individuals were excluded at the randomisation visit of the participant if they did not adhere to run-in treatment, were no longer willing to be randomised and followed for at least 3 years, were considered by a local investigator not to be suitable for randomisation, or experienced ketoacidosis, heart attack, stroke, or hospitalisation for heart failure, or hospitalisation for urinary tract infection or acute kidney injury during run-in

[a] SoC could include treatment with RAS-inhibitors, diuretics, and beta-blockers.
Abbreviations: ACE: angiotensin–converting–enzyme; ARB: angiotensin II receptor blocker; CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; RAS: renin-angiotensin system; SGLT2: sodium-glucose co-transporter-2; SoC: standard of care; T1DM: type 1 diabetes mellitus; T2DM: type 2 diabetes mellitus;
Source: NICE. TA942.[2]

A11. Priority question: EMPA-KIDNEY is assumed to be the only source of relevant clinical data for this review (CS, Addendum, p35). As published data from the EMPA-KIDNEY trial is not available for the specific subgroups in this review (CS addendum, Table 3), please clarify why other data sources for Empagliflozin were not considered for this submission.

EMPA-KIDNEY was the primary source of evidence on the efficacy and safety of empagliflozin as a treatment for CKD in its NICE appraisal in CKD (TA942) and formed the basis of the broad NICE recommendation for empagliflozin.[2] Based on this recommendation, EMPA-KIDNEY was deemed to provide suitable evidence across all CKD subgroups by the NICE Committee. As such, EMPA-KIDNEY was used as the source of clinical data for empagliflozin informing this review. AstraZeneca are not aware of any additional relevant subgroup analyses of empagliflozin as treatment for CKD that could have been used in addition to EMPA-KIDNEY.

Pre-specified subgroup analyses by baseline eGFR and uACR were conducted and presented in TA942, however the pre-specified subgroups do not align with the subgroups of interest in this appraisal.[2] Subgroup analyses are also published by The EMPA-KIDNEY Collaborative Group (2022, 2024).[17, 24] The overlap between the available pre-specified subgroups from EMPA-KIDNEY and the subgroups in this review was presented in Table 3 of the CS Addendum and discussed further in response to Clarification Question A13.

In TA942, the EAG concluded that for the primary outcome in EMPA-KIDNEY, subgroup analyses by baseline eGFR and T2D status were consistent with the overall population results. There was some evidence that empagliflozin demonstrates a greater treatment benefit in patients with higher (>300) uACR, however, empagliflozin was concluded to have an overall consistent treatment effect, regardless of T2D status, baseline eGFR and baseline uACR and this formed the basis of the broad NICE recommendation.[2] Moreover, the EAG concluded that “all subgroup analyses were consistent with the overall result for the key secondary outcomes” for empagliflozin.[2]

Assuming a consistent treatment effect for empagliflozin across CKD subgroups (as concluded by the EAG in TA742), as dapagliflozin has been shown to be at least as effective as empagliflozin in the overlapping populations of EMPA-KIDNEY and DAPA-CKD and the clinical benefit of dapagliflozin has been demonstrated to be consistent across the subgroups in this review, the clinical equivalence of the two SGLT2 inhibitors can be assumed to extend across all subgroups in this review. As outlined in the CS Addendum, there is no biological or scientific rationale why dapagliflozin and empagliflozin would have a different treatment effect in different eGFR and uACR subgroups, as supported by the broad licenses granted for both treatments (i.e., irrespective of eGFR or uACR measurements). The consideration of the efficacy of SGLT2 inhibitors as a class effect has historically applied across indications, as supported by UK Kidney Association clinical guidelines and the consistent NICE recommendations for dapagliflozin and empagliflozin in all other indications.[10, 20, 25-27]

A12. Priority question: Please clarify if the 'Optum Clinformatics' database examined in the second feasibility assessment of an ITC (CS addendum, p27) refers to the same data source of the OPTIMISE-CKD study (CS, Document B, Table 13).

If the Optum database used for the feasibility assessment is different to the database used for the OPTIMIZE-CKD study, please clarify:

a. Database design and objective of the database

b. Timeframe of the database

c. Patient eligibility criteria for inclusion in the database

d. Outcome data collected for the database which is relevant to the Decision Problem

e. Why this data source was not included in the submitted evidence for Dapagliflozin

Yes – AstraZeneca can confirm that the 'Optum Clinformatics Database' is the same data source as that used in the OPTIMISE-CKD study.

A13. Priority question: In the format of Table 3 of the CS addendum, please provide a summary of evidence of the effect of Empagliflozin for all outcomes defined in the NICE scope (CS, Document B, Table 1).

Where such evidence is not available from the EMPA-KIDNEY trial, please consider other data sources of Empagliflozin to inform this and/or please clearly state where no evidence is available.

Subgroup analyses from EMPA-KIDNEY are published by the EMPA-KIDNEY Collaborative Group for the primary outcome (progression of kidney disease or death from cardiovascular causes); these were presented in Table 3 of the CS Addendum.[17] Pre-specified subgroup analyses were conducted for key secondary endpoints in EMPA-KIDNEY and presented in Appendix E of TA942.[5] AstraZeneca submitted a Freedom of Information request to NICE and were provided with a copy of Appendix E of TA942; as such, a summary of the relevant subgroup analysis results for the primary endpoint and key secondary endpoints are presented in Table 12.

An additional EMPA-KIDNEY publication provides some further subgroup analyses, including expanded eGFR categories for select endpoints (primary endpoint and change in eGFR slope).[24] This does include a subgroup of patients with eGFR 20 to <30

ml/min/1.73m^2, however the results are highly consistent with the subgroup analyses presented in Table 12, so are not incorporated into Table 12 to allow comparison across endpoints.[24] For example, the HR for empagliflozin versus placebo for the primary endpoint (kidney disease progression or death from CV causes) for patients with eGFR 20 to <30 ml/min/1.73m^2 is 0.74 (95% CIs: 0.61, 0.89) versus 0.73 (0.62, 0.86) for patients with eGFR <30 ml/min/1.73m^2.[24]

Although some variation is seen in the treatment effect of empagliflozin across the subgroups (notably a decreased benefit in patients with baseline uACR <3.4 mg/mmol and 3.4–34 mg/mmol), the EAG in TA942 concluded that empagliflozin demonstrates a consistent treatment effect across CKD subgroups, as discussed in response to Clarification Question A11, and this formed the basis of the broad recommendation from NICE.[2] This is in line with the consistent treatment effect observed for dapagliflozin across CKD subgroups, as discussed in response to Questions 1 and 2 in the CS Addendum.

Table 12: Empagliflozin subgroup analyses for primary endpoint and key secondary endpoints in EMPA-KIDNEY presented in Appendix E of TA942

Subgroups in this review		Empagliflozin subgroup	Empagliflozin versus placebo (HR [95% CIs])				Absolute difference in mean annual rate of change in eGFR	
			Progression of kidney disease or death from cardiovascular causes	Time to occurrence of all-cause hospitalisation [d]	Time to first occurrence of HHF or CV death	Time to adjudicated death from any cause	Annual rate of change in eGFR from 2 months to final follow-up (total slope)	Annual rate of change in eGFR from 2 months to final follow-up (chronic slope)
1	Without T2D, eGFR ≥20–45 mL/min/1.73m^2, **uACR <22.6 mg/mmol**	uACR <3.4 mg/mmol	1.01 (0.66, 1.55)	0.80 (0.65, 0.99)	0.99 (0.58, 1.70)	0.94 (0.59, 1.51)	0.17 (-0.27, 0.60)	0.78 (0.32, 1.23)
		uACR 3.4–34 mg/mmol[a]	0.91 (0.65, 0.78)	0.83 (0.69, 0.99)	0.85 (0.57, 1.27)	0.97 (0.68, 1.40)	0.46 (0.09, 0.83)	0.1.20 (0.81, 1.59)
2	Without T2D, **eGFR ≥20–25** mL/min/1.73m^2, uACR ≥22.6 mg/mmol	eGFR <30 mL/min/1.73m^2 [b]	0.73 (0.62, 0.86)	0.88 (0.75, 1.03)	0.99 (0.71, 1.39)	0.86 (0.63, 1.16)	0.51 (0.15, 0.87)	1.01 (0.63, 1.39)
4	with T2D, **eGFR ≥20–25** mL/min/1.73m^2, irrespective of uACR							
3	With T2D, **eGFR >75–90** mL/min/1.73m^2, uACR ≥22.6 mg/mmol	eGFR >45 mL/min/1.73m^2 [c]	0.64 (0.44, 0.93)	0.91 (0.72, 1.14)	0.98 (0.39, 2.46)	0.67 (0.25, 1.75)	1.19 (0.92, 1.47)	2.01 (1.53, 2.49)
5	With T2D, **eGFR >75–90** mL/min/1.73m^2, irrespective of uACR							
Overall trial population			0.72 (0.64, 0.82)	0.68 (0.78, 0.95)	0.84 (0.67, 1.07)	0.87 (0.70, 1.08)	0.75 (0.54, 0.96)	1.37 (1.16, 1.59)

For annual rate of change in eGFR, a value over 0 indicates a benefit of empagliflozin versus placebo; a value below 0 indicates a benefit of placebo versus empagliflozin. [a] Outcomes for empagliflozin for patients with uACR 3.4–34 mg/mmol are not reported separately for different levels of eGFR or T2D status. [b] Outcomes for empagliflozin for patients with eGFR <30 mL/min/1.73m^2 are not reported separately for different levels of uACR or T2D status. [c] Outcomes for empagliflozin for patients with eGFR >45 mL/min/1.73m^2 are not reported separately for different levels of uACR or T2D status. [d] First and recurrent combined.
Abbreviations: eGFR: estimated glomerular filtration rate; HR: hazard ratio; T2D: type 2 diabetes; uACR: urine albumin-creatinine ratio.
Source: The EMPA-KIDNEY Collaborative Group.[17] NICE. TA942 Appendix E.[5]

A14. Priority question: Where aligning evidence is available across the five subgroups for this review for Dapagliflozin and Empagliflozin for outcomes defined in the NICE scope, please comment on the 'similarity' of effect sizes (e.g. magnitude and direction of effect, overlapping confidence intervals etc.)

As discussed in the CS Addendum and in response to Question A13, subgroup analyses from EMPA-KIDNEY are published for pre-specified baseline eGFR (<30 ml/min/1.73m^2, 30 to <45 ml/min/1.73m^2, ≥45 ml/min/1.73m^2) and uACR (<30, 30 to 300, >300 mg/g) subgroups.[17] An additional EMPA-KIDNEY publication provides some further subgroup analyses, however these do not align more closely with the subgroups in this review and provide consistent results with the subgroup analyses presented in response to Clarification Question A13.[24] As the published subgroup analyses do not completely align with the subgroups in this review, it is not possible to conduct a comparison of the treatment effect of empagliflozin and dapagliflozin in the specific subgroups in this review.

In the absence of completely aligned subgroup data, a naïve comparison of the available empagliflozin and dapagliflozin subgroups can be conducted; this was presented in response to Question 5 of the CS Addendum and discussed in Document B, Section B.3.9.1. Subgroup data from EMPA-KIDNEY demonstrate that the HR for the primary endpoint (kidney disease progression or death from CV causes) for patients with baseline uACR (<30 mg/g) was 1.01 (95% CIs: 0.66, 1.55]).[17] In contrast, a post-hoc analyses of DAPA-CKD demonstrates a consistent treatment benefit of dapagliflozin regardless of baseline uACR, which is further supported by RWE from OPTIMISE-CKD and Nakhleh *et al.*, 2024.[22, 28, 29]

Subgroup analyses of mean change in total eGFR slope per year by baseline uACR for dapagliflozin and empagliflozin can also be compared. When interpreting this endpoint, a value over zero indicates a benefit of dapagliflozin/empagliflozin versus placebo; a value below zero indicates a benefit of placebo versus dapagliflozin/empagliflozin. Based on EMPA-KIDNEY, in a subgroup of patients with baseline uACR of 30–300 mg/g, the difference in mean annual rate of change in total eGFR slope for empagliflozin and placebo was 0.45 (0.10, 0.81) ml/min/1.73m^2; the same value for patients with baseline uACR <30 mg/g was 0.16 (-0.26, 0.57) ml/min/1.73m^2 .[24] Although perfectly aligning subgroups are not available for patients receiving dapagliflozin, Tangri *et al.* (2024) provides data on patients with baseline uACR <200 mg/g.[30] In this subgroup, the difference in mean annual rate of change in eGFR for dapagliflozin and placebo was 1.07 (0.40, 1.74) ml/min/1.73m^2.[30] This naïve comparison show a directionally similar and statistically significant benefit of both empagliflozin and dapagliflozin in similar subgroups. Furthermore, as discussed in the CS Addendum, the impact of dapagliflozin on change in eGFR slope observed in Tangri *et al.* (2024) is similar to the benefit observed with dapagliflozin versus placebo in DAPA-CKD (change in total slope: 0.95 [95% CIs: 0.63, 1.727] ml/min/1.73m^2), supporting the consistent treatment effect of dapagliflozin across uACR subgroups.[30]

Other available empagliflozin subgroup data for patients with eGFR <30 mL/min/1.73m^2 and >45 mL/min/1.73m^2 demonstrate an overall consistent treatment benefit across endpoints, which is consistent with the available evidence for dapagliflozin.

Based on the available subgroup data for empagliflozin and evidence of a consistent treatment effect for dapagliflozin regardless of baseline eGFR and uACR, it is plausible to conclude that dapagliflozin is at least clinically equivalent to empagliflozin across all CKD subgroups considered within this review.

Section B: Clarification on cost-comparison data

B1. Priority question: In the CS addendum (p40), the company state that "due to the lack of published accurate data on the frequency of resource use and the clinical equivalence between dapagliflozin and empagliflozin, the current cost comparison analysis does not include resource use costs" and conclude that there is no difference in the resource use between dapagliflozin and empagliflozin. To support this conclusion, please provide an overview of the resource use and associated costs for dapagliflozin and provide justification for empagliflozin to be expected to be associated with equal resource use.

For patients with CKD, dapagliflozin and empagliflozin are both used in primary care and occasionally secondary care. They are both administered orally as one tablet once daily and available in 28-tablet pack priced at £36.59, as shown in Table 13. They have the same mechanism of action and are clinically equivalent, as demonstrated in the CS and the associated CS Addendum, meaning their resource costs are equivalent. Following the positive recommendation of empagliflozin in TA942, NICE published a joint resource impact report for empagliflozin and dapagliflozin which states that data from an ITC showed no clinically meaningful differences were found between empagliflozin and dapagliflozin across any of the trial outcomes (Section 1.5).[31] This was also recognised by NICE in the technology guidance for empagliflozin (TA942): "Results of an indirect comparison suggest that empagliflozin has a similar effectiveness to dapagliflozin, and it likely has similar safety." and "a cost comparison suggests that empagliflozin has similar costs to dapagliflozin." As such, there is no rationale to assume that the treatments do not incur equal resource use.

Table 13. Medicine acquisition costs of dapagliflozin and empagliflozin

Medicine	Formulation	Dose	Cost per	
			Unit[a]	Pack
Dapagliflozin	Oral tablets	5 mg or 10 mg tablet	£1.31 per unit	£36.59 per pack (Pack of 28)
Empagliflozin	Oral tablets	10 mg or 25 mg tablet	£1.31 per unit	£36.59 per pack (Pack of 28)

[a] Per tablet, which equates to cost per day.
Abbreviations: mg: milligram.

Furthermore, NHS England developed a joint resource impact template and resource impact report for dapagliflozin and empagliflozin for treating CKD (TA775 and TA942), therefore inherently confirming the same resource use is expected for dapagliflozin and empagliflozin.[31] The resource use and associated costs for both treatments are presented in

Table 14. Although the published template did not inflate the costs sourced from various publications to the current cost year, to reflect best practice, the costs shown in Table 14 are inflated to 2022/23 cost year.

Table 14. Dapagliflozin and empagliflozin resource use

Healthcare resource use category	Unit cost in resource impact template	Cost year in resource impact template	2022/2023 cost	Source
eGFR decline ≥ 50%	£3,030	2022/23	£3,030	TA942 and TA775 Resource Impact Template, sourced from company BI submission. Based on difference in annual healthcare costs in the Study of Heart and Renal Protection randomised trial between patients with CKD stage 4 (£3,694) versus stage 3 (£1,055), which is equivalent to a difference of ~50% in eGFR. Then inflated.[a 31]
Chronic dialysis	£32,360	NR [b]	£36,917	TA942 and TA775 Resource Impact Template, sourced from NICE NG107, this aligns with Organ Donation Registry Fact Sheet.[31, 32] Original 2016/17 cost (£30,591) from NG107 was inflated to 2022/23.
Kidney transplant first year cost (includes part year cost of immunosupressants)	£20,645	2021/22	£22,918	TA942 and TA775 Resource Impact Template, sourced from weighted average based on 2019/2020 National schedule of NHS costs, latest 2022/23 costs were extracted.[c 31]
Kidney transplant recurring cost (immunosupressants)	£5,000	2009	£7,250	NHS Blood and Transplant Organ Donation Registry Fact Sheet, inflated to 2022/23.[32]
Acute kidney injury	£3,069	2021/22 [d]	£2,697	TA942 and TA775 Resource Impact Template, sourced from weighted average based on 2019/20 National schedule of NHS costs, latest costs were extracted from 2022/23 data.[d 31]
Hospitalisation for heart failure	£3,163	2021/22	£2,816	TA942 and TA775 Resource Impact Template, sourced from weighted average based on 2019/20 National schedule of NHS costs, latest costs were extracted from 2022/23 data.[e 31]

[a] The original source cost year was not reported in the budget impact template, so it was assumed that the cost was inflated to 2022/23. [b] The cost provided in the budget impact template appears to be inflated as 2016/17 cost from NG107 was £30,591. However, the cost year was not reported in the budget impact template. Therefore, the 2022/23 costs were inflated from £30,591. [c] The budget impact template referenced 2019/20 National Schedule of NHS Costs, and used 2009 kidney transplant recurring costs in the calculation. The 2022/23 cost was taken from the 2022/23 National Schedule of NHS Costs using the same codes. Kidney transplant recurring costs was inflated before being used in the calculation. [d] The budget impact template referenced 2019/20 National Schedule of NHS Costs. However, the calculation table of the weighted average noted 2023/24 prices in the title row. In the current table, costs of the same codes were extracted from the 2022/23 National Schedule of NHS Costs and a weighted average was calculated. [e] The budget impact template referenced 2019/20 National Schedule of NHS Costs. It was assumed that the budget impact template inflated the 2021/22 weighted average

costs. In the current table, costs of the same codes were extracted from the 2022/23 National Schedule of NHS Costs and a weighted average was calculated.
Abbreviations: eGFR: estimated glomerular filtration rate; CKD: chronic kidney disease; BI: Boehringer Ingelheim; NHS: National Health Service; NR: not reported.

B2. Priority question: The company decision problem (CS, Document B, Table 1) defines five CKD population subgroups. Please justify that there are no expected differences in specific components of the cost comparison analysis (e.g., resource use, AEs, treatment dosing and discontinuation) across the five CKD subgroups, with supportive evidence.

Dapagliflozin and empagliflozin are administered as one tablet once daily and available in 28-tablet pack priced at £36.59 across all subgroups.[12, 19] Post-hoc analyses of DAPA-CKD demonstrate a consistent treatment benefit of dapagliflozin irrespective of baseline uACR, which is further supported by RWE from OPTIMISE-CKD and Nakhleh et al., 2024.[14, 22, 28, 29] Empagliflozin has the same mechanism of action and equivalent safety profile as dapagliflozin, demonstrated in Section B.3.9 in the CS and the CS Addendum. Therefore, there is no scientific or clinical rationale to believe that dapagliflozin incurs different resource use, AEs and discontinuation rates in any of the five CKD subgroups. Additionally, a cost comparison was made for the wider CKD population in TA942 based on the assumption of equivalency in all cost categories across subgroups for empagliflozin and dapagliflozin. This was accepted and considered appropriate for decision making as outlined in answer to B1.

B3. Priority question: Please provide a more comprehensive justification for the assumed rates of adverse events and their equivalence between the drugs (CS addendum, Table 7). Please provide the specific sources supporting these assumptions.

The adverse event rates in Table 7 in the CS Addendum were sourced from clinical trial data for dapagliflozin. Specifically, the rates were informed by the most common serious AEs reported in DAPA-CKD and the rate of genital infections and urinary tract infections (UTIs) reported in DECLARE-TIMI 58.[33, 34]

The rates of AEs are assumed equal for dapagliflozin and empagliflozin based on the equivalent safety profiles of the treatments. Detailed discussed of the equivalent safety profiles of the SGLT2 inhibitors was presented in response to Question 6 in the CS Addendum. In summary, evidence of the consistent safety profiles is provided by the safety outcomes observed across relevant RCTs and summarised in the SmPCs for empagliflozin and dapagliflozin. The safety profile of empagliflozin presented in the SmPC, based on placebo-controlled trials and post-marketing experience across indications, is presented in Table 15 and demonstrates consistency with the dapagliflozin safety profile.

This is further supported by an independent published meta-analysis investigating the safety of SGLT2 inhibitors which demonstrated broadly consistent safety profiles across SGLT2 inhibitors (including dapagliflozin and empagliflozin) in terms of ketoacidosis and lower leg amputation.[12, 13, 19, 35] Furthermore, the consistent safety profile of dapagliflozin and empagliflozin was supported by stakeholder comments in the draft scope for this review, with

Kidney Research UK stating that dapagliflozin is expected to be equally "safe as empagliflozin in the suggested population".[3]

The same AE rates were assumed for dapagliflozin and empagliflozin in the cost comparison analysis in TA942. As outlined in answer to B1, this was accepted and considered appropriate for decision making by the NICE Committee, with the Committee concluding that the empagliflozin has a similar effectiveness and safety to dapagliflozin.[2] There is no rationale as to why the safety profile of dapagliflozin and empagliflozin would differ in the subgroups in this review.

Table 15: Adverse events reported in SmPC for empagliflozin, based on placebo-controlled clinical studies and post-marketing experience across all licensed indications

System organ class	Very common	Common*	Uncommon**	Rare	Very rare
Infections and infestations		Vaginal moniliasis, vulvovaginitis, balanitis and other genital infections; Urinary tract infections (including pyelonephritis and urosepsis)		Necrotising fasciitis of the perineum (Fournier's gangrene)	
Metabolism and nutrition disorders	Hypoglycaemia (when used with SU or insulin)	Thirst	Ketoacidosis		
Gastrointestinal disorders		Constipation			
Skin and subcutaneous disorders		Pruritis (generalised); Rash	Urticaria; Angioedema		
Vascular disorders	Volume depletion				
Renal and urinary disorders		Increased urination	Dysuria		Tubulointerstitial nephritis
Investigations		Serum lipids increased	Blood creatinine increased/Glomerular filtration rate decreased; Haematocrit increased		

Further information on selected AEs is presented in the SmPC for dapagliflozin. * Reported in ≥2% of patients and ≥1% more and at least 3 more patients treated with dapagliflozin 10 mg compared with placebo. ** reported by the investigator as possible related, probably related or related to study treatment and reported in ≥0.2% of patients and ≥0.1% more and at least 3 more patients treated with dapagliflozin 10 mg compared with placebo.
Abbreviations: SmPC: Summary of Product Characteristics; T2D: type 2 diabetes.
Source: SmPC (empagliflozin)[19]

B4. Priority question: It is implied in the CS addendum (pp 37-38) that there is potential for empagliflozin to result in a higher cost than dapagliflozin to the NHS due to costs associated with titration of empagliflozin. Clinical advisors to the EAG consider that changes in dosing may also impact the efficacy of the drug (i.e., higher dose of empagliflozin may lead to its improved efficacy

due to better glycaemic control). Please also provide discussion of the changes in doses of empagliflozin and the impact on its clinical efficacy in the context of this cost-comparison analysis with Dapagliflozin.

As stated in the empagliflozin SmPC, the dosage can be increased from 10 mg to 25 mg (once daily) in patients tolerating empagliflozin 10 mg once daily who have an eGFR ≥60 ml/min/1.73m^2 and need tighter glycaemic control.[19] This indicates that a higher dose is only administered to patients when the expected outcomes aren't achieved at the 10 mg dose. Therefore, these patients are up-titrated to 25 mg with the purpose of trying to achieve the expected outcomes as opposed to improved efficacy. As such, there is no efficacy improvement expected as a result of empagliflozin's dose adjustment.

As discussed in Document B, Section B.4.6 and the response to Question 10 in the CS Addendum, titration of empagliflozin may lead to higher resource use and higher costs, as a result of potential primary care visits required for the dose adjustments for tolerating patients. In comparison, dapagliflozin provides consistent and simple posology across the whole CKD population irrespective of T2D status (demonstrated in the response to Question 2 in the addendum). With no additional healthcare resource use required, dapagliflozin has the potential to be less costly than empagliflozin. However, the cost impact of this is expected to be relatively small.

Due to the lack of accurate data and the expected small impact of this cost, the cost difference expected as a result of titration of empagliflozin was not included in the cost comparison model or included in the assessment of TA942. As such, the results of the cost comparison are likely to be conservative estimates for dapagliflozin.

Section C: Textual clarification and additional points

C1. Table 15 of CS, Document B describes 684 patients from the OPTIMISE-CKD study (Svensson et al 2024) without T2D, eGFR 15–60 mL/min/1.73 m2 and uACR ≥22.6 mg/mmol, whereas Table 2 of the CS addendum describes 648 patients with the same criteria in Subgroup 2. Please clarify which number of patients is correct and if applicable, please explain the discrepancy.

A typographical error was made in Table 2 of the CS Addendum, which should have stated 684 patients, instead of 648 patients, from Svensson *et al.* (2024) providing evidence for Subgroup 2, as per the Svensson *et al*. (2024) publication.[28]

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NICE National Institute for Health and Care Excellence

Cost Comparison Appraisal

Dapagliflozin for treating chronic kidney disease (review of TA775) [ID6411]

Patient Organisation Submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
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- Your response should not be longer than 10 pages.

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About you

1.Your name	[redacted]
2. Name of organisation	Kidney Research UK
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	Kidney Research UK is the leading kidney research charity in the UK. We fund and promote research into kidney disease and related topics; bring together patients and researchers in networks and clinical study groups; campaign for the adoption of best practice by the NHS and improved pathways and health outcomes and for kidney patients. Our latest annual report 2022/23 shows the majority of our income is from donations, gifts, and legacies. The remainder is from trusts, partnerships, investments, trading, and government funding. We are not a membership organisation but have an extensive supporter base and a significant number of active volunteers, many of whom are kidney patients.
4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.] **If so, please state the name of the company, amount, and purpose of funding.**	AstraZeneca £54,000 in 2023/24 for membership of Industry Partnership Programme and sponsorship of policy reports Boehringer Ingelheim - £45,780 in 2023/24 for membership of Industry Partnership Programme and sponsorship of policy reports

4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	We regularly engage with kidney patients through one-to-one interviews, focus groups, meetings and online groups to gather evidence on the realities of living with kidney disease, of undergoing dialysis, living with a kidney transplant and the hope new treatments bring.

Living with the condition

6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Living with kidney disease makes every day a challenge. It affects, and sometimes governs, every aspect of a person's life. There's no let-up. This puts a huge strain on people's emotional wellbeing. A survey carried out by Kidney Research UK in 2022 with 1,000 responses found that 67% of people with kidney disease had experienced symptoms of depression, 27% had considered self-harm or suicide and 36% couldn't fully take care of their physical health because of their mental health problems. Patients described the shock of a diagnosis, the strain of being on dialysis, the uncertainty of living with a transplant, and the impact of the disease on their ability to go to school, work, mental health and family relationships. Many described how their ability to work has been negatively affected by kidney disease, which can have a devastating impact particularly on young people: One young woman IgAN patient said "I've probably been on like sick leave now for six months, which is quite a long time. I work in a primary school and they've been really supportive, but obviously I can't be near them at the minute with lots of little children and lots of infections going around". Another patient said "..because of the issues with my kidneys. I had depression and as a result of having that I was having time off work and eventually they dismissed me due to health… I retired at the age of 53". The physical and emotional toll of kidney disease on family members is also significant, with loved ones supporting with medical appointments, medication, repeated travel for dialysis or support with home dialysis: "I chose PD [peritoneal dialysis] because I kind of hate needles really. Even though I've had loads and loads of blood tests, I'd still hate needles…And my wife, she had a panic attack the very first day we did it [PD] at home. She wanted to run away…And I sort of said, look, I've got it. You know, we've gone through the training. I've got all the notes actually stuck to the wall so I can read it without touching anything." "..we worked it through together and I think having an understanding partner is also key to keeping you on the rails really".

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	People who progress to kidney failure often find the burden of treatment is very significant. Many people on dialysis find living with four-hour dialysis sessions, three times a week every week, as well as the stringent fluid and dietary restrictions, very challenging. Receiving a kidney transplant, although not a cure, can make a huge difference to the health and quality of life of a kidney patient. People fortunate enough to receive a kidney transplant will still need to follow certain restrictions on their diet and lifestyle, as well as being on medication for the rest of their lives. In the case of deceased donations, the transplant comes with the emotional burden of knowing the donor has lost their life. Decisions regarding accepting a living donation can also be challenging. The introduction of NICE-approved SGLT2 inhibitors for people with CKD is considered a huge step forward, but uptake of these medications is currently low. At present, without these interventions, it can feel like there is "nothing between general diet and lifestyle advice, straight to dialysis" when patients are at the earlier stages of CKD. This "cliff edge" is viewed as being unlike other diseases. The uncertainty of knowing when this progression may occur also has a significant mental health burden. A person with kidney disease told us: "my progression has been steady, but I did have an episode several years ago where my function dropped by 5%. It is very worrying not knowing when that next drop will be".
8. Is there an unmet need for patients with this condition?	There is no cure for chronic kidney disease and limited options for medications that slow or prevent decline in kidney function. Progress in developing new pharmaceutical treatments has been extremely slow. In the UK, there are approximately 3.25 million people living with CKD stages 3-5. A further 3.9 million people are estimated to have CKD stages 1-2. Together reaching a total of 7.2 million – more than 10% of the entire population. The number of people affected by chronic kidney disease is growing due to an ageing population and the increasing prevalence of the risk factors associated with CKD, mainly diabetes, hypertension and obesity. Recently the NHS CVDPREVENT primary care audit confirmed CKD as a high-risk condition for cardiovascular disease. Increasing evidence from studies indicate that the benefits shown by SGLT2 inhibitors do not appear to be modified by the level of eGFR, by primary kidney diagnosis, or whether the patient also has diabetes.

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	Patients welcome the technology as giving another SGLT2i option for a broader group of kidney patients. Kidney patients welcome the chance to delay disease progression to kidney failure: "My general quality of life is still good at the moment, if there is something that can help me stay at this sort of level… that would be absolutely delightful and end up costing the NHS a whole lot less in the process." The existence of treatment options for people with earlier stage CKD should also encourage the early identification of kidney damage, which clinical audits show is hampered by a failure to carry out NICE recommended annual checks. As well as pharmaceutical options, early identification should also enable patients to implement diet and lifestyle changes to reduce their risk of further kidney damage. A recent study in Scotland showed that people with kidney failure are eight times more likely to have a heart attack and four times more likely to have a stroke than those without the condition [Gallacher et al, Kidney replacement therapy: trends in incidence, treatment, and outcomes of myocardial infarction and stroke in a nationwide Scottish study, March 2024]. Therefore, the evidence that the technology lowers the risk of death from cardiovascular causes is an important advantage

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	The main disadvantages of any treatment are the potential side effects, although the overall response from people with kidney disease was that the potential side effects would not outweigh the potential benefits. It is important that people are made aware of potential side effects and encouraged to report them, to support ongoing monitoring of these drugs over the long term so that patients can make informed decisions about their use. A kidney patient told us that "if the treatment is safe, that is reassuring, as is that it has been used for some time and is an established drug".

Patient population

11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	Kidney disease disproportionally impacts people from deprived communities and ethnic minority groups. They are more likely to develop kidney disease, progress faster to kidney failure and require dialysis or a transplant. People from ethnic minority groups wait on average longer for a kidney transplant due to a shortage of kidneys with a suitable tissue and blood match. People from deprived communities are also more likely to be diagnosed at a later stage of disease progression and die earlier than other socio-economic groups. “Some ethnic groups, particularly Bangladeshi, appear to be more sensitive to the combined effects of proteinuria and hypertension than other ethnic groups. Also, clinicians need to be aware that younger people with diabetes (<55 years) with CKD are at twice the risk of rapid progression of CKD compared with those >65 years and thus need closer monitoring, management of risk factors and early specialist review to delay progression.” (Mathur R, Dreyer G, Yaqoob MM, et al Ethnic differences in the progression of chronic kidney disease and risk of death in a UK diabetic population: an observational cohort study BMJOpen 2018;8:e020145. doi: 10.1136/bmjopen-2017-020145).

Other issues

13. Are there any other issues that you would like the committee to consider?	Key findings from Kidney Research UK's report *Kidney disease – a public health emergency* showed that the current economic burden of kidney disease in the UK is over £7 billion per year, with £6.4 billion being direct costs to the NHS. By 2033, if projected figures for the number of dialysis patients are realised, those figures could rise to as much as £13.9 billion and £10.9 billion respectively. Greater use of new medications such as SGLT-2 inhibitors is one of the interventions modelled that showed economic savings, as well as saving 10,000 lives in that time. It will be vitally important for NICE and the NHS to consider how to identify patients who might be eligible for the treatment. Currently, they are not routinely identified in primary care and targeted screening should be considered.

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission.	• Living with kidney disease makes every day a challenge. It affects, and sometimes governs, every aspect of a patient's life such as school, work, mental health, family relationships, income, and social life. • Patients welcome the technology as giving another SGLT2i option for a broader group of kidney patients, particularly those in the earlier stages of CKD. They welcome the chance to delay disease progression and prevent cardiovascular events with the positive health outcomes this would bring. • The NHS should consider targeted screening of CKD to identify those who are in the earlier stages of the disease and who could benefit from this technology. • People from deprived communities and ethnic minority groups could disproportionately benefit from the technology as they are more likely to be diagnosed with CKD, progress faster to kidney failure and die younger.

Thank you for your time.

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Cost Comparison Appraisal

Dapagliflozin for treating chronic kidney disease (review of TA775) [ID6411]

Professional organisation submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

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- Your response should not be longer than 13 pages.

NICE National Institute for Health and Care Excellence

About you

1. Your name	[redacted]
2. Name of organisation	UK Renal Pharmacy Group
3. Job title or position	[redacted]
4. Are you (please select Yes or No):	An employee or representative of a healthcare professional organisation that represents clinicians? Yes A specialist in the treatment of people with this condition? Yes A specialist in the clinical evidence base for this condition or technology? Yes Other (please specify):
5a. Brief description of the organisation (including who funds it).	The Renal Pharmacy Group is part of the The UK Kidney Association. The UKKA was created through merger of the Renal Association, British Renal Society and its affiliates, to support the multi-professional team with delivery of kidney care, education and research – enabling people to live well with kidney disease. UKKA is funded by its members, grants, events, project work and capitation.
5b. Has the organisation received any funding from the manufacturers of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal stakeholder list.] **If so, please state the name of manufacturer, amount, and purpose of funding.**	AstraZeneca - £357,000 for UKKA (of which £6,500 was for RPG) BI - £60,400 for UKKA (none to RPG)
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No

The aim of treatment for this condition

6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	To avoid/slow the progression of CKD.
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	Reduction in albuminuria Reduction in GFR rate of decline
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes

What is the expected place of the technology in current practice?

9. How is the condition currently treated in the NHS?	Lifestyle modification Blood pressure Control, Glycaemic control 1. RAAS inhibition 2. SGLT2i 3. Non-steroidal MRA

9a. Are any clinical guidelines used in the treatment of the condition, and if so, which?	NICE CG203 – Chronic Kidney Disease (assessment and management) UKKA – SGLT2 inhibition in adults with CKD KDIGO – Clinical Practice Guideline for evaluation and management of CKD
9b. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	Well defined.
9c. What impact would the technology have on the current pathway of care?	Expanding the criteria for use to match that of empagliflozin will remove the unnecessary complexity that is currently associated with prescribing SGLT2-i. Guidance would be simple, and use of empagliflozin or dapagliflozin can then be chosen based on the most cost-effective option / patient choice
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Yes
10a. How does healthcare resource use differ between the technology and current care?	Probably unchanged – however may have some increased healthcare resource available as there would be choice between which preparation to use (i.e. the most cost effective, so companies may drop prices to make their product more desirable?) – currently there is no choice available in many scenarios based on individual patient parameters dictating one particular treatment over the other.
10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Primary and secondary care.
10c. What investment is needed to introduce the	None.

technology? (For example, for facilities, equipment, or training.)	
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Not clinically meaningful (as we are able to use empagliflozin, for which the evidence base is there from EMPA-Kidney).
11a. Do you expect the technology to increase length of life more than current care?	No
11b. Do you expect the technology to increase health-related quality of life more than current care?	No
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	It depends on what the additional evidence the company is going to provide (that is mentioned in the scope document). I am not aware of any evidence available for the use of dapa below eGFR 25ml/min or in patients with low ACR. .

The use of the technology

13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant	Significantly easier. In my experience, dapagliflozin is rarely used. Empagliflozin guidance is much broader, so empagliflozin is always chosen. It is much simpler and efficient to prescribe empagliflozin for everyone as it can be used in every scenario

treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	that dapagliflozin can and more (so no reason to work out whether this patient also meets dapagliflozin criteria and then pick that one instead)
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	N/A
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	No. Unless dapagliflozin becomes cheaper than empagliflozin.
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	No
16a. Is the technology a 'step-change' in the management of the condition?	No

16b. Does the use of the technology address any particular unmet need of the patient population?	No
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	No change.

Sources of evidence

18. Do the clinical trials on the technology reflect current UK clinical practice?	Current TA is based on DAPA-CKD. Evidence from Declare-TIMI and DAPA-HF not included, which provide some additional data in higher GFR.
18a. If not, how could the results be extrapolated to the UK setting?	Likely to be a class effect with all SGLT2-i. EMPA-kidney provides that broader CKD data.
18b. What, in your view, are the most important outcomes, and were they measured in the trials?	GFR decline, reduction in proteinuria,
18c. If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	N/A

18d. Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	None
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
20. Are you aware of any new evidence for the comparator treatments since the publication of NICE technology appraisal guidance TA942?	No
21. How do data on real-world experience compare with the trial data?	Drugs are well tolerated, good effect on albuminuria reduction.

Equality

22a. Are there any potential equality issues that should be taken into account when considering this treatment?	None
22b. Consider whether these issues are different from issues with current care and why.	None.

Key messages

23. In up to 5 bullet points, please summarise the key messages of your submission.	• In support of matching the dapagliflozin NICE guidance to that of empagliflozin (pending additional evidence provided by the company as mentioned in scoping document) • Unlikely to have financial benefits as treatment cost is currently the same between the two, and will therefore remain the same (unless any upcoming price changes to either) • SGLT2i guidance is currently very complex having to differentiate GFR/albuminuria/diabetes status for each patient to determine whether dapa or empa can be used. – this needs to be simplified.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

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External Assessment Group Report

Cost comparison evaluation process

Dapagliflozin for the treatment of adults with chronic kidney disease (Review of TA775)

Produced by	Centre for Reviews and Dissemination (CRD) and Centre for Health Economics (CHE) Technology Assessment Group, University of York, Heslington, York, YO10 5DD
Authors	Mark Perry, Research Fellow, CRD Alexis Llewellyn, Research Fellow, CRD Joseph Lord, Research Fellow, CRD Melissa Harden, Senior Information Specialist, CRD Natalia Kunst, Senior Research Fellow, CHE Sarah Nevitt, Senior Research Fellow, CRD
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Date completed	05/09/2024 (amended 19/09/2024)

Source of funding

This report was commissioned by the NIHR Evidence Synthesis Programme as project number NIHR168093.

Declared competing interests of the authors

None

Acknowledgements

Dr James Fotheringham (Sheffield Teaching Hospitals NHS Trust) and Dr Hugh Gallagher (Epsom and St. Helier NHS Trust) provided expert clinical advice and commented on a draft of clinical effectiveness sections of the report.

Professor Claire Rothery (Centre for Health Economics, University of York) commented on a draft of cost comparison sections the report

Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.

This report should be referenced as follows: Perry M, Llewellyn A, Lord J, Harden M, Kunst N, Nevitt S. Dapagliflozin for the treatment of adults with chronic kidney disease (Review of TA775): Cost comparison evaluation process. CRD and CHE Technology Assessment Group, 2024.

Contributions of authors

Mark Perry wrote the critique of the clinical effectiveness evidence (Section 4) and contributed to the drafts for the background (Section 2), the critique of the decision problem (Section 3) and the critiques of the systematic review (Section 4).

Alexis Llewellyn wrote the Executive Summary (Section 1), Equalities and Innovation (Section 7), Conclusions and Areas of uncertainty (Section 8), and contributed to the drafts for the background (Section 2), critique of the decision problem (Section 3), and the critiques of the systematic review and clinical effectiveness evidence (Section 4).

Joseph Lord contributed to the drafts for the background (Section 2), the critique of the decision problem (Section 3), the critiques of the systematic review and clinical effectiveness evidence (Section 4).

Melissa Harden reviewed the systematic review searches and wrote sections of the report pertaining to the searches.

Natalia Kunst led the economics critique and wrote the critique of the cost comparison (Section 5) and cost comparison results (Section 6).

Sarah Nevitt oversaw the review of the clinical effectiveness evidence, and wrote, and commented on, drafts of the report as a whole.

Note on the text

All commercial-in-confidence (CIC) data have been highlighted in blue and underlined.

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List of abbreviations

A1	uACR <3 mg/mmol
A2	uACR 3-29 mg/mmol
A3	uACR ≥30 mg/mmol
ACE	Angiotensin-Converting Enzyme
ACEi	Angiotensin-Converting Enzyme inhibitor
ARB	Angiotensin-Receptor Blocker
ASCVD	Atherosclerotic Cardiovascular Disease
BMI	Body Mass Index
BP	Blood Pressure
CASP	Critical Appraisal Skills Programme
CI	Confidence Interval or Credible Interval
CKD	Chronic Kidney Disease
COPD	Chronic Obstructive Pulmonary Disease
CPRD	Clinical Practice Research Datalink
CS	Company Submission
CV	Cardiovascular
DBP	Diastolic Blood Pressure
EAG	External Assessment Group
eGFR	Estimated Glomerular Filtration Rate
EQ-5D	Euroqol-5D
ESKD	End Stage Kidney Disease
ESRD	End Stage Renal Disease
G1	eGFR >90 ml/min/1.73m^2
G2	eGFR 60-89 ml/min/1.73m^2
G3a	eGFR 45-59 ml/min/1.73m^2
G3b	eGFR 30-44 ml/min/1.73m^2
G4	eGFR 15-29 ml/min/1.73m^2
G5	eGFR <15 ml/min/1.73m^2
HbA1c	Glycated Haemoglobin
HF	Heart Failure
HR	Hazard Ratio
HR QoL	Health-Related Quality of Life
HTN	Hypertension
ICER	Incremental Cost Effectiveness Ratio
IQR	Interquartile Range
ITC	Indirect Treatment Comparison
KCCQ	Kansas City Cardiomyopathy Questionnaire
KDIGO	Kidney Disease Improving Global Outcomes
MI	Myocardial Infarction
MRA	Mineralocorticoid receptor antagonists
N/A	Not Available or Not Applicable
NHS	National Health Service
NICE	National Institute for Clinical and Health Excellence
NMA	Network Meta Analysis
NYHA	New York Heart Association
PCSK-9	Proprotein Convertase Subtilisin/Kexin Type 9
RASi	Renin-Angiotensin System Inhibitors
RCT	Randomised Controlled Trial
SBP	Systolic blood pressure
SD	Standard Deviation
SGLT2	Sodium-Glucose Co-Transporter-2
SLR	Systematic Literature Review
SOC	Standard Of Care
T2D	Type 2 Diabetes
uACR	Urinary Albumin Creatinine Ratio
UKKA	United Kingdom Kidney Association

EXTERNAL ASSESSMENT REPORT: COST COMPARISON EVALUATION PROCESS

1 EXECUTIVE SUMMARY

1.1 Summary of the decision problem

Issue 1 The company decision problem only includes a small subset of the NICE scope population

Report section	3, 3.1
Description of issue and why the EAG has identified it as important	The population in the company decision problem only includes 5 CKD subpopulations for which empagliflozin is recommended and dapagliflozin is not: • Adults with CKD, without T2D, and with: o eGFR ≥20–45 mL/min/1.73m^2 and uACR <22.6 mg/mmol (200 mg/g); or o eGFR 20–25 mL/min/1.73m^2 and a uACR ≥22.6 mg/mmol (≥200 mg/g); or o eGFR >75–90 mL/min/1.73m^2 and a uACR ≥22.6 mg/mmol (≥200 mg/g). • Adults with CKD, with T2D, and with: o eGFR ≥20–25 mL/min/1.73m^2; o or eGFR >75–90 mL/min/1.73m^2. Therefore, it omits the subpopulations from the NICE scope where both dapagliflozin and empagliflozin are recommended, i.e. people with T2D and eGFR range between 25 and 75 mL/min/1.73 m^2 irrespective of uACR and people without T2D, between 25 and 75 mL/min/1.73 m^2 and uACR ≥22.6 mg/mmol. The company chose to omit this population as it was recommended for dapagliflozin in TA775 and because dapagliflozin and empagliflozin have already been evaluated in TA942. The EAG considers that it is unclear whether the conclusions made in TA942 are directly applicable to the subpopulations for which both dapagliflozin and empagliflozin are recommended.
Impact on case for cost comparison	The company submission (CS) does not make a case for a cost comparison across the entire NICE scope population.
What additional evidence or analyses might help to resolve this key issue?	Robust evidence is required to show equivalence in effectiveness and safety between dapagliflozin and empagliflozin to inform a cost comparison across the entire NICE scope population.
Abbreviations: EAG: External Assessment Group; CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; T2D: type 2 diabetes mellitus; uACR: urine albumin-creatinine ratio; TA: Technology Appraisal	

1.2 Summary of the clinical evidence

Issue 2 Lack of direct evidence for dapagliflozin for the CKD subpopulations included in the company decision problem

Report section	4.1, **Error! Reference source not found.**, 4.3, 4.5
Description of issue and why the EAG has identified it as important	The evidence for dapagliflozin provided by the company is limited to inform the outcomes and the populations as defined in the NICE scope. No evidence was presented for the 5 CKD subpopulations in the company decision problem specifically for any of the outcomes in the NICE scope. The CS did not include a systematic review. Whilst the key CKD trials for dapagliflozin and empagliflozin were included in the CS, it is uncertain whether all relevant evidence to inform the decision problem has been accounted for.
Impact on case for cost comparison	The case for a cost comparison for the 5 subpopulations defined in the company decision problem is highly uncertain.
What additional evidence or analyses might help to resolve this key issue?	Robust evidence is required to show equivalence in effectiveness and safety between dapagliflozin and empagliflozin to support a cost comparison for these 5 CKD subpopulations. Individual patient data (IPD) from dapagliflozin studies may be used, where available, to show the effectiveness and safety of dapagliflozin in the 5 CKD subpopulations. See Issues 3 and 4 for further details.
Abbreviations: CKD = chronic kidney disease; CS = company submission; IPD = individual patient data; TA = Technology Appraisal	

Issue 3 Limited applicability of RCT evidence for dapagliflozin to the company decision problem.

Report section	4.2.1, 4.3
Description of issue and why the EAG has identified it as important	DAPA-CKD, the key trial informing TA775, excludes 4 of the 5 CKD subpopulations in the company decision problem; it includes evidence for the subpopulation with eGFR≥20–45 mL/min/1.73m^2 and uACR <22.6 mg/mmol (200 mg/g), without T2D, but does not present data specific to this subpopulation. Supportive RCT evidence (DECLARE-TIMI 58, DAPA-HF) includes broader, non-CKD specific populations, and has limited applicability to the 5 CKD subpopulations defined in the company decision problem.
Impact on case for cost comparison	As per Issue 2, the case for a cost comparison for the 5 CKD subpopulations in the company decision problem is highly uncertain.
What additional evidence or analyses might help to resolve this key issue?	Where available, IPD from dapagliflozin RCTs could be used to inform analyses for the following subpopulations: • eGFR ≥20–45 mL/min/1.73m^2 and uACR <22.6 mg/mmol (<200 mg/g), without T2D, from DAPA-CKD; • eGFR >75–90 mL/min/1.73m^2 and a uACR ≥22.6 mg/mmol (≥200 mg/g), without T2D, from DAPA-HF; • eGFR >75–90 mL/min/1.73m^2, with T2D, from DECLARE-TIMI 58 and DAPA-HF. However, these analyses would be limited as they would be post-hoc comparisons against placebo only and conducted in subgroups not stratified at randomisation. Furthermore, analyses of DAPA-HF would not account for differences in uACR levels (i.e. <22.6 [<200 mg/g] or ≥22.6 mg/mmol [≥200 mg/g]), as it was not measured in this trial. Therefore, this additional evidence would likely be insufficient to resolve this issue.
Abbreviations: CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; IPD = individual patient data; RCT = randomised controlled trial; T2D = type 2 diabetes mellitus; uACR = urine albumin-creatinine ratio;	

Issue 4 Limited internal validity and applicability of non-randomised evidence

Report section	4.2.1.1, 4.3
Description of issue and why the EAG has identified it as important	Two retrospective observational studies which were conducted outside of the UK were presented as supportive evidence for dapagliflozin. Both have significant design limitations and limited applicability to UK practice. No non-RCT evidence which directly informs the 5 CKD subpopulations defined in the company decision problem are presented. Results from OPTIMISE-CKD presented were from a retrospective analysis of USA and Japan claims data. Adherence to dapagliflozin and RASi therapy was limited. Adjusted data comparing dapagliflozin vs. standard of care only reported eGFR slopes, which are limited surrogate outcomes, with no breakdown by baseline eGFR. Nakhleh (2024) is a retrospective analysis of Israel maintenance data. Although the study includes individuals receiving dapagliflozin and empagliflozin, results are not presented separately by treatment received and no evidence comparing dapagliflozin and empagliflozin was presented. The study excludes patients with T2D, eGFR 20-25 mL/min/1.73m^2, and eGFR 75-90 mL/min/1.73m^2.
Impact on case for cost comparison	The case for a cost comparison requires robust evidence for the equivalence in effectiveness and safety of dapagliflozin and empagliflozin. The supportive non-RCT evidence is insufficient to inform a cost comparison.
What additional evidence or analyses might help to resolve this key issue?	Where available, additional analyses using IPD may inform eGFR slope analyses for adults with CKD, without T2D, and with eGFR ≥20–45 mL/min/1.73m^2 and uACR <22.6 mg/mmol (200 mg/g), including adjusted comparisons between dapagliflozin and empagliflozin (Nakhleh 2024), and matched comparisons between dapagliflozin initiators and non-initiators (OPTIMISE-CKD). However, these analyses would be limited post-hoc evaluations of surrogate outcomes in non-randomised, non-UK populations. As such, this additional evidence would likely be insufficient to resolve this issue.

Abbreviations: CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; non-RCT = non-randomised controlled trial; RASi = renin angiotensin system inhibitors; T2D = type 2 diabetes mellitus; uACR = urine albumin-creatinine ratio;

Issue 5 Lack of robust evidence to show the equivalence in effectiveness and safety between dapagliflozin and empagliflozin

Report section	4.3, 4.4, 2.3.2.2
Description of issue and why the EAG has identified it as important	Only a naïve comparison between DAPA-CKD and EMPA-KIDNEY was presented, which has inherent limitations. The EAG agrees with the company that a formal, statistical, ITC between dapagliflozin and empagliflozin does not appear feasible, due to differences in trial designs, populations and lack of available data for EMPA-KIDNEY. EMPA-KIDNEY was the only comparator evidence presented, and none of the broader evidence for empagliflozin (e.g. for mixed CKD/non-CKD populations presented in TA942) was included in the CS. There is insufficient evidence, including from the broader CKD and non-CKD evidence, to conclude that dapagliflozin and empagliflozin have equivalent effectiveness and safety. In the absence of direct evidence for the 5 CKD subpopulations in the company decision problem, there is insufficient evidence to show whether any interaction (including by T2D status, eGFR and/or uACR) is present, and whether it may affect the relative effectiveness and safety between these two treatments equally by T2D status and across different eGFR and uACR levels. Whilst there is no evidence of a significant difference in efficacy and safety between dapagliflozin and empagliflozin based on existing meta-analytic evidence, the EAG believes that the company has not made a sufficient case to show a SGLT2 inhibitor class effect in CKD.
Impact on case for cost comparison	There is a lack of robust evidence for the equivalence in effectiveness and safety between dapagliflozin and empagliflozin. This is required to support the case for a cost comparison.
What additional evidence or analyses might help to resolve this key issue?	Ideally, a well-conducted RCT comparing dapagliflozin and empagliflozin in the population under the NICE scope would help to resolve this issue. However, the EAG recognise that this scenario is unlikely; the company stated that no ongoing studies of dapagliflozin, including any studies compared with empagliflozin, are being conducted. In the absence of head-to-head trial data, an adjusted ITC of the relative effectiveness of dapagliflozin and empagliflozin including data for the 5 CKD subpopulations in the company decision problem might help to resolve this issue, although access to matching data for empagliflozin may be limited. Evidence included in this comparison should be informed by a systematic review of all relevant dapagliflozin and empagliflozin studies. An ITC comparing the relative safety data from DAPA-CKD and EMPA-KIDNEY should be presented where feasible, accounting for any limitations in overlap between the trial populations, and limited applicability of DAPA-CKD population to the company decision problem.

Abbreviations: CKD = chronic kidney disease; CS = company submission; eGFR = estimated glomerular filtration rate; ITC = indirect treatment comparison; RCT = randomised controlled trial; SGLT2 = Sodium-glucose cotransporter-2; T2D = type 2 diabetes mellitus; uACR = urine albumin-creatinine ratio;

1.3 Summary of the cost comparison evidence

The costs included in the company's cost comparison are drug acquisition, administration costs, and adverse events costs. The safety profile between dapagliflozin and empagliflozin was assumed equivalent. The probabilities of different AEs occurring was based on the DAPA-CKD study, which provided data only for dapagliflozin. The probabilities of AEs for empagliflozin were also based on data for dapagliflozin (i.e., assumed the same). Resource use associated with disease monitoring was not included but it was assumed to be the same for dapagliflozin and empagliflozin based on the expected similar mechanism of action, efficacy and safety profile. The company stated that exclusion of these costs was due to the lack of published accurate data on the frequency of resource use and the expected clinical equivalence between dapagliflozin and empagliflozin. Costs are estimated for a time horizon of five years. All costs are expressed in 2022/23 prices and undiscounted. The company decision problem defines five CKD subpopulations. However, the resource use and associated costs are not presented for each subpopulation considered and the company assumes that there is no scientific or clinical rationale to believe that dapagliflozin incurs different resource use, AEs and discontinuation rates across the five CKD subpopulations.

1.4 EAG critique of cost comparison approach to this technology assessment

The company's base-case analysis assumed that all resource use and associated costs of dapagliflozin and empagliflozin were equivalent. All estimates used in the cost comparison analysis were derived from the dapagliflozin studies and assumed to be the same for empagliflozin. These assumptions were based on the company's expectations due to similar mechanism of action, efficacy and safety profiles and were not supported by any direct evidence. No empirical data were provided to support these assumptions. The evidence provided to support the same efficacy and safety profile is uncertain. Due to the lack of underlying evidence, the EAG could not perform any evidence-based scenario analyses and establish the EAG preferred base case.

2 BACKGROUND

2.1 Introduction

This Evidence Assessment Group (EAG) report is a critique of the company's submission (CS) from AstraZeneca (herein referred to as 'the company') which informs the National Institute for Health and Care Excellence's (NICE's) review of health technology appraisal guidance TA775 'Dapagliflozin for treating chronic kidney disease', published in March 2022. [1]

Within TA775, the NICE committee recommended dapagliflozin as an add-on treatment for people receiving optimised standard care including a Renin-Angiotensin System inhibitor (RASi), unless contraindicated, with an estimated glomerular filtration rate (eGFR) of 25-75 mL/min/1.73 m^2 and either type 2 diabetes (T2D) or urine albumin-to-creatinine ratio (uACR) $\geq$22.6 mg/mmol. This recommended chronic kidney disease (CKD) population comprised of two subgroups considered by the committee; Subgroup 1 of people with an eGFR of 25 ml/min/1.73 m^2 to 75 ml/min/1.73 m^2, uACR $\geq$22.6 mg/mmol, with or without T2D, which was considered by the NICE committee to broadly reflect the population of the pivotal randomised controlled trial (RCT), DAPA-CKD[2] and Subgroup 2 of people with an eGFR of 25 ml/min/1.73 m^2 to 75 ml/min/1.73 m^2 and uACR<22.6 mg/mmol with T2D, which was informed by evidence from the DECLARE-TIMI 58 RCT[3].

An additional subgroup of people with an eGFR of 25 ml/min/1.73 m^2 to 75 ml/min/1.73 m^2, uACR<22.6 mg/mmol who *do not* have T2D was considered within TA775, but due to lack of direct clinical evidence and substantial uncertainty around the cost-effectiveness of dapagliflozin (added to standard of care [SoC]) compared to SoC, dapagliflozin was not recommended within this subgroup.

Subsequently in December 2023, TA942[4] recommended another SGLT2 inhibitor, empagliflozin as an add-on treatment for people receiving optimised standard care including a RASi, unless contraindicated, for a wider population of people with either an eGFR of 20-<45 mL/min/1.73 m^2 or an eGFR of 45-90 mL/min/1.73 m^2 accompanied by either T2D or uACR $\geq$22.6 mg/mmol, a population which broadly aligns with the population represented in pivotal RCT, EMPA-KIDNEY [5].

The company argues that the current differences within the recommendations for dapagliflozin and empagliflozin for CKD lead to difficulties in prescribing (CS addendum, p25) and within the context of the current review, proposes a cost comparison of the populations for which empagliflozin is recommended but dapagliflozin is not.

The CS for the current review appraisal presents evidence from three RCTs, which were presented within TA775, and two real-world evidence (RWE) studies (conducted subsequently to the submission of evidence for TA775) to support the clinical effectiveness for dapagliflozin within the CKD subpopulations for which empagliflozin was recommended in TA942 which were outside of the

TA775 recommendations. The comparator to dapagliflozin for this cost comparison is empagliflozin, and evidence from one comparator RCT, which was presented in TA942, is presented within the current CS. No other comparators are considered for this review, including SoC which was also a comparator for both dapagliflozin and empagliflozin in TA775 and TA942 respectively.

Two clinical experts advised the EAG during the writing of this report. The EAG received the main CS documentation (Documents A, B and appendices) on 20th June 2024 and a CS addendum document on 1st August 2024. Clarification on some aspects of the CS documents were requested from the company by the EAG via NICE on 7th August 2024 and a company response to the EAG clarification questions was received by the EAG on 22nd August 2024.

2.2 Overview of chronic kidney disease (CKD)

Section B.1.3 of Document B of the CS provides a clear description of the pathology, epidemiology, clinical features, adverse effects, risk factors and burden of CKD.

CKD is defined as an abnormality of kidney structure and function that has been present for at least 3 months. CKD tends to affect older people and can be a result of systemic disease such as T2D or hypertension (HTN). CKD may also result from primary kidney conditions such as glomerulonephritis. Regardless of the cause, the pathology of the disease is fairly homogeneous. Initial nephron loss leads to compensatory hyperfiltration and hypertrophy in surviving nephrons. The resulting increases in shear stress and wall tension in these nephrons may then lead to further nephron loss. This then leads to further compensatory changes, and hence progressive loss of nephrons may ensue due to a positive feedback loop.

The condition is initially asymptomatic, but subsequent symptoms may include swollen extremities, nausea, itchiness, shortness of breath and fatigue. The condition increases the risk of cardiovascular (CV) disease, T2D, HTN and premature mortality. Progression may continue until end stage kidney disease (ESKD), where dialysis or kidney transfusion may be the only useful treatments.

CKD diagnosis is based on measures of kidney function such as eGFR and the uACR. CKD classification is determined by the combination of six eGFR categories (G1>90 ml/min/1.73m^2, G2=60-89 ml/min/1.73m^2, G3a=45-59 ml/min/1.73m^2, G3b=30-44 ml/min/1.73m^2, G4=15-29 ml/min/1.73m^2, and G5<15 ml/min/1.73m^2) and three uACR categories (A1<3 mg/mmol, A2=3-29 mg/mmol and A3$\geq$30 mg/mmol). There are therefore 18 possible combinations, each of which is associated with a risk of adverse consequences: G1A1 and G2A1 are low risk and considered non-CKD if there are no other markers of kidney damage. G1A2, G2A2 and G3aA1 are considered moderate risk, whilst G3bA1, G3aA2, G1A3 and GaA3 are considered high risk. All other combinations (i.e., G3aA3) are considered very high risk (CS, Document B, Table 3).

The Kidney and Liver Disease Heath Survey for England [6] in 2016 showed that 2% of adults self-report having a medical CKD diagnosis. However, the survey also showed that eGFR and urinary albumin measurements suggest 15% of adults at or over 35 years have CKD (stage 1 to 5), indicating a high level of undiagnosed disease.

The burden of CKD on patients is significant. People with CKD stage 5 may have an EQ-5D utility score of 0.73, compared to a score of 0.85 in patients with stage 1-2, whilst people undergoing dialysis may have decrements in quality of life comparable to people with cancer. Carers of dialysis patients are also burdened, experiencing decreases in quality of life comparable to carers of people with cancer. The economic burden on the NHS rises with progressing stages of CKD and is largely dependent on increased hospitalisation rates due to complications such as acute kidney injury, heart failure (HF), myocardial infarction (MI) or venous thromboembolism.

2.3 Description of CKD treatment

2.3.1 Clinical pathway

Initial SoC treatment for CKD comprises individually optimised therapy which may involve cardiovascular management with statins, as well as antiplatelets (for secondary prevention), alongside treatment of accompanying HTN and T2D, and the management of complications. SoC treatment that is used to control disease progression includes RASi such as angiotensin-converting enzyme (ACE) inhibitors or angiotensin-receptor blockers (ARBs) where albuminuria is present. If SoC approaches do not control CKD, then current NICE recommendations are to augment SoC with either empagliflozin or dapagliflozin, which are both sodium-glucose co-transporter-2 (SGLT2) inhibitors.

2.3.2 Case for cost comparison

The NICE guide to the methods of technology appraisal states that "for the acceptance of a cost comparison case, evidence in support of similarity between the intervention and comparator technologies, in terms of overall health outcomes, must be presented." [7]

Evidence to support the cost comparison case presented in the CS includes:

- Naïve comparisons of dapagliflozin treatment effect estimates from three RCTs and two RWE studies and empagliflozin treatment effect estimates from the EMPA-KIDNEY RCT within CKD subpopulations for which empagliflozin is currently recommended but dapagliflozin is not (CS Document B, Section B.3.9.1; CS addendum pp. 27-29, company response to clarification question A14)
- Discussion of the similar mechanisms of action of SGLT2 inhibitors (CS addendum, pp. 25-26).
- United Kingdom Kidney Association (UKKA) guidelines on the use of SGLT2 inhibitors in the treatment of CKD[8] (CS addendum, p25)

- Stakeholder comments on the importance of aligning the recommendations for dapagliflozin and empagliflozin for patients with CKD (CS addendum, p25)
- Supportive evidence from RCTs, meta-analyses and network meta-analyses of SGLT2 inhibitors including evidence from wider populations and non-CKD populations (CS Document B, Section 3.6.4; CS addendum pp.13-22, company response to clarification question A8).

An EAG critique of the naïve comparisons of the clinical effectiveness outcomes and safety from studies of dapagliflozin and empagliflozin is provided in Section 4. A summary and EAG critique of the other evidence sources presented to support the cost comparison case is presented below.

2.3.2.1 Similar mechanisms of action of SGLT2 inhibitors

Referring to product information documents,[9, 10] the company states that, "*Dapagliflozin and empagliflozin are both members of a class of medications called SGLT2 inhibitors. The overall mechanism of SGLT2 inhibitors involves blocking the action of the SGLT2 receptor in the kidneys. Normally, the SGLT2 receptor reabsorbs glucose from the urine back into the bloodstream. By inhibiting this receptor, SGLT2 inhibitors prevent the reabsorption of glucose, leading to increased urinary glucose excretion and lower blood sugar levels*" (CS addendum, pp. 25-26). The company also cites evidence[11-13] showing how both empagliflozin and dapagliflozin show similar high selectivity for SGLT2 receptors over SGLT1 receptors versus phlorizin, which might contribute to shared patterns of efficacy and safety. The company concludes that there is no scientific rationale that would suggest that the clinical efficacy and safety of empagliflozin differs from dapagliflozin.

In addition, the company refers to the results of RCTs and meta-analyses[2 14 15] that are purported to show similar effects from dapagliflozin and empagliflozin and to support a 'class effect' of SGLT2 inhibitors. The company additionally refers to the UKKA guidelines[8] as being supportive of a class effect, based upon their lack of differentiation between dapagliflozin and empagliflozin. In the company response to clarification question A8, the company also infer that the narrow 95% CIs intervals around the eGFR pre-post treatment change in the mixed dapagliflozin/empagliflozin study[16] as support of the evidence of a class effect.

2.3.2.2 Summary of systematic review evidence for SGLT2 inhibitors in CKD

The CS addendum (pp. 26-32) provides a summary of two systematic reviews and meta-analyses of SLGT2 inhibitors in CKD, including an independent systematic review by Herrington (2022) [in guideline by Nuffield Department of Population Health Renal Studies Group (2022)][17] and the network meta-analysis (NMA) presented as part of the company submission for TA942.[4] Appendix 1, Table 17 presents a summary of these reviews.

Baigent (2022) included 13 placebo-controlled RCTs of populations with HF or CKD, or with T2D and high risk atherosclerotic cardiovascular disease (ASCVD) [in guideline by Nuffield Department of Population Health Renal Studies Group (2022)].[17] Trials of SLGT2 inhibitors dapagliflozin,

empagliflozin, canagliflozin, ertugliflozin and sotagliflozin were included. Four trials were conducted in CKD populations specifically (including the EMPA-KIDNEY trial of empagliflozin and the DAPA-CKA trial of dapagliflozin). The review found that SGLT2 inhibitors were effective at reducing the risk of CKD progression, CVD death of hospitalisation for HF and acute kidney injury and did not significantly reduce the risk of non-CVD death. Results were broadly similar irrespective of T2D status, baseline eGFR, and uACR. Visual inspection of forest plots indicated potential variation in the risk of amputation across trials (a significantly increased risk of amputation with canagliflozin in T2D). Although no tests for heterogeneity were reported, a sensitivity analysis showed that the canagliflozin trial in T2D (CANVAS program) had a notable impact on the pooled estimates for amputation risk (see CS addendum, Figure 18).

The NMA conducted within the TA942 CS included 13 placebo-controlled RCTs including CKD-specific and wider CKD populations, with or without other comorbidities such as T2DM or HF. Trials of empagliflozin (n=4), dapagliflozin (n=5), canagliflozin (n=2) and finerenone (n=2) were included. The review found generally similar treatment effects between SGLT2 inhibitors. No statistically significant differences were found between the SGLT2 inhibitors for any of the reported effectiveness outcomes within TA942 CS Document B. There was no evidence of heterogeneity, except for the comparison between dapagliflozin and placebo for the outcome of 3-point major adverse cardiovascular event (3P-MACE+ and 3P-MACE) (I^2=90%, p<0.01). The EAG does not have access to further details of the NMA presented in Appendix N of TA942 CS.

The EAG conducted a pragmatic Medline search for systematic reviews evaluating the effectiveness and safety of SGLT2 inhibitors in CKD to complement the evidence presented by the company. One additional systematic review was identified. Qiu (2021)[18] evaluated the efficacy safety of SGLT2 inhibitors in patients with CKD, T2D and chronic HF. Results are reported in Appendix 1, Table 17. Eight RCTs were included, evaluating dapagliflozin (n=3), empagliflozin (n=2), ertugliflozin (n=1), and canagliflozin (n=2). Although the review searches were not sufficiently recent to include EMPA-KIDNEY and identified fewer studies, results are generally similar to the review by Baigent (2022). Heterogeneity tests found no statistically significant heterogeneity except amputation risk (I^2=58.9%, p=0.017). The EAG is not aware of any other NMAs comparing SGLT2 inhibitors in CKD.

2.3.2.3 Alignment of current dapagliflozin and empagliflozin recommendations

The company provide stakeholder comments on the complexities of prescribing dapagliflozin and empagliflozin for chronic CKD due to the differences in the CKD populations currently recommended by NICE (CS addendum, p25).

EAG comments: The EAG considers the meta-analyses by Baigent (2022) and Qiu (2021) to be well-conducted; whilst no evidence of heterogeneity was found for effectiveness outcomes, the relatively limited number of CKD trials, differences in trial designs and lack of direct and indirect comparisons from these reviews means that the relative effectiveness of SGLT2 inhibitors is uncertain.

The NMA evidence presented in TA942 includes the totality of the DAPA-CKD population (including CKD with T2D and eGFR 25-75 mL/min/1.73 m^2, and no T2D, eGFR 25-75 mL/min/1.73 m^2 and uACR $\geq$22.6). TA942, Warwick Evidence EAG report, Section 3.3.7, concluded that the NMA methodology and results were satisfactory. However, comparisons between trials are limited by differences in definitions of CKD and populations, and all indirect comparisons were anchored in placebo, therefore loop-consistency could not be assessed. The NMA reflects the overlapping populations in the DAPA-CKD and EMPA-KIDNEY trials and does not assess the relative efficacy of the two SGLT2 inhibitors in the specific subpopulations of interest in this review. In addition, the NMA included canagliflozin and finerenone. These therapies are beyond the scope of this appraisal and inclusion of data from trials of these additional SGLT2 inhibitors may have influenced comparisons between dapagliflozin and empagliflozin.

Whilst systematic review shows evidence that SGLT2 inhibitors are effective in CKD populations when added to SoC compared to placebo, it is insufficient to demonstrate equivalence of specific SGLT2 inhibitors. The lack of head-to-head comparison and differences in trial populations and designs mean the evidence is too limited to confirm that these therapies have equivalent effectiveness, or to confirm whether dapagliflozin and empagliflozin have equivalent effectiveness in CKD and across T2D, eGFR and uACR levels. Whilst there is no evidence of a significant variation across SGLT2 inhibitor trials for most evaluated safety outcomes across SGLT2 inhibitors, evidence of heterogeneity in amputation risk means that the strength of evidence for the equivalence in safety across SGLT2 inhibitors is more uncertain. Clinical advice to the EAG noted that the existence of a 'class effect', whereby SGLT2 inhibitors have equivalent efficacy and safety, is not certain.

Clinical advisors to the EAG do not believe that there are significant complexities in prescribing due to the different recommended populations for the two drugs, and noted that in practice, prescribing empagliflozin was simpler due to its broader indication. They noted difficulties in prescribing due to differences in uACR thresholds for eligibility for SLGT2 and ACE inhibitors, and that there are some patients eligible for SGLT2 inhibitors but not ACE inhibitors whilst the data showing the benefits of SGLT2 inhibitors are largely in people prescribed an ACE inhibitor or ARB with an SGLT2 inhibitor.

3 CRITIQUE OF THE DECISION PROBLEM IN THE COMPANY'S SUBMISSION

The company's decision problem partially aligns with the final scope issued by NICE (Table 1).

Table 1 Summary of the decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
Population	People with CKD who have an eGFR of: • 20 mL/min/1.73 m^2 to less than 45 mL/min/1.73 m^2 or • 45 mL/min/1.73 m^2 to 90 mL/min/1.73 m^2 and have either: • T2D or • a uACR of 22.6 mg/mmol or more	Adults with CKD, without T2D, and with: • eGFR ≥20–45 mL/min/1.73m^2 and uACR <22.6 mg/mmol; or • eGFR 20–25 mL/min/1.73m^2 and a uACR ≥22.6 mg/mmol; or • eGFR >75–90 mL/min/1.73m^2 and a uACR ≥22.6 mg/mmol. Adults with CKD, with T2D, and with: • eGFR ≥20–25 mL/min/1.73m^2; or • eGFR >75–90 mL/min/1.73m^2.	The aim of this review is to align the populations in the recommendations for dapagliflozin and empagliflozin in TA775 and TA942 respectively. The population in the NICE scope has been partially addressed in TA775, and therefore the data presented within the company submission is aimed at the population where empagliflozin has a recommendation and dapagliflozin currently doesn't. This is because NICE have already evaluated the two technologies in cost comparison in TA942. It is expected that a positive recommendation following this review will result in a final recommendation of dapagliflozin in CKD in TA775 in the population proposed by NICE in the final scope.	The aim of this review is to compare costs between dapagliflozin and empagliflozin in the NICE scope population. This requires robust evidence that the two treatments have equivalent clinical efficacy and safety across the NICE scope population, as well as for the 5 CKD subpopulations defined in the company decision problem (i.e., the populations where empagliflozin is currently recommended but dapagliflozin is not). Conclusions made within TA942 may not be directly applicable to the current NICE scope population.
Intervention	Dapagliflozin	Dapagliflozin	N/A	None
Comparator(s)	Empagliflozin	Empagliflozin	N/A	None
Outcomes	The outcome measures to be considered include: • morbidity including cardiovascular outcomes, disease progression (such as kidney replacement, kidney failure) and markers of disease progression (such as eGFR), albuminuria) • mortality • hospitalisation • adverse effects of treatment • health-related quality of life.	This appraisal conducts a naïve comparison of the two pivotal clinical trials for dapagliflozin and empagliflozin, DAPA-CKD and EMPA-KIDNEY, respectively. Data from other non-CKD RCTs for dapagliflozin and two RWE studies are also included.	The outcomes proposed in the scope have been included in TA775 in which dapagliflozin demonstrated effectiveness in adults with CKD. NICE has previously concluded that dapagliflozin and empagliflozin have similar effectiveness and safety based on a published ITC. Additionally, it was not feasible to conduct an ITC in the specific subgroups within the decision problem versus empagliflozin due to a lack of matched cohorts and comparable datasets for analysis. For this reason, this appraisal conducts a naïve comparison of the primary endpoints in the two pivotal clinical trials for dapagliflozin and empagliflozin, DAPA-CKD and EMPA-KIDNEY, respectively, thereby addressing uncertainties raised in TA775 which led to a restricted population in the recommendation.	Outcomes are broadly in line with the NICE scope. Limited data informing the outcomes listed in the NICE scope are available for dapagliflozin and empagliflozin, and where available, data are not directly applicable to the CKD subpopulations defined in the company decision problem. Therefore, the comparative efficacy and safety of dapagliflozin and empagliflozin within the company defined CKD subpopulations is highly uncertain.
Economic analysis	The reference case stipulates that the cost effectiveness of	Taking into account the previous cost-effectiveness and cost	Dapagliflozin and empagliflozin are expected to have no differences in cost or resource use in the	The company's base-case analysis assumed that all resource use and

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
	treatments should be expressed in terms of incremental cost per quality-adjusted life year. If the technology is likely to provide similar or greater health benefits at similar or lower cost than technologies recommended in published NICE technology appraisal guidance for the same indication, a cost comparison may be carried out. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account.	comparison analyses completed in TA775 and TA942, a full cost comparison analysis has not been conducted for this appraisal. Instead, it is assumed that the availability of dapagliflozin in this patient population will not incur a differential cost to empagliflozin in the same group of patients. Senior leads at NICE have acknowledged that the company will make best use of the submission template but have also recognised that certain elements of the template cannot be populated.	subgroups in the decision problem. The acquisition costs of dapagliflozin and empagliflozin are equivalent at £36.59 per pack, with no confidential commercial arrangements and the same method and frequency of administration with no difference in patient monitoring, follow-up, adverse events or adherence in this population.[19, 20] The resource use of the population with non-T2D CKD and uACR <22.6 mg/mmol is estimated to have no or negligible differential considering the clinical equivalence of dapagliflozin and empagliflozin. There is no expected change to service provision or management in this population, specifically. In patients with CKD and T2D, empagliflozin has a higher cost than dapagliflozin to the NHS. The empagliflozin SmPC states that for patients with T2D "the recommended starting dose is 10 mg empagliflozin once daily for monotherapy and add-on combination therapy with other medicinal products for the treatment of diabetes. In patients tolerating empagliflozin 10 mg once daily who have an eGFR ≥60 mL/min/1.73 m^2 and need tighter glycaemic control, the dose can be increased to 25 mg once daily".[10] Therefore, these patients in clinical practice may have their dosing up-titrated to 25 mg once daily with associated additional SoC testing and potential primary care visit, while this dosing is 10 mg for dapagliflozin.[9] Costs associated with up-titration can substantially impact the overall cost comparison between treatments. On the other hand, dapagliflozin provides consistent and simple posology across the whole CKD population irrespective of T2D status (with the exception of patients with severe hepatic impairment who are initiated at 5 mg before increasing dose to 10 mg if tolerated), thereby alleviating pressure from an already burdened primary care system through the elimination of additional testing, patient visits, and clinician time. Additionally, dapagliflozin previously demonstrated an ICER of £17,000 in a subgroup analysis in TA775, indicating a cost effective use in this patient population.[1] While uncertainty in the estimates of	associated costs of dapagliflozin and empagliflozin were equivalent. All estimates used in the cost comparison analysis were derived from the dapagliflozin studies and assumed to be the same for empagliflozin. These assumptions were based on the company's expectations due to similar mechanism of action, efficacy and safety profiles and were not supported by any direct evidence. The evidence provided to support the same efficacy and safety profile is uncertain. Due to the lack of underlying evidence, the EAG could not perform any evidence-based scenario analyses and establish the EAG preferred base case.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
			empagliflozin's ICER in this patient group was much greater, it was still included in the final recommended population.[4] Therefore, this appraisal focuses solely on demonstrating the clinical equivalency in the population within the decision problem.	

Source: adapted from CS Table 1, pp12-15
Abbreviations: CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate, ICER = incremental cost effectiveness ratio; N/A = not applicable; NHS = National Health Service; SmPC = summary of medicinal product characteristics; SoC = standard of care; T2D = type 2 diabetes; uACR = urine albumin-to-creatinine ratio.

3.1 Population

The NICE scope represents the population that is recommended for empagliflozin, to allow the company to submit evidence supporting extension of the recommended dapagliflozin population to that of the empagliflozin population, as part of a cost comparison analysis. The company's decision problem is a subset of the NICE scope population, including five CKD subpopulations for which empagliflozin is recommended and dapagliflozin is not:

- Adults with CKD, without T2D, and with:
    - eGFR ≥20–45 mL/min/1.73m^2 and uACR <22.6 mg/mmol (200 mg/g); or
    - eGFR 20–25 mL/min/1.73m^2 and a uACR ≥22.6 mg/mmol (≥200 mg/g); or
    - eGFR >75–90 mL/min/1.73m^2 and a uACR ≥22.6 mg/mmol (≥200 mg/g).
- Adults with CKD, with T2D, and with:
    - eGFR ≥20–25 mL/min/1.73m^2;
    - or eGFR >75–90 mL/min/1.73m^2.

Therefore, it omits the subpopulations from the NICE scope where both dapagliflozin and empagliflozin are recommended, i.e. people with T2D and eGFR range between 25 and 75 mL/min/1.73 m^2 irrespective of uACR and people without T2D, between 25 and 75 mL/min/1.73 m^2 and uACR ≥22.6 mg/mmol. The company have omitted this population from their submission as their aim within this review is to align the populations that dapagliflozin and empagliflozin are recommended for, rather than to re-evaluate the population which was recommended for dapagliflozin within TA775 (company response to clarification question A1) and state that empagliflozin was evaluated in TA942 via a cost comparison versus dapagliflozin in the recommended dapagliflozin recommended populations (CS Document B, Table 1).

EAG comments: The company assume that cost-equivalence between dapagliflozin and empagliflozin in these two subpopulations has already been shown in TA942; the company state in CS Document B (Section B.2.1, p28) that, "*Based on the cost comparison, the committee concluded that empagliflozin had similar effectiveness, safety and cost to that of dapagliflozin*".

The final appraisal document for TA942 (p2) states that "results of an indirect comparison suggest that empagliflozin has a similar effectiveness to dapagliflozin, and it likely has similar safety."

The EAG notes that several aspects limit the applicability of the indirect comparison presented in TA942, and the conclusions made within TA942, to this appraisal. Firstly, as further discussed in Section 2.3.2.2, there are limitations to the applicability of the results of the TA942 NMA to this appraisal due to the inclusion of additional SGLT2 inhibitors. Secondly, the trials included in the TA942 NMA included a wider population for empagliflozin than for dapagliflozin. Therefore, it is unclear whether the results and conclusions made from the TA942 NMA are directly applicable to the subpopulations for which both dapagliflozin and empagliflozin are recommended.

It must also be emphasised that due to the differences in the populations included in the TA942 NMA for dapagliflozin and empagliflozin, the cost comparison between empagliflozin and dapagliflozin made within the TA942 CS is not valid for decision making, as a cost comparison must always be performed in the same population.[7] For this reason, the empagliflozin recommendation made by the NICE committee cannot have been based on the cost comparison presented in the TA942 CS, rather the NICE committee accepted the TA942 NMA conclusion of clinical similarity between dapagliflozin and empagliflozin and recommended empagliflozin based upon a cost-effectiveness analysis between empagliflozin and SoC alone within a population which broadly aligns with the direct evidence provided by the EMPA-KIDNEY trial.

Therefore, the EAG does not consider that it is valid to assume clinical similarity and cost equivalence in the populations for which dapagliflozin and empagliflozin are both recommended based on the NMA and the committee recommendations made within TA942. Instead, the EAG considers that robust evidence is required to show equivalence in effectiveness and safety between dapagliflozin and empagliflozin to inform a cost comparison across the entire NICE scope population.

3.2 Intervention

Both the NICE scope and decision problem agree that the intervention is dapagliflozin.

EAG comments: The dose of dapagliflozin is not specified in the NICE scope or nor the company decision problem. The licenced dose for CKD is 10mg once daily; individuals with severe hepatic impairment may start at 5mg before increasing dose to 10 mg if tolerated, although clinical advice to the EAG is that this is very rarely done in practice.

3.3 Comparator

Both the NICE scope and decision problem agree that the comparator is empagliflozin.

EAG comments: The dose of empagliflozin is not specified in the scope or decision problem. The licenced dose for empagliflozin in CKD is 10mg once daily; 25mg once daily is indicated as a higher dose for T2D (if necessary and tolerated), and there are no exclusions specified for people with CKD within the T2D population. Thus, the higher dose might conceivably be used in those with T2D and CKD. However, clinical advisers noted that empagliflozin dose increases were uncommon in practice when used to treat CKD.

3.4 Outcomes

Overall, the outcomes (reported in the CS Document B, CS addendum and in response to clarification) are broadly in line with the NICE scope.

However, for dapagliflozin, evidence was not available for all outcomes defined in the NICE scope for any of the five company defined CKD subpopulations and where evidence is available, the samples of patients from the dapagliflozin studies do not meet the specific company defined CKD subpopulation definitions. Therefore, the applicability of the effect estimates and conclusions of the dapagliflozin studies to the specific definitions of the subpopulations is unknown. No health-related quality of life (HRQoL) data, nor adverse event (AE) data is available for any of the five CKD subpopulations for dapagliflozin.

No evidence relating to empagliflozin for any clinical efficacy outcomes specified in the NICE scope are provided in the CS documents and AE data are not available for the five CKD subpopulations. Therefore, the comparative efficacy and safety of dapagliflozin and empagliflozin within the company defined CKD subpopulations is highly uncertain.

Clinical effectiveness and safety evidence are discussed further in Section 4.3 and 4.4.

3.5 Economic analysis

The company's base-case analysis assumed that all resource use and associated costs of dapagliflozin and empagliflozin were equivalent. All estimates used in the cost comparison analysis were derived from the dapagliflozin studies and assumed to be the same for empagliflozin. These assumptions were based on the company's expectations due to similar mechanism of action, efficacy and safety profiles and were not supported by any direct evidence. The evidence provided to support the same efficacy and safety profile is uncertain.

The cost comparison is discussed further in Section 5 and Section 6.

4 CRITIQUE OF CLINICAL EFFECTIVENESS EVIDENCE

4.1 Literature review methods

4.1.1 Summary of systematic literature review (SLR) conducted for the current appraisal

No SLR has been undertaken by the company. The company claims that the NICE template for cost comparison submissions states: "*an SLR for clinical evidence is not required*" (CS addendum, p35). As the company did not carry out an SLR, there were no search strategies reported within the CS. The company identified studies for their submission by selecting key studies presented in the previous related technology appraisals: TA775 and TA942, supplemented by RWE for dapagliflozin which was not available at the time of evidence submission for TA775.

EAG comments: The EAG were unable to find the statement indicating that an SLR was not required in the NICE cost comparison submission template and are concerned that the evidence used in the submission may be incomplete and at risk of selection bias. The company approach to study identification lacks transparency and the EAG does not have access to the previous search strategies within the submissions for TA942 or TA775. The last reported searches for studies of dapagliflozin and the comparator drug empagliflozin was October 2022.[21] The company did not update these searches using systematic search methods, therefore there is potential for missing unpublished and published studies, particularly for the comparator drug empagliflozin.

Three studies included in the SR for TA775 [Kohan (2014),[22] Fioretto (2018),[23] Pollock (2019)[24]] and two studies included in the CS for TA942 [Kohan (2014),[22] Dekkers (2018)[25]] were not included in the CS for the current cost comparison. In response to clarification question A3, the company explained that Kohan (2014),[22] Fioretto (2018),[23] and Pollock (2019)[24] were not included because the populations within these studies do not overlap with the subpopulations of interest to the review. Other reasons cited by the company for exclusion were that the data were from "*small populations exclusively involving patients with T2D and comorbid CKD*". The EAG is unclear why this would prevent consideration of these studies, given that a small population does not prohibit useful data and that wider population RCTs (DECLARE-TIMI 58 and DAPA-HF) are included.

The company explained that Dekkers (2018)[25] was not included because "*Dekkers (2018) is a pooled analysis of 11 phase III RCTs of dapagliflozin (5 mg or 10 mg) in combination with other T2D medications, including metformin, insulin and thiazolidinediones. Neither the dapagliflozin dose nor the combination treatments represent standard of care for patients with CKD so this study was deemed unsuitable to provide supportive evidence for dapagliflozin in the populations of interest in this review*". The EAG considers this reason for exclusion to be valid.

4.2 Included studies

Three RCTs and two RWE studies (reported in 6 papers) are presented in the CS documents to support the clinical effectiveness of dapagliflozin. **Error! Not a valid bookmark self-reference.** summarises these studies.

Table 2 Characteristics of the included Dapagliflozin studies

Study	DAPA-CKD subpopulation	OPTIMISE-CKD Svensson *et al.*, 2024 Tangri *et al.*, 2024	Nakhleh *et al*., 2024	DECLARE-TIMI 58	DAPA-HF
Study design	Phase III, international, multi-centre, open-label RCT	Multinational, observational, longitudinal cohort study	Retrospective observational study	Phase III, randomised, multinational, double-blind, placebo-controlled trial	Phase III, randomised, multinational, placebo-controlled trial
Population	Adults aged 18 years and over at the time of consent, with an eGFR ≥25 to ≤75 mL/min/1.73 m^2 at screening, and a uACR ≥22.6 mg/mmol to ≤≤565 mg/mmol, who are stable and on maximum tolerated labelled dose of an ACE inhibitor or ARB for at least four weeks before screening, if not medically contraindicated	Adults aged 18 years and over as of study index date, with first-ever registered laboratory-confirmed CKD or CKD diagnosis, defined as having either two eGFR measurements ≤60 mL/min/1.73m^2 taken ≥90 days apart or a first eGFR measurement ≤60 mL/min/1.73 m^2 followed by a first CKD diagnosis	Adults aged over 18 years, with baseline eGFR of 25–60 mL/min/1.73 m^2 and who have received an SGLT2 inhibitor (i.e., empagliflozin or dapagliflozin) between September 2020 and November 2022	Patients 40 years or older who have T2D, a glycated haemoglobin level of at least 6.5% but less than 12.0%, and a creatinine clearance of 60 ml or more per minute, with multiple risk factors for or have established atherosclerotic CV disease (defined as clinically evident ischemic heart disease, ischemic CV disease, or peripheral artery disease)	Adults aged 18 years and over, an ejection fraction of 40% or less, and NYHA class II, III, or IV HF symptoms.
Intervention(s)	Dapagliflozin 10 mg, daily	Dapagliflozin 10 mg, daily	Dapagliflozin 10 mg, daily or empagliflozin (10 or 25 mg)	Dapagliflozin 10 mg, daily	Dapagliflozin 10 mg, daily
Comparator(s)	Placebo	N/A	N/A	Placebo	Placebo
Reported outcomes[a]	Primary outcomes Time to first occurrence of any of: ≥50% sustained decline in eGFR from baseline Reaching ESKD CV death Renal death Secondary outcomes Time to first occurrence of any of: ≥50% sustained decline in	eGFR change from baseline over time following dapagliflozin initiation in patients with CKD and without T2D Risk of cardiorenal hospitalisation in patients with CKD and without T2D initiated with dapagliflozin	Differences in changes of eGFR slope between baseline and follow-up periods	Primary outcomes Time to first event of: CV death MI Ischemic stroke Secondary outcomes Hospitalisation for Congestive HF The composite endpoint of CV death, MI, ischemic stroke, hospitalisation for HF, hospitalisation for unstable angina pectoris or	Primary outcomes Time to first occurrence of any of: CV death HF Hospitalisation Urgent HF visit Secondary outcomes Time to first occurrence of any of CV death or HF hospitalisation Total number of (first and recurrent) HF hospitalisations and CV death

Study	DAPA-CKD subpopulation	OPTIMISE-CKD Svensson *et al.*, 2024 Tangri *et al.*, 2024	Nakhleh *et al.*, 2024	DECLARE-TIMI 58	DAPA-HF
	eGFR from baseline Reaching ESKD Renal death CV death Hospitalisation for HF Death from any cause			hospitalisation for any revascularisation All-cause mortality Body weight change from baseline	Change from baseline at 8 months in the overall KCCQ summary score Time to the first occurrence of: ≥50% sustained[b] decline in eGFR, reaching ESRD (sustained[b] eGFR <15 ml/min/1.73m^2 or, chronic[b] dialysis treatment or, receiving a renal transplant), or renal death Time to death from any cause
Follow-up duration	Median 2.4 years	Up to 12 months	Up to 24 months	Median 4.2 years	Median 18.2 months

Source: adapted from CS Document B, Table 7

Footnotes: [a]Endpoints from DAPA-CKD are listed in order of the hierarchical testing sequence. [b]As defined in the Clinical Event Adjudication (CEA) charter.

Abbreviations: ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; CKD = chronic kidney disease; CV = cardiovascular; CVD = cardiovascular disease; eGFR = estimated glomerular filtration rate; ESKD = end stage kidney disease; ESRD = end stage renal disease; HF = heart failure; KCCQ = Kansas City cardiomyopathy questionnaire; MI = myocardial infarction; NYHA = New York Heart Association; N/A = not applicable; RCT = randomised controlled trial; T2D = type 2 diabetes; uACR = urine albumin-to-creatinine ratio.

4.2.1 Study methodology, patient and disease characteristics

Information provided below is derived from the CS, Document B (Section B.3.3 to B.3.5) and CS addendum (pp. 3-24), supplemented by primary study publications, where necessary.

4.2.1.1 CKD-specific studies

4.3 In 3 studies (DAPA-CKD, [2] OPTIMIZE-CKD, [26 27] and Nakhleh et al., 2024 [16]), all recruited patients had a diagnosis of CKD, as detailed in Included studies

Three RCTs and two RWE studies (reported in 6 papers) are presented in the CS documents to support the clinical effectiveness of dapagliflozin. **Error! Not a valid bookmark self-reference.** summarises these studies.

Table 2.

DAPA-CKD

DAPA-CKD was the only CKD-specific RCT [2] and was the pivotal trial presented in the TA775 CS. The overall trial population comprised 4,304 patients, randomised to dapagliflozin (n=2152) and placebo (n=2152) over a median follow-up time of 2.4 years. This trial presents no major methodological concerns, as reflected by the company's quality appraisal (CS, Document B, Table 25).

A post-hoc analysis of DAPA-CKD stratified by T2D status is presented in CS Document B, Section B.3.6.1 and CS addendum (pp. 8-9), [28] evaluating difference between dapagliflozin and placebo in annual rate of eGFR decline and uACR changes in participants *without T2D* across the different baseline uACR groups (3.4-33.9 mg/mmol and ≥33.9mg/mmol).

Only the results from the subgroup with albuminuria and without T2D (n=1,398) are of relevance to the subpopulations defined in the company decision problem. The characteristics of the subgroup are reproduced below (**Error! Not a valid bookmark self-reference.**).

Table 3 Baseline characteristics of DAPA-CKD participants with albuminuria and without T2D in the post-hoc analysis

Characteristic	KDIGO stage A2 albuminuria (uACR 3.4 to <33.9 mg/mmol) (n=136)[a]	KDIGO stage A3 albuminuria (uACR ≥33.9 mg/mmol) (n=1,262)
Mean age, years (SD)	61 (15)	56 (15)
Female sex, n (%)	49 (36)	411 (33)
Mean eGFR (SD)	41 (11)	42 (12)
Median uACR	245	955

Source: CS Document B, Table 12
Footnotes: a. Of the 136 participants with KDIGO stage A2 albuminuria, 24 had uACR 34 to <22.6 mg/mmol at baseline.
Abbreviations: eGFR = estimated glomerular filtration rate (mL/min/1.73 m^2); KDIGO = Kidney Disease Improving Global Outcomes; SD = standard deviation; T2 = type 2 diabetes; uACR = urine albumin-to-creatinine ratio.

No inferential statistical analysis was performed for the between uACR group effect on dapagliflozin efficacy and no critical appraisal of the subgroup analysis was provided by the company.

EAG comments: The EAG notes the limited relevance of the DAPA-CKD trial population to the CKD subpopulations defined company decision problem (Table 1) as individuals with eGFR<25 mL/min/1.73m^2 and >75 mL/min/1.73m^2 were excluded, and separate characteristics and results were not provided for individuals with and without T2D

The small number of characteristics reported for the DAPA-CKD subgroup does not allow a comprehensive comparison of dapagliflozin and placebo group equivalence or an appraisal of the representativeness of the subgroup participants to the target population. Thus, the level of internal and external validity is difficult to gauge. However, compared with UK Clinical Practice Research Datalink (CPRD) data,[29] the DAPA-CKD subgroup includes a population that is substantially younger than the UK CKD population without T2D and has substantially higher uACR levels overall (see Appendix 2).

OPTIMISE-CKD

Results from OPTIMISE-CKD, an observational cohort study, were presented in two separate publications, Svensson *et al.* (2024) [26] and Tangri *et.al* (2024).[30] Svensson *et al.* (2024) is a retrospective analysis of dapagliflozin initiators while Tangri *et.al* (2024) is a retrospective analysis comparing dapagliflozin initiators and non-initiators using propensity score matching.

The company carried out a single quality assessment of methodology of the OPTIMISE-CKD studies using a modified version of the CASP checklist for cohort studies (CS, Document B, Table 26), which did not identify any limitations.

Svensson et al. (2024)

Svensson *et al.* (2024) [26] retrospectively analysed claims data for 10,805 CKD patients from the USA who initiated dapagliflozin 10mg once daily and had a baseline uACR measurement between April 2021 and March 2023. The study was an observational cohort study of a single treatment (dapagliflozin), with 12-month follow-up. Comparisons were made between subgroups defined by high uACR (>22.6 mg/mmol) and low uACR (3–22.6 mg/mmol). Differences in eGFR slopes between the uACR subgroups were not subject to inferential statistical analysis. eGFR slopes for each separate uACR subgroup were adjusted for baseline eGFR, age, sex, HF and RASi. Hospitalisation data were formally analysed between uACR subgroups, using Cox regression models, adjusting for age, sex, HF, CKD diagnosis, MI, stroke and peripheral arterial disease.

Characteristics of those with a uACR measurement of >3.4mg/mmol are summarised in Table 4.

Table 4 Characteristics of patients with CKD, with and without T2D in OPTIMISE-CKD (Svensson *et al.* 2024)[26]

	Non-T2D		T2D	
Baseline characteristics[a]	**Low uACR** (3.4-22.6 mg/mmol)	**High uACR** (≥22.6 mg/mmol)	**Low uACR** (3.4-22.6 mg/mmol)	**High uACR** (≥22.6 mg/mmol)
Number of patients, n	796	684	2411	1983
Age, years, mean (SD)	75 (8)	74 (9)	74 (8)	72 (8)
Female, n (%)	336 (42)	264 (39)	1079 (45)	797 (40)
Days since 1st CKD diagnosis	1347 (618-2024)	1169 (538-2067)	1064 (464-1870)	1100 (481-1931)
Co-morbidities				
ASCVD				
MI, n (%)	215 (27)	144 (21)	456 (19)	399 (20)
Stroke, n (%)	282 (35)	222 (32)	748 (31)	602 (30)
Peripheral artery disease, n (%)	318 (40)	255 (37)	826 (34)	712 (36)
Atrial fibrillation/flutter, n (%)	306 (38)	193 (28)	595 (25)	388 (20)
HF, n (%)	431 (54)	269 (39)	927 (38)	773 (39)
CKD diagnosis, n (%)	750 (94)	665 (97)	2241 (93)	1921 (97)
Cancer, n (%)	333 (42)	277 (40)	828 (34)	571 (29)
Laboratory measurements[b]				
eGFR, mL/min/1.73 m², median (IQR)	47 (37-61)	41 (31-55)	50 (38-66)	44 (34-58)
45–59 (Stage 3a), n (%)	197 (25)	162 (24)	655 (28)	483 (25)
30–44 (Stage 3b), n (%)	280 (36)	241 (36)	701 (30)	687 (36)
15–29 (Stage 4), n (%)	82 (11)	143 (21)	255 (11)	325 (17)
Creatinine, mg/dL, median (IQR)	1.3 (1.0-1.6)	1.5 (1.2-1.9)	1.2 (1.0-1.6)	1.4 (1.1-1.8)
uACR, mg/mmol, median (IQR)	7.8 (5.2-12.4)	74.0 (40.7-146.1)	7.9 (5.2-12.6)	70.5 (37.6-155.2)
Renoprotective treatment				
RASi, n (%)	491 (62)	494 (72)	1860 (77)	1585 (80)
SGLT2 inhibitor, n (%)	0 (0)	0 (0)	0 (0)	0 (0)

Source: Adapted from CS Document B, Table 15
Footnotes: [a]Characteristics for 4931 patients with uACR 0-3.4 mg/mmol were not available; [b] Laboratory measurements represent the last registered value in the year prior to incident CKD.
Abbreviations = ASCVD = atherosclerotic cardiovascular disease; BP = blood pressure; CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; HF = heart failure; IQR = interquartile range; MI = myocardial infarction; N/A = not available or not applicable; RASi = renin–angiotensin system inhibitor; SD = standard deviation; SGLT2 = sodium–glucose co-transporter-2; T2D = type 2 diabetes; uACR = urine albumin-creatinine ratio.

Tangri et al. (2024)

Tangri *et al.* (2024) [27] retrospectively analysed electronic health records and claims data from Japan and the USA in patients with CKD stages 3-4 with/without T2D and uACR <22.6 mg/mmol. Follow up was until the earliest of the following: loss to follow up, death or end of study period (2023).

Outcomes were compared for 2972 patients who initiated dapagliflozin 10mg once daily with 2972 propensity-matched untreated patients ('non-initiators'). Propensity matching was described as including 'all variables in the full baseline table'; these included sex, age, BMI, comorbidities, medications and baseline eGFR and uACR. Clinical advice to the EAG confirmed that these variables were appropriate. A subgroup analysis was performed with 275 patients without T2D who initiated

dapagliflozin 10mg once daily compared with 275 propensity-matched untreated patients. RASi was used by 85% of dapagliflozin initiators in the full cohort and 79% of dapagliflozin initiators in the subgroup. Further characteristics of these cohorts are presented in CS Document B, Table 19.

EAG comment: Clinical advisers to the EAG noted that Table 4 did not represent patient with normal ACR and eGFR 20-45 mL/min/1.73 m^2, and those with eGFR>60 mL/min/1.73 m^2 and raised uACR. The EAG notes some differences between the characteristics of the patients within the OPTIMISE-CKD studies and the UK CKD population, for example, the proportion of females (with uACR $\geq$3.4mg/mmol) recruited into the Svensson *et al.*(2024) study is lower than the UK CKD population (see Appendix 2). Furthermore, the OPTIMISE-CKD data were collected in USA and Japan where clinical practice and ethnicity mix will likely differ from that in the UK. In addition, only 62% to 80% of the OPTIMISE-CKD participants received RASi therapy, which does not align with the current UK recommendation dapagliflozin should be added to optimised RASi therapy (unless contra-indicated). Overall, the applicability of the OPTIMISE-CKD study population to the NICE scope is limited.

The company did not present the full CASP checklist for cohort studies nor any rationale for modifying the checklist, therefore limitations of OPTIMISE-CKD study may have been missed by the company's quality assessment. The EAG has identified the following limitations:

- Svensson *et al.* (2024) did not compare to another treatment and made comparisons only of subgroups defined by uACR, which limits the applicability of the results to the NICE scope.
- The 12-months follow-up within Svensson *et al.* (2024) may not have been sufficient to identify a clinically meaningful and unbiased result in eGFR slopes.[31]
- Tangri *et al.* (2024) is a non-randomised, retrospective comparison between dapagliflozin initiators and non-initiators and reasons for initiating vs. not initiating dapagliflozin were not reported. Despite propensity matching, non-initiators were older and had a higher eGFR and lower comorbidity burden than dapagliflozin initiators. Although the propensity-matching method used in Tangri *et al.* (2024) appears appropriate, there remains a risk of residual confounding due to systematic unadjusted differences between dapagliflozin initiators and non-initiators.

Nakhleh et al. (2024)

The study by Nakhleh *et al.* (2024) [16] consisted of 354 adults without T2D and an eGFR of 25-60 mL/min/1.73m^2 who initiated dapagliflozin or empagliflozin between September 2020 and November 2022 at an Israeli health maintenance organisation (Table 5).

Table 5 Baseline patient demographics and clinical characteristics in Nakhleh *et al.* (2024)[16]

Characteristic	Statistics (n=354)
Age, mean (SD), years	72.8 (11.8)
Female, n (%)	92 (26.0)
Age category, n (%) 18–64 years 65–74 years ≥75 years	 72 (20.3) 110 (31.1) 172 (48.6)
Socioeconomic status, n (%) 1-3 4-5 6-7 8-10	 31 (8.8) 71 (20.1) 107 (30.2) 145 (41.0)
Current smoker, n (%) No Yes Missing	 154 (43.5) 14 (4.0) 186 (52.5)
BMI, mean (SD), kg/m^2	29.1 (5.4)
Ejection fraction, n (%) <40% 40–49% 50–59% ≥60% Missing	 77 (21.8) 17 (4.8) 13 (3.7) 61 (17.2) 186 (52.5)
HF, n (%)	165 (46.6)
RAS inhibitors, n (%)	322 (91.0)
ACE inhibitors, n (%)	125 (35.3)
ARBs, n (%)	244 (68.9)
eGFR category, n (%) 45–60 mL/min/1.73 m^2 25–45 mL/min/1.73 m^2	 191 (54.0) 163 (46.0)
uACR category, n (%) <3.4 mg/mmol (<30mg/g) 3.4–33.9 mg/mmol (30-300mg/g) ≥33.9 mg/mmol (≥300mg/g) Missing	 146 (41.2) 81 (22.9) 74 (20.9) 53 (15.0)
KDIGO risk category, n (%) Moderate High Very high	 127 (35.9) 102 (28.8) 125 (35.3)
Source: Adapted from CS Document B, Table 22 AbbreviationsACE = angiotensin-converting enzyme; ARB = angiotensin II receptor blocker; ASCVD = atherosclerotic cardiovascular disease; BMI = body mass index; COPD = chronic obstructive pulmonary disease; DBP = diastolic blood pressure; eGFR = estimated glomerular filtration rate; HbA1c = glycated haemoglobin; HF = heart failure; HTN = hypertension; KDIGO = Kidney Disease = Improving Global Outcomes; MI = myocardial infarction; PCSK-9 = proprotein convertase subtilisin/kexin type 9; RAS = renin-angiotensin system; SBP = systolic blood pressure; SD = standard deviation; uACR = urinary albumin to creatinine ratio.	

Nakhleh *et al.* (2024) was a retrospective single arm observational cohort study, which evaluated the change in eGFR slope over the period before to after SGLT2 inhibitor (dapagliflozin [~75%] or

empagliflozin [~25%]) administration, without a control arm. The study followed patients over 4 years: for 2 years prior to baseline (i.e. the onset of SGLT2 inhibitor) and for 2 years after baseline.

Change in eGFR slope was evaluated in several separate subgroup analyses. These included subgroup analyses for different eGFR categories (25-45 mL/min/1.73 m^2 and 45-60 mL/min/1.73 m^2) and also for different uACR categories (<3.4 mg/mmol, 3.4-33.9mg/mmol, ≥33.9mg/mmol and 'missing'). The magnitude of differences in eGFR slope change between the subgroups were not quantified, although p-values were presented.

The company carried out a quality assessment using a modified version of the CASP checklist for cohort studies (CS, Document B, Table 26), which identifies that all confounding factors have not been identified nor adjusted for in the design or analysis of this study.

EAG comment: Although Nakhleh (2024) included both dapagliflozin and empagliflozin, no separate data were presented for the cohorts receiving dapagliflozin and empagliflozin. In response to clarification question A8, the company argue that because 75% of participants used dapagliflozin in the study, it can be considered generalisable to a dapagliflozin study and note the consistency of results in this study with that of the DAPA-CKD trial. The EAG acknowledges the consistency of the results of the Nakhleh *et al.* (2024) study with the results of the DAPA-CKD RCT, but notes that the results of these studies may not be directly comparable due to the differences in the study designs (i.e., placebo controlled RCT and an uncontrolled single arm registry study) and the respective objectives of such designs and relative biases associated with each design, as well as differences in the populations which could be recruited to randomised controlled and observational studies

Age and BMI in the Nakhleh *et al.* (2024) study are broadly reflective of UK CKD population (see Appendix 2), although the study was conducted in Israel, with a likely different ethnicity mix and differences in clinical practice to the UK. The study also had a low proportion of females compared to the UK CKD population. Patients with eGFR 60-90 mL/min/1.73 m^2 are not represented, which limits the applicability of the study to the NICE scope.

The company acknowledge the limitations relating to potential confounding, and as a consequence, the presented data for each subgroup category thus represented the observed change from pre to post SLGT2 administration, without control for the effects of non-treatment factors. However, the company did not present the full CASP checklist for cohort studies nor any rationale for modifying the checklist, therefore additional limitations of Nakhleh *et al.* (2024) study may have been missed by the company's quality assessment. The EAG also notes that analyses did not evaluate the effect of dapagliflozin and empagliflozin separately, which limits the applicability of the results to the company decision problem and to the NICE scope.

4.3.1.1 Wider population studies

DECLARE-TIMI 58[3, 32] and DAPA-HF[14, 33] were not conducted in a CKD-specific population. DECLARE-TIMI 58 was conducted in individuals with type 2 diabetes with or without established atherosclerotic cardiovascular disease and mostly with preserved renal function. DAPA-HF included patients with heart failure and reduced ejection fraction. However, both trials included a subset of individuals with CKD. Subgroup analyses from CKD patients in these trials as supportive evidence is presented (CS Document B, Sections B.3.6.4.1 and B.3.6.4.2 and CS addendum, pp16-21).

DECLARE-TIMI 58

The DECLARE-TIMI-58 RCT compared dapagliflozin to placebo over a median follow up of 4.2 years. A critical appraisal of the DECLARE-TIMI-58 RCT was not carried out by the company, but reference is made to the appraisal performed for TA288.[34] The conclusion from the EAG report for TA288 is that the quality of DECLARE-TIMI 58 is 'good.' (Section 4.1.4 of Cummins [2012]).[35]

The CKD subgroup in DECLARE TIMI 58[36] was formed by excluding those from the overall cohort with an eGFR >60 mL/min/1.73 m^2 *and* a uACR of <3 mg/mmol. This left the included CKD subgroup with an eGFR ≤60 mL/min/1.73 m^2 *or* a uACR ≥3 mg/mmol, confirmed by the company in response to clarification question A5 (**Error! Not a valid bookmark self-reference.**)

Table 6 eGFR and uACR inclusion criteria of the DECLARE-TIMI 58 trial subgroup analysis

	eGFR ≤60 mL/min/1.73 m^2	eGFR >60 mL/min/1.73 m^2
uACR <3mg/mmol	INCLUDED	EXCLUDED
uACR ≥3mg/mmol	INCLUDED	INCLUDED
Abbreviations: eGFR = estimated glomerular filtration rate; uACR = urinary albumin creatinine ratio		

A total of 5969 patients (out of 17,160) were included in the CKD subgroup. Within this CKD subgroup, differences between dapagliflozin and placebo were separately compared across different strata defined by eGFR category (<60, 60-90 and >90 mL/min/1.73 m^2), use of RASi (Yes/No) or uACR category (<22.6mg/mmol, ≥22.6mg/mmol). Randomisation was therefore preserved throughout all subgroup analyses. A p-value for interaction was provided to indicate differences in effect between stratum categories, but it is unclear what statistical method was used. No critical appraisal of the subgroup analysis was provided by the company.

In response to clarification question A6, the company provided the baseline characteristics of CKD and non-CKD participants stratified by eGFR level (<60 ml/min/1.73m^2, 60 to <90 ml/min/1.73m^2 and ≥90 ml/min/1.73m^2).

EAG comment: Clinical advice to the EAG is that the inclusion criteria used for the CKD subgroup are appropriate as they broadly reflect KDIGO criteria for CKD, although they do not include criteria for chronicity. The lack of available baseline characteristics for the CKD subgroup makes it difficult to appraise its applicability to the NICE scope. However, the restriction of DECLARE-TIMI 58 to a T2D population with established ASCVD or multiple ASCVD risk factors limits the applicability of the CKD subgroup to the NICE scope.

DAPA-HF

The DAPA-HF RCT[14] compared dapagliflozin to placebo comparing dapagliflozin to placebo in 4744 patients with NYHA II-IV HF and an ejection fraction ≤40%, over a follow up of 18 months. This trial presents no major methodological concerns, as reflected by the company's quality appraisal (CS Document B, Table 28). The DAPA-HF RCT was not focussed on renal outcomes and uACR was not measured in the trial.

The DAPA-HF RCT was not in a CKD-specific population, and so the study performed a subgroup analysis, [37] dividing the population into two subgroups with individuals with eGFR <60 mL/min/1.73 m^2 (41%) defined to have CKD and those with eGFR ≥60 mL/min/1.73 m^2 (59%) not to have CKD. No critical appraisal of the subgroup analysis was provided by the company. In response to clarification question A6, the company provided baseline characteristics, stratified by eGFR <60 ml/min/1.73m^2 or >60 ml/min/1.73m^2 (EAG comment**:** Analysis was focussed on comparisons of the dapagliflozin versus placebo effect between the two eGFR groups, only one of which was defined as a CKD population. Therefore, no comparisons were made between different eGFR ranges within a CKD population, but instead between a CKD population (<60 mL/min/1.73 m^2) and an ostensibly non-CKD (≥60 mL/min/1.73 m^2) population. Clinical advice to the EAG is that the single criterion definition of CKD as an eGFR of <60 mL/min/1.73 m^2 may miss out approximately half the CKD population. The >60 mL/min/1.73 m^2 eGFR group is therefore likely to include a mixed population of CKD and non-CKD patients. The lack of ACR measurement means that the prevalence of CKD in this study is unknown. Comparisons between <60 and ≥60 mL/min/1.73 m^2 described in CS Document B addendum (pp.16-17 and 20-21) are of limited relevance to the NICE scope.

The characteristics of the DAPA-HF cohort with eGFR <60 mL/min/1.73m^2 were similar to the UK CKD population for age but differed for the proportion of females and the proportion with T2D at baseline (see Appendix 2). RASi use, ethnicity and uACR were unavailable for DAPA-HF. Furthermore, the restriction of DAPA-HF to a HF population limits its applicability to the NICE scope.

Table 7).

EAG comment: Analysis was focussed on comparisons of the dapagliflozin versus placebo effect between the two eGFR groups, only one of which was defined as a CKD population. Therefore, no

comparisons were made between different eGFR ranges within a CKD population, but instead between a CKD population (<60 mL/min/1.73 m^2) and an ostensibly non-CKD (≥60 mL/min/1.73 m^2) population. Clinical advice to the EAG is that the single criterion definition of CKD as an eGFR of <60 mL/min/1.73 m^2 may miss out approximately half the CKD population. The >60 mL/min/1.73 m^2 eGFR group is therefore likely to include a mixed population of CKD and non-CKD patients. The lack of ACR measurement means that the prevalence of CKD in this study is unknown. Comparisons between <60 and ≥60 mL/min/1.73 m^2 described in CS Document B addendum (pp.16-17 and 20-21) are of limited relevance to the NICE scope.

The characteristics of the DAPA-HF cohort with eGFR <60 mL/min/1.73m^2 were similar to the UK CKD population for age but differed for the proportion of females and the proportion with T2D at baseline (see Appendix 2). RASi use, ethnicity and uACR were unavailable for DAPA-HF. Furthermore, the restriction of DAPA-HF to a HF population limits its applicability to the NICE scope.

Table 7 Baseline characteristics by baseline eGFR subgroups in DAPA-HF

Baseline characteristic	**eGFR <60 ml/min/1.73m^2 (n=1,926)**	**eGFR ≥60 ml/min/1.73m^2 (n=2,816)**
Baseline eGFR, ml/min/1.73m^2	47.0 ± 8.0	78.7 ± 13.5
Age, years	70.9 ± 9.0	63.2 ± 11.0
Female sex, N (%)	534 (27.7)	575 (20.4)
Geographic region, N (%)		
Asia/Pacific	365 (19.0)	731 (26.0)
Europe	891 (46.3)	1,263 (44.9)
Norther America	305 (15.8)	370 (13.1)
South America	365 (19.0)	452 (16.1)
New York Heart Association class		
II	1,267 (65.8)	1,934 (68.7)
III	645 (33.5)	853 (30.3)
IV	14 (0.7)	29 (1.0)
Heart rate, bpm	70.7 ± 11.6	72.0 ± 11.7
Baseline systolic blood pressure, mmHg	121.7 ± 16.2	121.9 ± 16.4
Baseline ejection fraction, %	31.3 ± 6.6	30.9 ± 6.9
Baseline N-terminal pro-B-type natriuretic peptide, pg/mL, median (interquartile range)	1,823.8 (1,060.2–3,326.2)	1261.1 (769.9–2,207.7)
Body mass index, kg/m^2	28.4 ± 5.8	28.0 ± 6.0
Main cause of heart failure		
Ischemic	1,174 (61.0)	1,498 (53.2)
Nonischaemic	605 (31.4)	1,082 (38.4)
Unknown	147 (7.6)	236 (8.4)
T2D status at baseline		
Yes	982 (51.0)	1,157 (41.1)
Patients with T2D at baseline		
Haemoglobin A1c, %	6.6 ± 1.4	6.4 ± 1.3
Biguanide	406 (21.1)	624 (22.2)
Sulfonylurea	198 (10.3)	242 (8.6)
Dipeptidyl peptidase 4 inhibitor	164 (8.5)	146 (5.2)

Baseline characteristic	eGFR <60 ml/min/1.73m^2 (n=1,926)	eGFR ≥60 ml/min/1.73m^2 (n=2,816)
Glucagon-like peptide 1-receptor agonist	15 (0.8)	6 (0.2)
Insulin	304 (15.8)	236 (8.4)
Source: Table 7, company response to clarification question A6 Abbreviations: CRT: cardiac resynchronisation therapy; eGFR: estimated glomerular filtration rate; T2D: type 2 diabetes		

4.4 Evidence of clinical similarity between dapagliflozin and empagliflozin

Before a cost comparison analysis can be performed between dapagliflozin and empagliflozin, it is essential to provide evidence of clinical similarity, in terms of overall health outcomes (Section 2.3.2). Evidence of equivalent efficacy between dapagliflozin and empagliflozin in each of the five CKD subpopulations, (as defined in the company decision problem, Table 1) is provided below. Information provided below is derived from the CS Document B (Section B.3.6), the CS addendum (pp. 3-24), supplemented by primary study publications, where necessary.

In the results sections below for consistency, uACR has been expressed in mg/mmol. Where results have been expressed as mg/g in the CS documents or primary study publications, mg/g values have been multiplied by 0.11312 [1 mmol of creatinine has a mass of 0.11312g]

Morbidity outcomes reported in the dapagliflozin studies included eGFR slope and albuminuria. eGFR slope measures the rate of eGFR change per year. A positive value indicates an increase in eGFR, and so is an indicator of benefit. Thresholds for minimum effects on change in GFR slope that provide high confidence for significant treatment effects on the clinical end point have been shown by Inker (2019)[38] to be 0.5 to 1.0. Inker (2019)[38]showed that such differences strongly predict benefits on clinical end points such as doubling of serum creatinine, GFR<15 ml/min per 1.73 m^2, or ESKD. A lower level of albuminuria (measured by uACR) denotes a benefit, and so a negative change and/or difference also indicates a beneficial effect. Levey (2020)[31] have suggested that a 30% reduction in albuminuria over 2 years represents a clinically important effect.

4.4.1 Subpopulation 1: No T2D, eGFR 20-45 mL/min/1.73 m^2, uACR <22.6 mg/mmol

Evidence for dapagliflozin's effects on eGFR slope, albuminuria and hospitalisation in this subpopulation is provided in **Error! Not a valid bookmark self-reference.**.

Table 8 Summary of the effects of dapagliflozin on eGFR slope, albuminuria and hospitalisation in Subpopulation 1 ***(no T2D, eGFR 20-45 mL/min/1.73 m^2, uACR <22.6 mg/mmol)***

Study	Definition of study sample that is relevant to the subpopulation and comments	Findings	Comments
OPTIMISE-CKD: Svensson, 2024[26]	No T2D, uACR <22.6 mg/mmol, eGFR 15-60 mL/min/1.73 m^2 • Correctly aligned in terms of use of non-T2D group. • uACR correctly aligned. • Lack of alignment in terms of eGFR. eGFR range in the evidence is wider than in the subpopulation (eGFR 15-60 mL/min/1.73 m^2 compared to eGFR 20-45 mL/min/1.73 m^2)	eGFR slope In participants on dapagliflozin in the relevant sample [no T2D, uACR <22.6 mg/mmol, and eGFR 15-60 mL/min/1.73 m^2], the unadjusted single arm eGFR was measured at +0.33 (95% CI: -0.64, 1.37) [n=2345]. The fully adjusted result was +0.42(95% CI: -0.76, 1.20) [n=2345] [CS addendum, Figure 3, p12]. The unadjusted eGFR slope for the sample on dapagliflozin with different baseline uACR ≥22.6 mg/mmol (but also with no T2D and eGFR range of 15-60 mL/min/1.73 m^2) was +0.38 (95% CI: -0.46, 1.38) [n=684]. The fully adjusted result was -0.51(95% CI: -2.63, 1.07) [n=684] [CS addendum, Figure 3, p12 and Svensson *et al* 2024]. Hospitalisation There were no differences in rates of hospitalisation for cardiorenal complications reported for dapagliflozin recipients between the 'no T2D, uACR <22.6 mg/mmol, eGFR 15-60 mL/min/1.73 m^2' group and the 'no T2D, uACR ≥22.6 mg/mmol, eGFR 15-60 mL/min/1.73 m^2' group. For the 'broad'[a] definition of cardiorenal complications the HR (for high uACR vs low uACR groups) was 1.03 (95% CI: 0.77, 1.37) [n=3029] and for the for the 'strict'[b] definition of cardiorenal complications the HR was 1.07(95% CI: 0.66, 1.72) [n=3029] (CS Document B, Figure 12, p 77).	eGFR slope Results from a single arm, non-comparative data only. Although the point estimates for both the lower (<22.6 mg/mmol) and higher uACR groups indicate a benefit for dapagliflozin, summary point estimates do not reach thresholds for minimal effect, [38] and are imprecise as shown by the wide confidence intervals. The clinical relevance of these findings is uncertain. Visual inspection of the eGFR slope results indicates no evidence of a significant difference in eGFR slope by baseline uACR level, although no formal between-group statistical analysis is presented. Hospitalisation In both definitions of cardiorenal complications, results support the notion that uACR levels don't affect dapagliflozin efficacy. However, this does not demonstrate efficacy in the <22.6 mg/mmol (in combination with no T2D and eGFR 15-60 mL/min/1.73 m^2) group, as it is not reported if the absolute effects in the comparator arm would be deemed beneficial or harmful.

Study	Definition of study sample that is relevant to the subpopulation and comments	Findings	Comments
OPTIMISE-CKD: Tangri *et al*, 2024[27]	No T2D, uACR 3.4 to 22.6 mg/mmol,[c] eGFR 25-60 mL/min/1.73 m^2 • Aligned with non-T2D group. • uACR slightly misaligned (excludes 0 to 3.4 mg/mmol). • eGFR range is significantly wider than subpopulation 1, with an additional range from 45-60 mL/min/1.73 m^2; it also excludes 20-25 mL/min/1.73 m^2.	The eGFR slope difference between those initiating dapagliflozin and those not initiating dapagliflozin for this study sample positively favoured dapagliflozin: +1.28(95% CI: -1.56, 4.12) [n=550] [CS addendum, pp 10-11].	The point estimate of between-group difference (+1.28) is deemed by the company to be a clinically effective difference.[38] Clinical advice to the EAG is that such a difference is likely to be clinically important over a period of several years. However, follow-up is limited, and effect estimates are imprecise, as shown by the wide confidence interval. No analysis was performed comparing across uACR groups.
Nakhleh *et al*, 2024[16]	No T2D, uACR 3.4-33.9 mg/mmol[c] eGFR 25-60 mL/min/1.73 m^2 • Correctly aligned in terms of use of non-T2D group. • uACR misaligned with 0-22.6 mg/mmol range • eGFR range wider – possibility of differential effects at eGFR 20-45 mL/min/1.73 m^2 compared to overall 25-60 mL/min/1.73 m^2 range.	The eGFR slope changed from baseline to post-dapagliflozin treatment (within-group) by a mean of +3.79(95% CI: 1.15,6.43) [n=81] [Figure 5, p14, CS addendum] in the relevant sample with 'no T2D, uACR 3.4-33.9mg/mmol and eGFR 25-60 mL/min/1.73 m^2'. The pre-post change in the 'no T2D, uACR $\geq$33.9mg/mmol and eGFR 25-60 mL/min/1.73 m^2' sample was: +1.47(95% CI: -0.26, 3.2) [n=74] [Figure 5, p14, CS addendum], The pre-post change in the 'no T2D, uACR 0-3.4 mg/mmol and eGFR 25-60 mL/min/1.73 m^2' sample was: +5.1(95% CI: 3.31,6.88) [n=146] [Figure 5, p14, CS addendum] When the uACR groups were pooled, the more relevant eGFR category of 25-45 mL/min/1.73 m^2 suggested possible efficacy (pre-post change in eGFR slope of 5.67(95% CI: 4.03, 7.30) [n=163], which was superior, but in the same direction, to the eGFR category of 45-60 mL/min/1.73 m^2 [change in eGFR slope of 2.41(95% CI: 0.93,3.90) [n=191]], p=0.004 [Figure 5, p14, CS addendum].	The positive eGFR changes in the relevant 'no T2D, uACR 3.4-33.9mg/mmol and eGFR 25-60 mL/min/1.73 m^2' sample, as well as those in the other two samples, may indicate efficacy of dapagliflozin. However, the lack of a comparator arm means there is no control for intervening effects such as the placebo effect or regression to the mean, and so the changes cannot necessarily be wholly attributed to a treatment effect.
DAPA-CKD subgroup analysis[28]	No T2D, uACR 3.4 to <33.9 mg/mmol[c] and eGFR 25-75 mL/min/1.73 m^2 • Correctly aligned in terms of use of non-T2D group.	eGFR slope For results from week 2 until final follow up (median 2.4 years), the subgroup analysis with 'no T2D, uACR 3.4 to <33.9 mg/mmol and eGFR 25-75 mL/min/1.73 m^2' showed a benefit for dapagliflozin	eGFR slope For the eGFR slope analyses, the 2 weeks to final follow up results are probably more clinically relevant than the 0-2 weeks results, as early changes in eGFR may be spurious. The post 2 weeks results indicate

Study	Definition of study sample that is relevant to the subpopulation and comments	Findings	Comments
	• uACR misaligned (should be 0-22.6 mg/mmol). • eGFR wider – possibility of differential effects at eGFR 20-45 mL/min/1.73 m^2 compared to overall 25-75 mL/min/1.73 m^2 range.	(versus placebo), with an eGFR slope difference of +1.8(95% CI: 0.4, 3.1), n=136 [CS addendum, p9]. The eGFR slope difference between dapagliflozin and placebo (2weeks to final follow up) in the sample with 'no T2D, uACR ≥33.9 mg/mmol and eGFR 25-75 mL/min/1.73 m^2', was +1.2(95% CI: 0.6, 1.8) [p9, CS addendum, p9]. eGFR slope difference (vs placebo) for the period from baseline to week 2 was similar between uACR groups: the eGFR slope difference was -2.4(95% CI: -4.5, -0.4) for the uACR 3.4-33.9 mg/mmol group, and -2.0(95% CI: -2.7, -1.3) for the ≥33.9 mg/mmol uACR group [CS addendum, p9]. Albuminuria The percentage difference (between dapagliflozin and placebo) for change of uACR for the relevant sample with 'no T2D, uACR 3.4 to <33.9 mg/mmol and eGFR 25-75 mL/min/1.73 m^2' was -16(95% CI: -41.8, 21.3) [n=136] [CS addendum, Figure 1, p9]. The percentage difference (between dapagliflozin and placebo) for change of uACR for the sample with 'no T2D, uACR ≥33.9 mg/mmol and eGFR 25-75 mL/min/1.73 m^2' was -14.6(95% CI: -22.9, -5.3)] [n=1262] [CS addendum, Figure 1, p9].	efficacy for dapagliflozin (versus placebo) in the relevant sample after week 2, and efficacy does not appear to be affected by uACR levels. Albuminuria The point estimate change in albuminuria in the relevant sample indicates possible efficacy for dapagliflozin, although the effect is imprecise as shown by the wide confidence interval, and the clinical relevance of this estimate is uncertain.[31] A similar effect is seen in the 'no T2D, uACR ≥33.9 mg/mmol and eGFR 25-75 mL/min/1.73 m^2' sample. However, confidence intervals for the ≥33.9 mg/mmol uACR group are more precise

Sources: CS addendum, pp8-9;[28], pp8-14; Svensson, 2024;[26]Tangri, 2024;[27]DAPA-CKD subgroup analysis;[28] Nakhleh *et al*, 2024[16]
Abbreviations: CI = confidence interval; CS = company submission; eGFR = estimated glomerular filtration rate; ESKD = end stage kidney disease; HR = hazard ratio; T2D = type 2 diabetes; uACR = urinary albumin creatinine ratio
Footnotes: a = patients with a diagnosis of cardiorenal complication (CKD or HF) in an in-hospital setting; b = restricted to patients with a hospital admission where a cardiorenal complication was the main diagnosis; c Some uACR values expressed in mg/mmol in the CS addendum are inaccurate conversions from values expressed in mg/g in the primary papers: uACR=30 mg/g is expressed as 3 mg/mmol, when it is actually 3.4mg/mmol, and uACR=300mg/g is expressed as 30 mg/mmol, when it is actually 33.9 mg/mmol.

4.4.1.1 Evidence of efficacy of dapagliflozin in Subpopulation 1 (no T2D, eGFR 20-45 mL/min/1.73 m^2, uACR <22.6 mg/mmol)

Morbidity: markers of disease progression (eGFR slope and albuminuria)

In general, results for eGFR slope suggest that people with uACR <22.6 mg/mmol (or 3.4-33.9 mg/mmol, or <33.9 mg/mmol) in combination with no T2D and eGFR ranges of 15-60, 25-60 or 25-75 mL/min/1.73 m^2 may experience benefit from dapagliflozin in terms of a positive eGFR slope. This benefit is at a similar level to people with uACR levels of ≥22.6 mg/mmol (or ≥33.9mg/mmol) in combination with no T2D and eGFR ranges of 15-60, 25-60 or 25-75 mL/min/1.73 m^2. Estimates of benefit from dapagliflozin at both low and high uACR levels are precise in the Nakhleh *et al* (2024) [16] and DAPA-CKD[28] trials but imprecise in the two OPTIMISE-CKD[26, 27] studies.

Considering only the point estimates, results for albuminuria suggest possible benefits from dapagliflozin (compared to placebo) in terms of reduced albuminuria for people with lower uACR levels, in combination with no T2D and an eGFR of 25-75 mL/min/1.73 m^2. These benefits are similar to those in people with higher uACR levels (≥33.9 mg/mmol), in combination with no T2D and an eGFR of 25-75 mL/min/1.73 m^2. Only the effects in the higher uACR group (≥33.9 mg/mmol) are precise, whilst those in the lower uACR group (3.4 to <33.9 mg/mmol) are not.

EAG comments: Whilst evidence is in the non-T2D population, and the uACR ranges in the evidence are at (or close to) that of the subpopulation definition, eGFR ranges in the evidence are not generally in alignment with the subpopulation eGFR definition of 20-45 mL/min/1.73 m^2. Therefore, it is unclear if the effect estimates for dapagliflozin are applicable to the precisely defined subpopulation of 'no T2D, eGFR 20-45 mL/min/1.73 m^2, uACR <22.6 mg/mmol'. Furthermore, the effect estimate presented is imprecise and the clinical relevance of the reduction in uACR in this subgroup analysis is uncertain (see Table 8).

When uACR categories were pooled in Nakhleh *et al.* (2024), the 'no T2D and eGFR 25-45 mL/min/1.73 m^2' group showed similar dapagliflozin benefits to the 'no T2D and eGFR 45-60 mL/min/1.73m^2 group', suggesting that eGFR levels close to the subgroup range are, when considered alone, associated with dapagliflozin benefits that are comparable to those at other eGFR levels. Nakhleh *et al.* (2024) was in a mixed dapagliflozin/empagliflozin population and separate results by treatment were not reported.

The non-statistically significant difference of 1.28 (95% CI: -1.56, 4.12) in the Tangri *et al.* (2024)[27] study was deemed by the company to be clinically important[38]. However, the limited follow-up and uncertainty around this point estimate, reflected in the confidence intervals, should be considered when drawing conclusions.

Hospitalisation for cardiorenal complications

Evidence for dapagliflozin's effects on hospitalisation for cardiorenal complications in this subpopulation is based on data from a single-arm retrospective cohort study. In general, results suggest that uACR levels <22.6 mg/mmol (in combination with no T2D and eGFR 15-60 mL/min/1.73 m^2) make little difference to the beneficial effects of dapagliflozin on reducing hospitalisation for cardiorenal complications, compared with higher uACR levels (in combination with no T2D and eGFR 15-60 mL/min/1.73 m^2).

EAG comments: The relative effects measures between uACR groups demonstrate that uACR levels do not affect the efficacy of dapagliflozin in reducing hospitalisation. However, this does not demonstrate efficacy in the <22.6 mg/mmol (in combination with no T2D and eGFR 15-60 mL/min/1.73 m^2) group, as it is not reported if the absolute effects in the comparator arm would be deemed beneficial or harmful.

Whilst evidence is in the correct non-T2D stratum, eGFR levels in the evidence are not in alignment with the subpopulation eGFR definition of 20-45 mL/min/1.73 m^2. Therefore, it is unclear if the effect estimates for dapagliflozin are applicable to the precisely defined subpopulation of 'no T2D, eGFR 20-45 mL/min/1.73 m^2, uACR <22.6 mg/mmol'.

Mortality

No evidence is reported for dapagliflozin for Subpopulation 1.

Health-related quality of life (HRQoL)

No evidence is reported for dapagliflozin for Subpopulation 1.

In response to clarification question A2, during the clarification process, the company provided HRQoL from DAPA-CKD. These showed [redacted] in between the dapagliflozin and placebo groups at baseline and [redacted] from baseline in KDQOL-36 scores [redacted] at 12, 24 and 36 months. [redacted] for SF-12 composite scores.

4.4.1.2 Evidence of efficacy of empagliflozin in Subpopulation 1 (no T2D, eGFR 20-45 mL/min/1.73 m^2, uACR <22.6 mg/mmol)

No evidence relating to empagliflozin for any outcomes specified in the NICE scope are provided in the provided in the CS documents. Therefore, the comparative efficacy of dapagliflozin and empagliflozin within Subpopulation 1 for these clinical outcomes is unknown.

4.4.2 Subpopulation 2: No T2D, eGFR 20-25 mL/min/1.73 m^2, uACR ≥22.6 mg/mmol

Evidence for dapagliflozin's effects on eGFR slope and hospitalisation in this subpopulation is provided in in **Error! Not a valid bookmark self-reference.**.

Table 9 Summary of the effects of dapagliflozin on eGFR slope and hospitalisation in Subpopulation 2 *(no T2D, eGFR 20-25 mL/min/1.73 m^2, uACR ≥22.6 mg/mmol).*

Study	Definition of study sample that is relevant to the subpopulation and comments	Findings	Comments
OPTIMISE-CKD Svensson, 2024[26]	No T2D, uACR ≥22.6 mg/mmol, eGFR 15-60 mL/min/1.73 m^2 • Correctly aligned in terms of use of non-T2D group. • uACR correctly aligned. • Lack of alignment in terms of eGFR. eGFR range in the evidence is excessively wide – there is the possibility of differential effects at eGFR 20-25 mL/min/1.73 m^2 compared to the measured eGFR 15-60 mL/min/1.73 m^2 range.	eGFR In dapagliflozin participants in this subpopulation (no T2D, uACR ≥22.6 mg/mmol, eGFR 15-60 mL/min/1.73 m^2), the unadjusted single arm eGFR was measured as +0.40 (95% CI: -0.46, 1.38) [n=684] The fully adjusted result was -0.03 (95% CI: -2.88, 1.46) [n=684] [CS addendum, Figure 6, p15]. The unadjusted eGFR slope for dapagliflozin participants in the subpopulation that had a uACR 3 to 22.6mg/mmol (but who also had no T2D and the same eGFR range of 15-60) was similar, at +0.79 (95% CI: -0.59, 2.56) [n=796]. The fully adjusted result for this comparison groups was 0.42(95% CI: -0.76, 1.20) [n=796] [CS addendum, Figure 6, p15]. Hospitalisation due to cardiorenal complications For the 'broad'[a] definition of cardiorenal complications the HR (for high uACR [≥22.6 mg/mmol] vs low [0-22.6 mg/mmol] uACR) was 1.03 (95% CI: 0.77, 1.37) [n=3029] and for the 'strict'[b] definition it was 1.07(95% CI: 0.66, 1.72) [n=3029] [CS Document B, Figure 12, p77].	eGFR Results are imprecise as shown by the wide confidence intervals. No formal statistical analysis was presented comparing high and low-uACR groups, making comparisons between these subgroups uncertain. Hospitalisation due to cardiorenal complications No differences in rates of hospitalisation for cardiorenal complications were reported between uACR ≥22.6mg/mmol (in combination with no T2D and eGFR of 15-60 mL/min/1.73 m^2) and <22.6mg/mmol (in combination with no T2D and eGFR of 15-60 mL/min/1.73 m^2). In both cases, results support notion that uACR levels don't affect dapagliflozin efficacy. However, this does not demonstrate efficacy in the <22.6 mg/mmol (in combination with no T2D and eGFR 15-60 mL/min/1.73 m^2) group, as it is not reported if the absolute effects in the comparator arm would be deemed beneficial or harmful. Data were also provided relative to the less relevant 3.4 to 22.6 uACR group. These can be seen in CS addendum, p15.

Sources: CS addendum, pp15; Svensson, 2024;[26]

Abbreviations: CI = confidence interval; CS = company submission; eGFR = estimated glomerular filtration rate; ESKD = end stage kidney disease; HR = hazard ratio; T2D = type 2 diabetes; uACR = urinary albumin creatinine ratio

Footnotes: a = patients with a diagnosis of cardiorenal complication (CKD or HF) in an in-hospital setting; b = restricted to patients with a hospital admission where a cardiorenal complication was the main diagnosis

4.4.2.1 Evidence of efficacy of dapagliflozin in subpopulation 2 (no T2D, eGFR 20-25 mL/min/1.73 m^2, uACR ≥22.6 mg/mmol).

Morbidity: markers of disease progression (eGFR slope)

Point estimates suggest that people with uACR levels ≥22.6 mg/mmol, in combination with no T2D and eGFR of 15-60 mL/min/1.73 m^2, may gain benefits from dapagliflozin, though there is uncertainty in the estimate. Results are similar to those in people with lower uACR levels, in combination with no T2D and eGFR of 15-60.

Hospitalisation for cardiorenal complications

In general, results suggest that uACR levels ≥22.6 mg/mmol (in combination with no T2D and eGFR of 15-60 mL/min/1.73 m^2) make little difference to the effects of dapagliflozin on hospitalisation for cardiorenal complications, compared with lower uACR levels (in combination with no T2D and eGFR of 15-60 mL/min/1.73 m^2).

EAG comments: Results for Subpopulation 2 are based on a single, non-comparative retrospective analysis of non-UK data. eGFR slope results were imprecise as shown by the wide confidence intervals, and did not meet minimal thresholds by Inker (2019).[38]

The relative effects measures for hospitalisation due to renal complications between uACR groups demonstrate that uACR levels do not affect the level of dapagliflozin efficacy. However, this does not demonstrate efficacy in the <22.6 mg/mmol (in combination with no T2D and eGFR 15-60 mL/min/1.73 m^2) group, as it is not reported if the absolute effects in the comparator arm would be deemed beneficial or harmful.

Whilst evidence is in the correct non-T2D stratum and uACR category, eGFR levels in the evidence are not in alignment with the subpopulation eGFR definition of 20-25 mL/min/1.73 m^2. Therefore, it is unclear if the effect estimates for dapagliflozin are applicable this precisely defined subpopulation.

Mortality

No evidence is reported for dapagliflozin for Subpopulation 2.

Health-related quality of life (HRQoL)

No evidence is reported for dapagliflozin for Subpopulation 2.

4.4.2.2 Evidence of efficacy of empagliflozin in Subpopulation 2 (no T2D, eGFR 20-25 mL/min/1.73 m^2, uACR ≥22.6 mg/mmol).

No evidence relating to empagliflozin for any outcomes specified in the NICE scope are provided in the provided in the CS documents. Therefore, the comparative efficacy of dapagliflozin and empagliflozin within Subpopulation 2 for these clinical outcomes is unknown.

4.4.3 Subpopulation 3: No T2D, eGFR 75-90 mL/min/1.73 m^2, uACR ≥22.6 mg/mmol

Evidence for the effects of dapagliflozin on 1) HF hospitalisation or urgent HF visit, 2) CV death, HF hospitalisation or urgent HF visit, 3) CV death and 4) death from any cause in this subpopulation is provided in Table 10

Table 10 Summary of the effects of dapagliflozin on hospitalisation and mortality outcomes *(no T2D, eGFR 75-90 mL/min/1.73 m^2, uACR ≥22.6 mg/mmol).*

Study	Definition of study sample that is relevant to the subpopulation and comments	Findings	Comments
DAPA-HF[37]	No restriction on T2D, no restriction on uACR, eGFR >60 mL/min/1.73 m^2 The evidence provided by the company is not relevant to this subpopulation, because none of the characteristics match the subpopulation definition.	HF hospitalisation or urgent HF visit *eGFR <60 mL/min/1.73 m^2* HR for dapagliflozin vs placebo 0.66(95% CI: 0.51, 0.82) [n=1926] *eGFR >60 mL/min/1.73 m^2* HR for dapagliflozin vs placebo 0.75(95% CI: 0.59, 0.95) [n=2816] The interaction p value (for the comparison between eGFR groups) is 0.46 CV death, HF hospitalisation or urgent HF visit *eGFR <60* mL/min/1.73 m^2 HR for dapagliflozin vs placebo 0.72(95% CI: 0.59, 0.86) [n=1926] *eGFR >60* mL/min/1.73 m^2 HR for dapagliflozin vs placebo 0.76(95% CI: 0.63, 0.92) [n=2816] The interaction p value (for the comparison between eGFR groups) is 0.64 CV death *eGFR <60* mL/min/1.73 m^2 HR for dapagliflozin vs placebo 0.88(95% CI: 0.69, 1.13) [n=1926] *eGFR >60* mL/min/1.73 m^2 HR for dapagliflozin vs placebo 0.76(95% CI: 0.59, 0.98) [n=2816] The interaction p value (for the comparison between eGFR groups) is 0.41 Death from any cause *eGFR <60* mL/min/1.73 m^2 HR for dapagliflozin vs placebo 0.85(95% CI: 0.68, 1.06) [n=1926] *eGFR >60* mL/min/1.73 m^2 HR for dapagliflozin vs placebo 0.81(95% CI: 0.64, 1.02) [n=2816] The interaction p value (for the comparison between eGFR groups) is 0.76	The subpopulation of participants with eGFR*>60 mL/min/1.73 m^2* includes an unclear mix of CKD and non-CKD participants with HF. The lack of reporting by T2D and uACR status limits the applicability of this evidence to Subpopulation 3.

Sources: CS addendum, pp. 16-17; DAPA-HF[37]

Abbreviations: CI = confidence interval; CKD = chronic kidney disease; CS = company submission; eGFR = estimated glomerular filtration rate; ESKD = end stage kidney disease; T2D = type 2 diabetes; uACR = urinary albumin creatinine ratio

4.4.3.1 Evidence of efficacy of dapagliflozin in Subpopulation 3 (no T2D, eGFR 75-90 mL/min/1.73 m^2, uACR ≥22.6 mg/mmol).

Morbidity

No evidence is reported for dapagliflozin for Subpopulation 3.

Hospitalisation and mortality

Evidence for the effects of dapagliflozin on composite outcomes of HF hospitalisation or urgent HF visit, CV death, HF hospitalisation or urgent HF visit, CV death, death from any cause in this subpopulation are provided in **Error! Reference source not found.**.

EAG comments: Evidence for Subpopulation 3 is restricted to a subgroup analysis from a single RCT of patients with HF, stratified by baseline eGFR. Results were not reported by T2D and uACR status. The subpopulation of participants with eGFR>60 mL/min/1.73 m^2 includes an unclear mix of CKD and non-CKD participants with HF. Overall, the applicability of the CS evidence to Subpopulation 3 is significantly limited.

Health-related quality of life (HRQoL)

No evidence is reported for dapagliflozin for Subpopulation 3.

4.4.3.2 Evidence of efficacy of empagliflozin in Subpopulation 3 (no T2D, eGFR 75-90 mL/min/1.73 m^2, uACR ≥22.6 mg/mmol).

No evidence relating to empagliflozin for any outcomes specified in the NICE scope are provided in the provided in the CS documents. Therefore, the comparative efficacy of dapagliflozin and empagliflozin within Subpopulation 3 for these clinical outcomes is unknown.

4.4.4 Subpopulation 4: T2D, eGFR 20-25 mL/min/1.73 m^2

4.4.4.1 Evidence of efficacy of dapagliflozin in Subpopulation 4 (T2D, eGFR 20-25 mL/min/1.73 m^2).

Morbidity: markers of disease progression (eGFR slope and albuminuria)

Evidence for the effects of dapagliflozin on eGFR slope in this subpopulation is provided in Table 11.

Table 11 Summary of the effects of dapagliflozin on eGFR slope in Subpopulation 4 *(T2D, eGFR 20-25 mL/min/1.73 m^2).*

Study	Definition of study sample that is relevant to the subpopulation and comments	Findings	Comments
OPTIMISE-CKD: Svensson, 2024[26]	T2D, eGFR 15-60 mL/min/1.73 m^2 • Correctly aligned in terms of use of T2D group. • eGFR significantly wider	For the 3.4 to 22.6 mg/mmol uACR group, unadjusted eGFR slope was 0.26(95% CI: -0.33, 1.09) [n=796]. The fully adjusted result was 0.41(95% CI: -0.14, 1.13). For the ≥22.6 mg/mmol uACR group, unadjusted eGFR slope was -1.45(95% CI: -2.2, -0.71) [n=684]. The fully adjusted result was -1.73(95% CI: -2.48, -0.72).	eGFR slopes do not meet clinically meaningful thresholds, although estimates are imprecise as shown by the wide confidence intervals and derived from a retrospective analysis of a single-arm cohort. OPTIMISE-CKD includes a significantly wider eGFR range than Subpopulation 4, hence its applicability the Subpopulation 4 is uncertain.
Sources: CS addendum, pp17-18; OPTIMISE - Svensson, 2024[26] Abbreviations: CI = confidence interval; CS = company submission; eGFR = estimated glomerular filtration rate; ESKD = end stage kidney disease; T2D = type 2 diabetes; uACR = urinary albumin creatinine ratio			

EAG comment: eGFR slopes do not meet clinically meaningful thresholds, although estimates are imprecise as shown by the wide confidence intervals and derived from a retrospective analysis of a single-arm cohort. OPTIMISE-CKD includes a significantly wider eGFR range than the definition of Subpopulation 4, hence the applicability of these effect estimates to Subpopulation 4 is uncertain.

Mortality

No evidence is reported for dapagliflozin for Subpopulation 4.

Hospitalisation

No evidence is reported for dapagliflozin for Subpopulation 4.

Health-related quality of life (HRQoL)

No evidence is reported for dapagliflozin for Subpopulation 4.

4.4.4.2 Evidence of efficacy of empagliflozin in Subpopulation 4 (T2D, eGFR 20-25 mL/min/1.73 m^2).

No evidence relating to empagliflozin for any outcomes specified in the NICE scope are provided in the provided in the CS documents. Therefore, the comparative efficacy of dapagliflozin and empagliflozin within Subpopulation 4 for these clinical outcomes is unknown.

4.4.5 Subpopulation 5: T2D, eGFR 75-90 mL/min/1.73 m^2

Evidence for the effects of dapagliflozin on morbidity, hospitalisation and mortality outcomes in this subpopulation are provided in Table 12.

Table 12 Summary of the effects of dapagliflozin on morbidity, hospitalisation and mortality outcomes in Subpopulation 5 *(T2D, eGFR 75-90 mL/min/1.73 m^2).*

Study	Definition of study sample that is relevant to the subpopulation and comments	Findings	Comments
DECLARE-TIMI-58[36]	TD2, eGFR 60-90 mL/min/1.73 m^2 • Correctly aligned in terms of use of T2D group. • eGFR wider than 75-90 mL/min/1.73 m^2	Co-primary endpoint In the 60-90 mL/min/1.73 m^2 eGFR group, the efficacy of dapagliflozin (vs placebo) was HR 0.79 (95% CI: 0.66, 0.95) [n=7732]. This was similar to the <60 mL/min/1.73 m^2 eGFR group [CS addendum, Figure 9, p20]. Renal endpoint In the 60-90 mL/min/1.73 m^2 eGFR group, the efficacy of dapagliflozin (vs placebo) was HR 0.54(95% CI: 0.40, 0.73) [n=7732]. This was similar to the <60 mL/min/1.73 m^2 eGFR group [HR 0.60(95% CI: 0.35, 1.02) [n=1265] and the >90 mL/min/1.73 m^2 eGFR group [0.50(95% CI: 0.34, 0.73)] [n=4162]. The p value for interaction was 0.87 [CS addendum, Figure 9, p20]. Cardiorenal endpoint In the 60-90 mL/min/1.73 m^2 eGFR group, the efficacy of dapagliflozin (vs placebo) was HR 0.76(95% CI: 0.63, 0.93) [n=7732]. This was similar to the <60 mL/min/1.73 m^2 eGFR group [HR 0.77(0.54, 1.09)] [n=1265] and the >90 mL/min/1.73 m^2 eGFR group [0.79(95% CI: 0.63, 0.99)] [n=4162]. The p value for interaction was 0.97[CS addendum, Figure 9, p20].	These results show a clinically meaningful improvement in morbidity outcomes. The inclusion of eGFR 60-75 mL/min/1.73m^2 and the exclusion of participants without ASCVD limits the applicability of these results to Subpopulation 5.
DAPA-HF[37]	No restriction on T2D, no restriction on uACR, eGFR >60 mL/min/1.73 m^2 The relevance of this evidence is very uncertain as none of the characteristics match the subpopulation definition.	<u>HF hospitalisation or urgent HF visit</u> *eGFR >60 mL/min/1.73 m^2* HR for dapagliflozin vs placebo 0.75(95% CI: 0.59, 0.95) [n=2816] <u>CV death, HF hospitalisation or urgent HF visit</u> Dapagliflozin is similarly efficacious (against placebo) between the eGFR<60 mL/min/1.73 m^2 and eGFR>60 mL/min/1.73 m^2 groups [CS addendum, Figure 7, p17]: *eGFR <60* mL/min/1.73 m^2 HR for dapagliflozin vs placebo 0.72(95% CI: 0.59, 0.86) [n=1926]	The lack of reporting by T2D and uACR status limits the applicability of this evidence to Subpopulation 5. The subpopulation of participants with eGFR>*60 mL/min/1.73 m^2* includes an unclear mix of CKD and non-CKD participants with HF.

		eGFR >60 mL/min/1.73 m^2 HR for dapagliflozin vs placebo 0.76(95% CI: 0.63, 0.92) [n=2816] The interaction p value (for the comparison between eGFR groups) is 0.64 <u>CV death</u> Dapagliflozin is similarly efficacious (against placebo), with some uncertainty, between the eGFR<60 mL/min/1.73 m^2 and eGFR>60 mL/min/1.73 m^2 groups [CS addendum, Figure 7, p17]: *eGFR <60* mL/min/1.73 m^2 HR for dapagliflozin vs placebo 0.88(95% CI: 0.69, 1.13) [n=1926] *eGFR >60* mL/min/1.73 m^2 HR for dapagliflozin vs placebo 0.76(95% CI: 0.59, 0.98) [n=2816] The interaction p value (for the comparison between eGFR groups) is 0.41 <u>Death from any cause</u> Dapagliflozin is similarly efficacious (against placebo), with some uncertainty, between the eGFR<60 mL/min/1.73 m^2 and eGFR>60 mL/min/1.73 m^2 groups for the 'Death from any cause' outcome [[CS addendum, Figure 7, p17]: *eGFR <60* mL/min/1.73 m^2 HR for dapagliflozin vs placebo 0.85(95% CI: 0.68, 1.06) [n=1926] *eGFR >60* mL/min/1.73 m^2 HR for dapagliflozin vs placebo 0.81(95% CI: 0.64, 1.02) [n=2816] The interaction p value (for the comparison between eGFR groups) is 0.76	
Sources: CS addendum, pp. 19-21; DECLARE-TIMI-58[36]; DAPA-HF[37] Abbreviations: CI = confidence interval; CS = company submission; eGFR = estimated glomerular filtration rate; ESKD = end stage kidney disease; HR = Hazard Ratio; T2D = type 2 diabetes; uACR = urinary albumin creatinine ratio			

4.4.5.1 Evidence of efficacy of dapagliflozin in Subpopulation 5 (T2D, eGFR 75-90 mL/min/1.73 m^2).

Morbidity

Evidence for the effects of dapagliflozin on the co-primary endpoint of the DECLARE-TIMI 58 RCT, the renal endpoint (40% or greater sustained eGFR decline, end stage renal disease, or renal death) and the cardiorenal endpoint (40% or greater sustained eGFR decline, end stage renal disease, renal death, or cardiovascular death) show a clinically meaningful improvement in morbidity outcomes for people with T2D and eGFR levels in the 60-90 mL/min/1.73 m^2 range.

EAG comment: The inclusion of eGFR 60-75 mL/min/1.73m^2 and the exclusion of participants without ASCVD limits the applicability of these results to subpopulation 5.

Hospitalisation and mortality

Evidence for the effects of dapagliflozin on composite outcomes of HF hospitalisation or urgent HF visit, CV death, HF hospitalisation or urgent HF visit, CV death, death from any cause in this subpopulation are provided in Table 12.

EAG comment: The relevance of this evidence to Subpopulation 5 is very uncertain as none of the characteristics match the subpopulation definition. Furthermore, the subpopulation of participants with eGFR>60 mL/min/1.73 m^2 includes an unclear mix of CKD and non-CKD participants with HF.

Health-related quality of life (HRQoL)

No evidence is reported for dapagliflozin for Subpopulation 5.

4.4.5.2 Evidence of efficacy of empagliflozin in Subpopulation 5 (T2D, eGFR 75-90 mL/min/1.73 m^2).

No evidence relating to empagliflozin for any outcomes specified in the NICE scope are provided in the provided in the CS documents. Therefore, the comparative efficacy of dapagliflozin and empagliflozin within Subpopulation 5 for these clinical outcomes is unknown.

4.5 Adverse events

Safety data is presented in CS Document B, Section 2.3.2.2, with further details provided in the Addendum (Section 6) and company response to clarification questions A2 and B3.

A summary of safety outcomes from the dapagliflozin RCTs and the EMPA-KIDNEY RCT is presented in

Table 13. In the absence of an ITC, safety results for dapagliflozin and empagliflozin were presented as a naïve, unadjusted comparison. Additional summary AE data from the post-hoc subgroup of the DAPA-CKD trial, from the DAPA-HF trial and general AE data reported in the SmPC for all indications of dapagliflozin is presented in Appendix 3.

EAG comment: CS Document B, Section 3.10, states that "dapagliflozin and empagliflozin have been established to have similar safety profiles in the population in scope according to the ITC presented in TA942".

Whilst there is no conclusive evidence of a difference in safety profiles between dapagliflozin and empagliflozin generally (see Section 2.3.2.2), the EAG believes that the evidence presented in the CS is insufficient to conclude that dapagliflozin and empagliflozin have equivalent safety for the population under the NICE scope. The limited number of CKD trials, differences in trial designs and lack of direct and indirect comparisons means that the relative safety of dapagliflozin and empagliflozin is uncertain. In addition, none of the AE data provided within the CS documents or company response to clarification question A2 are specific to any of the five company defined CKD subpopulations.

Table 13 Safety outcomes for dapagliflozin in DAPA-CKD, DAPA-HF and DECLARE-TIMI 58, and empagliflozin in EMPA-KIDNEY

	DAPA-CKD		DAPA-HF		DECLARE-TIMI 58		EMPA-KIDNEY	
	Dapagliflozin (n=2,149)	**Placebo (n=2,149)**	**Dapagliflozin (n=2,368)**	**Placebo (n=2,368)**	**Dapagliflozin (n=8,574)**	**Placebo (n=8,569)**	**Empagliflozin (n=3,304)**	**Placebo (n=3,305)**
Discontinuation due to AE	118 (5.5)	123 (5.7)	111 (4.7)	116 (4.0)	693 (8.1)	592 (6.9)	232 (7.0)	315 (9.5)
Any serious AE	633 (29.5)	729 (33.9)	846 (35.7)	951 (40.2)	2,925 (34.1)	3,100 (36.2)	NR	NR
AEs of interest								
Volume depletion	127 (5.9)	90 (4.2)	178 (7.5)	162 (6.8)	213 (2.5)	207 (2.4)	98 (3.0)	90 (2.7)
Renal AE	155 (7.2)	188 (8.7)	153 (6.5)	170 (7.2)	NR	NR	NR	NR
Fracture	85 (4.0)	69 (3.2)	49 (2.1)	50 (2.1)	457 (5.3)	440 (5.1)	133 (4.0)	123 (3.7)
Amputation	35 (1.6)	39 (1.8)	13 (0.5)	12 (0.5)	123 (1.4)	113 (1.3)	28 (0.8)	19 (0.6)
Major hypoglycaemia	14 (0.7)	28 (1.3)	4 (0.2)	4 (0.2)	58 (0.7)	83 (1.0)	77 (2.3)	77 (2.3)
Diabetic ketoacidosis	0 (0.0)	2 (<0.1)	3 (0.1)	0 (0.0)	27 (0.3)	12 (0.1)	6 (0.2)	1 (<0.1)
Fournier's gangrene	NR	NR	0 (0.0)	1 (<0.1)	NR	NR	NR	NR
Acute kidney injury	NR	NR	NR	NR	125 (1.5)	175 (2.0)	107 (3.2)[a]	135 (4.1)[a]
Genital infection	NR	NR	NR	NR	76 (0.9)	9 (0.1)	1 (<0.1)[b]	1 (<0.1)[b]
UTI	NR	NR	NR	NR	127 (1.5)	133 (1.6)	52 (1.6)[c]	54 (1.6)[c]
Bladder cancer	NR	NR	NR	NR	45 (0.5)	45 (0.5)	NR	NR
Breast cancer	NR	NR	NR	NR	35 (0.4)	35 (0.4)	NR	NR
Hypersensitivity	NR	NR	NR	NR	32 (0.4)	36 (0.4)	NR	NR
Hepatic event	NR	NR	NR	NR	82 (1.0)	87 (1.0)	NR	NR

Source: Table 5, company response to clarification question A2
a Reported as 'serious acute kidney injury'. b Reported as 'serious genital infection'. c Reported as 'serious urinary tract infection'.
Abbreviations: AE: adverse event; NR: not reported; UTI: urinary tract infection.

4.6 EAG commentary of clinical efficacy and safety evidence

The EAG has two general concerns about the relevance and applicability of evidence presented in the CS documents to the NICE scope.

Firstly, for all five CKD subpopulations defined in the company decision problem, the samples of patients from the dapagliflozin studies do not meet the specific subpopulation definitions, mostly in terms of the precise eGFR ranges of the subpopulations and therefore the applicability of the effect estimates and conclusions of the studies may not be applicable to the specific definitions of the subpopulations. Furthermore, for Subpopulation 5 (T2D and eGFR 75-90 mL/min/1.73 m^2), the only evidence available for hospitalisation and mortality outcomes is from a study of individuals with HF, eGFR >60 mL/min/1.73 m^2 and no restrictions on uACR or T2D. Therefore, the relevance of this evidence to Subpopulation 5 is very uncertain. Evidence was not available for all outcomes defined in the NICE scope (Table 1) for any of the five company defined CKD subpopulations, and no HRQoL, nor AE data is available for any of the five CKD subpopulations. Therefore, dapagliflozin efficacy in terms of these clinical outcomes remains uncertain within all five CKD subpopulations.

In response to clarification question A4, the company were asked to provide additional evidence that were more closely aligned to the five CKD subpopulations using individual participant data (IPD) from the dapagliflozin studies, where available. The company did not provide these, on the basis that each sample would be small and therefore produce imprecise results.

The company has acknowledged the lack of direct alignment of the dapagliflozin studies with the five CKD subpopulations, and that direct evidence for the efficacy of dapagliflozin within the subpopulations has not been demonstrated. Therefore, the company has also attempted to demonstrate that within each of the 'T2D' and 'no T2D' populations:

1. differing ranges of eGFR *considered alone* (with all uACR categories that are present being pooled) do not markedly change the efficacy of dapagliflozin (CS addendum, pp. 23-24)
2. differing categories of uACR *considered alone* (with all eGFR ranges that are present being pooled) do not markedly change the efficacy of dapagliflozin (CS addendum pp. 21-22)

This approach generally suggests that samples with lower uACR values (<22.6 mg/mmol) experience similar dapagliflozin efficacy to populations with higher uACR values (≥22.6 mg/mmol). Similarly, this approach generally suggests that effectiveness results are consistent across eGFR values. However, this approach does not account for the possibility of interactions between uACR and eGFR. In response to a clarification question A9 request from the EAG, the company replied that analyses exploring the interaction of multiple variables are not available.

Furthermore, clinical advice noted that eGFR and uACR may contribute independently and additively to morbidity and mortality outcomes, although whether and how these may interact with dapagliflozin treatment effects is uncertain.

Secondly, no evidence relating to empagliflozin for any outcomes specified in the NICE scope are provided in the CS documents. Evidence provided by the company (CS addendum, Table 3 and in response to clarification question A13) from the EMPA-KIDNEY trial is summarised in Table 14. The company were 'not aware' of any other sources of relevant evidence for empagliflozin (response to clarification question A11).

The lack of relevant evidence for empagliflozin in these subpopulations means it is not possible to directly compare effect sizes of efficacy or safety for dapagliflozin and empagliflozin in any of the five CKD subpopulations. In response to clarification questions A10 and A12, the company confirmed that following a feasibility assessment, an ITC of dapagliflozin and empagliflozin using either the DAPA-CKD trial or the observational OPTIMISE-CKD data and the EMPA-KIDNEY trial were not possible due to "*lack of comparable datasets, introducing significant bias and violating the assumptions required for both anchored and unanchored indirect comparison methods.*"

To the knowledge of the company and to the EAG, the only existing NMA including both dapagliflozin and empagliflozin was conducted to inform TA942 (see Section 2.3.2.2 for further details). The company acknowledge that the relevance of the results of this NMA to the five CKD subpopulations is very limited, only partially including populations which meet the definition of Subpopulation 1 but with no comparative data available for the populations defined in Subpopulations 2 to 5 (response to clarification question A10).

Furthermore, the EAG notes the lack of alignment of the outcome data available for empagliflozin (i.e. the primary and secondary endpoint data as defined within EMPA-KIDNEY) with the outcomes defined in the NICE scope and also the lack of concordance of the available empagliflozin evidence with the evidence presented in the CS documents for dapagliflozin for the five CKD subpopulations. Therefore, the comparative efficacy of dapagliflozin and empagliflozin within each of the five CKD subpopulations for these clinical outcomes is unknown and the EAG does not consider that clinical similarity has been demonstrated for the populations and for the outcomes defined in the NICE scope.

Table 14 Empagliflozin subpopulation analyses for primary endpoint and key secondary endpoints in EMPA-KIDNEY (presented in Appendix E of TA942)

Subpopulations in this review		Empagliflozin subpopulation	Empagliflozin versus placebo (HR [95% CIs])				Absolute difference in mean annual rate of change in eGFR	
			Progression of kidney disease or death from cardiovascular causes	Time to occurrence of all-cause hospitalisation [d]	Time to first occurrence of HHF or CV death	Time to adjudicated death from any cause	Annual rate of change in eGFR from 2 months to final follow-up (total slope)	Annual rate of change in eGFR from 2 months to final follow-up (chronic slope)
1	Without T2D, eGFR ≥20–45 mL/min/1.73m^2, uACR <22.6 mg/mmol	uACR <3.4 mg/mmol	1.01 (0.66, 1.55)	0.80 (0.65, 0.99)	0.99 (0.58, 1.70)	0.94 (0.59, 1.51)	0.17 (-0.27, 0.60)	0.78 (0.32, 1.23)
		uACR 3.4–34 mg/mmol[a]	0.91 (0.65, 0.78)	0.83 (0.69, 0.99)	0.85 (0.57, 1.27)	0.97 (0.68, 1.40)	0.46 (0.09, 0.83)	0.1.20 (0.81, 1.59)
2	Without T2D, eGFR ≥20–25 mL/min/1.73m^2, uACR ≥22.6 mg/mmol	eGFR <30 mL/min/1.73m^2 [b]	0.73 (0.62, 0.86)	0.88 (0.75, 1.03)	0.99 (0.71, 1.39)	0.86 (0.63, 1.16)	0.51 (0.15, 0.87)	1.01 (0.63, 1.39)
4	with T2D, eGFR ≥20–25 mL/min/1.73m^2, irrespective of uACR							
3	With T2D, eGFR >75–90 mL/min/1.73m^2, uACR ≥22.6 mg/mmol	eGFR >45 mL/min/1.73m^2 [c]	0.64 (0.44, 0.93)	0.91 (0.72, 1.14)	0.98 (0.39, 2.46)	0.67 (0.25, 1.75)	1.19 (0.92, 1.47)	2.01 (1.53, 2.49)
5	With T2D, eGFR >75–90 mL/min/1.73m^2, irrespective of uACR							
Overall trial population			0.72 (0.64, 0.82)	0.68 (0.78, 0.95)	0.84 (0.67, 1.07)	0.87 (0.70, 1.08)	0.75 (0.54, 0.96)	1.37 (1.16, 1.59)

Source: Table 12, company response to clarification questions A10 and A12 taken from the EMPA-KIDNEY Collaborative Group.17 NICE. TA942 Appendix E.5
For annual rate of change in eGFR, a value over 0 indicates a benefit of empagliflozin versus placebo; a value below 0 indicates a benefit of placebo versus empagliflozin. a Outcomes for empagliflozin for patients with uACR 3.4–34 mg/mmol are not reported separately for different levels of eGFR or T2D status. b Outcomes for empagliflozin for patients with eGFR <30 mL/min/1.73m^2 are not reported separately for different levels of uACR or T2D status. c Outcomes for empagliflozin for patients with eGFR >45 mL/min/1.73m^2 are not reported separately for different levels of uACR or T2D status. d First and recurrent combined.
Abbreviations: eGFR: estimated glomerular filtration rate; HR: hazard ratio; T2D: type 2 diabetes; uACR: urine albumin-creatinine ratio.

5 CRITIQUE OF COST COMPARISON EVIDENCE

The appropriateness of assessing the cost-effectiveness of dapagliflozin in the context of a cost comparison analysis relies on the validity of the assumption of equivalent efficacy, in terms of the outcomes specified in the NICE scope, i.e., morbidity, including cardiovascular outcomes, disease progression (such as kidney replacement, kidney failure) and markers of disease progression (such as eGFR), albuminuria), mortality, hospitalisation, adverse effects of treatment, and health-related quality of life for dapagliflozin and its comparator of empagliflozin. The EAG critique of the cost comparison evidence assumes that it is appropriate for the assessment to proceed as a cost comparison analysis and seeks to answer under what circumstances dapagliflozin is likely to be cost saving or equivalent in cost to the selected comparator.

The EAG highlights throughout the subsequent subsections, features of the cost comparison that may be affected by uncertainty surrounding the validity of assuming equivalent efficacy and safety of dapagliflozin to empagliflozin.

5.1 Summary of costs and assumptions

The company presented a cost comparison analysis between dapagliflozin 10mg once daily and empagliflozin 10mg once daily, henceforth referred to as dapagliflozin and empagliflozin, respectively.[9, 10] Empagliflozin 25mg once daily is indicated as a higher dose for patients with T2D. The company identified studies for their submission by selecting key studies presented in the previous related technology appraisals: TA775 and TA942 and supplemented them with RWE for dapagliflozin (Section 4.1).

The costs included in the company's cost comparison are drug acquisition (CS addendum, Table 6), administration costs (CS addendum, Table 6), and adverse events costs (CS addendum, Table 8). Costs are estimated for a time horizon of five years. All costs are expressed in 2022/23 prices and undiscounted. The company decision problem (CS, Document B, Table 1) defines five CKD subpopulations. However, the resource use and associated costs are not presented for each subpopulation considered. In response to clarification question B2, the company indicated that there is no scientific or clinical rationale to believe that dapagliflozin incurs different resource use, AEs and discontinuation rates across the five CKD subpopulations. A summary of costs applied in the cost comparison for the company base-case analysis after clarification stage is presented in Table 15. A brief description of the parameterisation and assumptions of the cost comparison are presented in the following sub-sections.

Table 15 Summary of costs in the cost comparison analysis

	Dapagliflozin	Empagliflozin	Source	Comment
Dose	10mg once daily	10 mg once daily		
Mode of administration	Oral	Oral		
Drug acquisition unit cost	£36.59 per pack, pack size 28 (list price)	£36.59 per pack, pack size 28 (list price)	British National Formulary[19, 20]	
Annual drug acquisition cost	£477 (list price)	£477 (list price)		
Administration cost	£0	£0		
Monitoring costs	Not provided	Not provided	-	Due to the lack of published accurate data on the frequency of resource use and the expected clinical equivalence between dapagliflozin and empagliflozin, the current cost comparison analysis does not include resource use and costs associated with disease monitoring
Adverse Events: Annual probability				
Volume depletion	0.031	0.031	DAPA-CKD[2]	Empagliflozin assumed the same as dapagliflozin due to similar mechanism of action, and expected equivalent efficacy and safety profiles
Major hypoglycaemic event	0.003	0.003		
Bone fractures	0.020	0.020		
Amputation	0.009	0.009		
Genital infections	[redacted]	[redacted]	DECLARE-TIMI 58[39]	Calculated based on the event incidence rate in DECLARE-TIMI 58 and proportion of patients with comorbid T2D in the base case
UTI	[redacted]	[redacted]		
Adverse Events: Costs				
Volume depletion	£49.00	£49.00	PSSRU 2023[40]	Assumed one GP visit
Major hypoglycaemic event	£468.96	£468.96	Hammer (2009)[41]	Severe hypoglycaemic events
Bone fractures	£2,023.00	£2,023.00	NHS Reference Costs 2022/23[42]	Total HRG, weighted average of HE11, HE21, HE41, HE31, HE51 and HE71
Amputation	£12,506.38	£12,506.38	Alva (2015)[43]	Inpatient care cost and outpatient care cost
Genital infections	£49.00	£49.00	PSSRU 2023[40]	Assumed one GP visit
UTI	£49.00	£49.00	PSSRU 2023[40]	Assumed one GP visit
Abbreviations: CS = company submission; HRG = Healthcare Resource Groups; T2D = type 2 diabetes; UTI = urinary tract infection.				

5.1.1 Acquisition costs

Acquisition costs for dapagliflozin and empagliflozin are presented for the drug's list price from the British National Formulary (BNF) 2024, which are £36.59 per 28-dose pack for each drug, with no

confidential commercial arrangements.[19, 20] The annual and total drug acquisition costs in Table 15 assume the dosing schedules stipulated in the intervention and comparators' SmPC documents. The company's analysis did not consider the effect of dose interruptions or adjustment upon acquisition costs. The company stated that for patients with CKD with T2D, there is potential for empagliflozin to result in a higher cost than dapagliflozin (CS Document B, Section 4.6 and CS addendum, p37). The SmPC for empagliflozin suggests an increase in dosage to 25 mg for patients with T2D who have an eGFR ≥60 mL/min/1.73 m^2 and need tighter glycaemic control.[10]

5.1.2 Administration cost

Both treatments are administered orally, and the cost comparison analysis assumed no administration costs.

5.1.3 Adverse Events

The cost comparison analysis included the most common serious AEs reported in the DAPA-CKD trial. Although genital and urinary tract infections (UTIs) were not routinely collected in DAPA-CKD trial, these AEs were included in the analysis for the proportion of patients with comorbid T2D at baseline, based on the data from the DECLARE-TIMI 58 trial. Both DAPA-CKD and DECLARE-TIMI 58 trials provided AE data only for dapagliflozin and the company assumed the same safety profile for empagliflozin. The company referred to TA942, which was deemed to demonstrate similar safety profiles in the population in scope between empagliflozin and dapagliflozin, and to the opinions of clinical experts, who expected similar safety profiles for both treatments (CS Document B, Section B.3.10). Available AE data for empagliflozin from the EMPA-KIDNEY trial were compared to safety data from the dapagliflozin RCTs, although none were specific to any of the CKD subpopulations defined in the CS (Table 13). Included AEs and the annual probabilities of their occurrence and associated costs per event are provided in Table 15.

5.1.4 Monitoring costs

Resource use associated with disease monitoring was assumed to be the same for dapagliflozin and empagliflozin based on the expected similar mechanism of action, efficacy and safety profile (CS addendum, p40). The company stated that this assumption was accepted for decision making in the cost comparison analysis conducted in TA942, and formed the basis of the NICE recommendation for empagliflozin.[4] Further, the company did not include any resource use associated with disease monitoring and stated that exclusion of these costs was due to the lack of published accurate data on the frequency of resource use and the expected clinical equivalence between dapagliflozin and empagliflozin.

5.1.5 Treatment discontinuation rates

The discontinuation rate of dapagliflozin was derived from the DAPA-CKD trial, with a constant probability of discontinuation applied to all patients receiving treatment with dapagliflozin in each modelled cycle. Although DAPA-CKD trial provides data only for dapagliflozin, the company assumed the same discontinuation probabilities for empagliflozin. The company assessed this assumption as valid due to the similar mechanism of action of the two drugs, their expected clinical efficacy equivalency and similar safety profile (CS addendum, pp. 37-38).

5.1.6 Time horizon

The cost comparison analysis presented results over a 5-year time horizon from the UK National Health Service (NHS) perspective. No discount rate was applied in the analysis.

5.1.7 Assumptions

The key assumptions underlying the company's cost comparison analysis are as follows:

- Dapagliflozin is the intervention and empagliflozin is the comparator for the five CKD subpopulations considered in the company decision problem (Table 1).
- All resource use and costs are assumed to be the same across the five CKD subpopulations due to the lack of subpopulation-specific evidence.
- Equivalent clinical effectiveness, in terms of morbidity including cardiovascular outcomes, disease progression (such as kidney replacement, kidney failure) and markers of disease progression (such as eGFR, albuminuria), disease-related mortality, and health-related quality of life between dapagliflozin and its comparator of empagliflozin.
- Equivalent safety profile between dapagliflozin and empagliflozin. The probabilities of different AEs occurring was based on the DAPA-CKD trial, which provided data only for dapagliflozin. The probabilities of AEs for empagliflozin were assumed to be the same. The EMPA-KIDNEY trial provided safety outcomes for empagliflozin, but the company did not use these data in their cost comparison analysis.
- Resource use and costs associated with disease management are assumed the same for dapagliflozin and empagliflozin. However, this is an assumption and resource use associated with disease management was excluded from the analysis due to the lack of data.
- Patients discontinue treatment with dapagliflozin in the company's base case analysis based on data derived from the DAPA-CKD trial, which provides data only for dapagliflozin. The company assumed the same probability of discontinuation for empagliflozin justifying this assumption with the similar mechanism of action of the two drugs, their expected clinical efficacy equivalency and similar safety profile.
- A time horizon of 5 years is used to compare the costs of dapagliflozin and empagliflozin.
- Discounting of costs is not included in the company's base-case analysis.

5.2 EAG critique of cost comparison analysis

The EAG conducted a technical validation of the executable model by cross-checking values against the company submission and auditing formulae. The EAG detected no errors in the executable model.

The EAG critique focuses on the following aspects of the cost comparison analysis:

- Uncertainty in the existing clinical evidence for equivalence of treatment effect;
- Adverse events;
- Acquisition costs
- Administration costs;
- Treatment discontinuation;
- Time horizon and discounting.

5.2.1 Uncertainty in the existing clinical evidence

As discussed in Section 4.6, the EAG is concerned that no evidence for the efficacy of empagliflozin is provided for any of the five CKD company defined subpopulations. The lack of relevant evidence for empagliflozin in these subpopulations means it is not possible to directly compare effect sizes of efficacy or safety for dapagliflozin and empagliflozin in any of the five CKD subpopulations. Therefore, the comparative efficacy of dapagliflozin and empagliflozin within each of the five CKD subpopulations for these clinical outcomes is unknown and the EAG does not consider that clinical similarity has been demonstrated for the populations and for the outcomes defined in the NICE scope.

5.2.2 Adverse events

A key assumption in a cost comparison analysis is the equivalence (or very similar) safety profile between the interventions under comparison. Only substantial differences between interventions in costs directly relating to health outcomes that indicate that the intervention and comparator may not provide similar overall health benefits should be considered. In their cost comparison analysis, the company included the most common serious AEs reported for dapagliflozin in the DAPA-CKD trial, and genital and UTIs that occurred in patients with comorbid T2D at baseline in the DECLARE-TIMI 58 trial. The company made an underlying assumption that the safety profile of empagliflozin is comparable between the treatments and assumed the same rates of the adverse events even though the underlying evidence included only patients receiving dapagliflozin.

The company referred to TA942, which was deemed to demonstrate similar safety profiles in the population considered between empagliflozin and dapagliflozin, and to the opinions of clinical experts, who also expect similar safety profiles to be shared by both treatments. As further described in Section 4.5, the company provided data on the adverse effects of empagliflozin from the EMPA-KIDNEY trial compared to adverse event data from the dapagliflozin RCTs, which suggested similar

adverse effects across treatments, including. suggested similar levels of ketoacidosis and lower limb amputation across the treatments, although none of the adverse event data provided were specific to any of the subpopulations. Although the safety profile seems similar between the treatments, the EAG highlights the uncertainty in this assumption because of the lack of specific data confirming this assumption. Amputation is associated with high costs and the safety outcome for this AE differs slightly in the DAPA-CKD (proportion of patients: 1.6%, Table 13) and EMPA-KIDNEY (proportion of patients: 2.8%; Table 13) trials. Major hypoglycaemic event was also associated with slightly different safety outcomes, which were less favourable for empagliflozin (2.3% for empagliflozin and 0.7% for dapagliflozin). However, the company included only serious AEs from DAPA-CKD in their base-case cost comparison analysis and did not provide comparative estimates from EMPA-KIDNEY.

HRQoL impact of the AEs is not included. The EAG notes that if the differences in AEs are considered sufficiently important for inclusion in the cost comparison, then the HRQoL impact (utility decrement) for the AEs should also be considered.

5.2.3 Acquisition costs

Acquisition costs for dapagliflozin and empagliflozin are presented for the drugs' list price from the BNF 2024.[19] The annual and total drug acquisition costs in Table 15 assume the dosing schedules stipulated in the intervention and comparator's SmPCs. The company's analysis did not consider the effect of dose interruptions upon acquisition costs. The company indicated that SmPC for empagliflozin suggests an increase in dosage to 25 mg for patients with T2D who have an eGFR ≥60 mL/min/1.73 m^2 and need tighter glycaemic control, which may lead to higher acquisition costs for empagliflozin than for dapagliflozin.[10] The EAG discussed this assumption with the clinical experts who indicated that the increased dose of empagliflozin in patients with T2D may also lead to an improved treatment effectiveness. Thus, the assumption that the increased dose of empagliflozin would only impact its costs and have no impact on its effectiveness may be too simplified and is not supported by any evidence. This assumption was not included in the company's base-case analysis.

5.2.4 Administration costs

Given that both treatments are administrated orally, the cost comparison analysis assumed that there were no administration costs, which EAG assessed as a reasonable assumption.

5.2.5 Treatment discontinuation

The discontinuation rate of dapagliflozin was derived from the DAPA-CKD trial and assumed the same for empagliflozin. Although this assumption was based on the similar mechanism of action of the two drugs, their expected clinical efficacy equivalency and similar safety profile, no empirical data are provided to support this assumption.

5.2.6 Time horizon and discounting

The cost comparison analysis presented results over a 5-year time horizon from the UK National Health Service (NHS) perspective. No justification for the 5-year time horizon was provided. The analysis performed for TA775 and TA942 implemented a lifetime and 50-year time horizons, respectively. Furthermore, no discount rate was applied in the company's base-case analysis. The EAG indicates that a discount rate should be applied when a time horizon over 1 year is used. However, given that the company assumed all resource use and costs to be identical for dapagliflozin and empagliflozin, a different time horizon or discount rate would not change the results.

6 COMPANY AND EAG COST COMPARISON RESULTS

The following section details the results of the company's base case and scenario analyses, followed by the EAG's preferred base case. All results include the list price for dapagliflozin and empagliflozin.

6.1 Company cost comparison results

The company presented mean annual costs per patient for dapagliflozin and empagliflozin. The results of the company's base case can be seen in Table 16.

Under the company's assumptions and using the lists prices, dapagliflozin has a 5-year drug acquisition cost of £2,083.50, which is equivalent to the acquisition cost of empagliflozin. Furthermore, both dapagliflozin and empagliflozin are associated with AE costs of [redacted].

The company did not present any sensitivity or scenario analyses.

Table 16 Company base-case results (adapted from Table 9, pg. 41, CS addendum)

Technology	Drug Acquisition Costs	Administration Costs	AE Costs	Disease Management Costs	Total Costs
Dapagliflozin	£2,083.50	£0	[redacted]	[redacted]	[redacted]
Empagliflozin	£2,083.50	£0	[redacted]	[redacted]	[redacted]
Incremental value	£0	£0	£0	£0	£0

6.2 Results of EAG preferred base case

The company base-case analysis assumed that all resource use and associated costs of dapagliflozin and empagliflozin were equivalent. All estimates used in the cost comparison analysis were derived from the dapagliflozin studies and assumed to be the same for empagliflozin. These assumptions were based on the company's expectations due to similar mechanism of action, efficacy and safety profiles and were not supported by any direct evidence. The evidence provided to support a clinically similar efficacy and safety profile is very uncertain (Section 4.6). Consequently, due to the lack of underlying evidence, the EAG could not perform any evidence-based scenario analyses.

7 EQUALITIES AND INNOVATION

The company did not raise any equality issues (CS Document B, Section B.1.4).

As per the original TA775 appraisal, CKD continues to disproportionally affect people from Black, Asian, and minority ethnic groups and lower socioeconomic backgrounds, and people from these groups are likelier to have faster progression to kidney failure and to die earlier.[44] In addition, ACE inhibitors or ARBs uptake differs by ethnicity and socioeconomic status.[45] Given the alignment in populations between dapagliflozin and empagliflozin in the company decision problem and the similarity between the two therapies in mode of administration and expected resource use, the EAG believes that equality issues are likely to affect dapagliflozin and empagliflozin similarly.

The critique of the company's case for similarity between dapagliflozin and empagliflozin is discussed in Section 2.3.2.1 and Section 4.6.

8 EAG COMMENTARY ON THE ROBUSTNESS OF EVIDENCE SUBMITTED BY THE COMPANY

8.1 Conclusions

The company decision problem only includes five CKD subpopulations for which empagliflozin is recommended and dapagliflozin is not. The company chose to omit the subpopulations from the NICE scope where both dapagliflozin and empagliflozin are recommended from its decision problem, because it was included in the previous TA775. Whilst the EAG accepts that evidence for the five CKD subpopulations is required to broaden the indication for dapagliflozin in line with that of empagliflozin (TA942), the EAG does not consider that it is valid to assume clinical similarity and cost-equivalence in the populations for which dapagliflozin and empagliflozin are both recommended, based on the conclusions of TA942 and that robust evidence is required to show equivalence in effectiveness and safety between dapagliflozin and empagliflozin to inform a cost comparison across the entire NICE scope population for the current appraisal.

No evidence was presented for the five CKD subpopulations defined in the company decision problem specifically. Due to design limitations and the limited overlap between the evidence in the CS and the five CKD subpopulations defined by the company, the applicability of the evidence to the company decision problem is uncertain. No new systematic review was presented in the CS. Whilst there is no evidence from existing systematic reviews that the effectiveness of dapagliflozin and empagliflozin differ significantly by T2D, baseline eGFR and uACR, the evidence is insufficient to demonstrate equivalence in effectiveness and safety between these therapies across the NICE scope population. Whilst the EAG agrees that an adjusted ITC comparing the efficacy and safety of dapagliflozin and empagliflozin in the five CKD subpopulations is not feasible, the lack of adjusted ITC significantly limits the strength of the CS.

The company's base-case analysis for their cost comparison assumed that all resource use and associated costs of dapagliflozin and empagliflozin were equivalent. All estimates used in the cost comparison analysis were derived from the dapagliflozin studies and assumed to be the same for empagliflozin. These assumptions were based on the company's expectations due to similar mechanism of action, efficacy and safety profiles and were not supported by any direct evidence.

Overall, the case for a cost comparison between dapagliflozin and empagliflozin is highly uncertain.

8.2 Areas of uncertainty

Robust evidence, preferably from an RCT, is required to show equivalence in effectiveness and safety between dapagliflozin and empagliflozin to inform a cost comparison across the entire NICE scope population, including the five CKD subpopulations as defined in the CS. In the absence of an RCT in the relevant populations, IPD from existing dapagliflozin studies may be used, where available, to inform conclusions on the effectiveness and safety of dapagliflozin in the five CKD subpopulations against placebo and empagliflozin. However, the EAG acknowledges that the feasibility of an ITC against empagliflozin is likely to be limited without access to empagliflozin trial data in matching subpopulations.

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APPENDICES

APPENDIX 1. SUMMARY OF SYSTEMATIC REVIEW EVIDENCE FOR SGLT2 INHIBITORS FOR CKD

Table 17 Summary of systematic review and meta-analyses of SGLT2 inhibitors for CKD

Study	Study selection criteria	No. of studies & synthesis method	Main results	CKD subpopulation	Heterogeneity	Conclusions and uncertainties
Baigent (2022)[17]	**Population:** Adults (≥18 years), with heart failure or chronic kidney disease, or with type 2 diabetes and high risk of atherosclerotic cardiovascular disease. **Intervention:** SGLT2 inhibitors - dapagliflozin 10mg, canagliflozin 100-300mg, ertugliflozin 5mg or 15mg, empagliflozin 10 mg or 25 mg, sotagliflozin 200 - 400mg, canagliflozin 100mg. Comparator: Placebo. **Outcome:** Kidney disease progression, acute kidney injury, and a composite of cardiovascular death or hospitalisation for heart failure, death from cardiovascular and non-cardiovascular disease or hospitalisation for heart failure ketoacidosis and lower limb amputation. Study design: RCTs	Total: 13 Dapagliflozin: 4 Empagliflozin: 4 Pairwise meta-analysis	Compared with placebo, allocation to an SGLT2 inhibitor: • reduced the risk of kidney disease progression by 37% (RR 0.63, 0.58 – 0.69). (similar for patients with and without diabetes). • acute kidney injury: RR 0.77 (0.70 – 0.84). • cardiovascular death or hospitalisation for HF: RR 0.77 (0.74 – 0.81). • cardiovascular death: RR 0.86 (0.81 – 0.92). • did not significantly reduce risk of non-cardiovascular death. • based on absolute effects, the absolute benefits of SGLT2 inhibition outweighed any serious hazards of ketoacidosis or amputation.	The RRs based on the results of the four CKD trials were similar. In these trials, SGLT2 inhibitors reduced the risk of kidney disease progression by 40% (0·60, 0·53–0·69).	Results were broadly similar irrespective of baseline eGFR, both for patients with, and without diabetes. Tests for heterogeneity by diabetes status were not statistically significant. There was no statistically significant trend in analyses by baseline uACR and by baseline eGFR.	SGLT2 inhibitors safely reduce the risk of kidney disease progression, acute kidney injury, cardiovascular death, and hospitalisation for heart failure in patients with chronic kidney disease or heart failure, irrespective of diabetes status. For the CKD trials, results were similar across the range of primary kidney diagnoses studied. The data from these large trials therefore support a central role for SGLT2 inhibitors as a disease-modifying therapy for chronic kidney disease, irrespective of diabetes status, primary kidney diagnosis, or level of kidney function.

Study	Study selection criteria	No. of studies & synthesis method	Main results	CKD subpopulation	Heterogeneity	Conclusions and uncertainties
TA942 (2024)[4]	**Population:** CKD and CKD populations, with or without other comorbidities such as T2D or HF. **Interventions**: Empagliflozin. **Comparator:** Canagliflozin, dapagliflozin and finerenone. **Outcome:** Composite renal outcomes, progression to ESKD/ESRD, HHF, CV death, a composite of HHF or CV death, 3P-MACE+, all-cause mortality, and ACH. The composite renal outcomes were defined as follows: 1.) eGFR decline, ESKD, or renal death or 2.) eGFR decline, ESKD, or CV or renal death; for both composite outcomes eGFR decline thresholds of 40%, 50%, and 57% were considered. Study design: RCTs	Total: 13 Dapagliflozin: 5 Empagliflozin: 4 Network meta-analysis	Empagliflozin was associated with a lower rate of ACH admissions than finerenone (OR 0.92 [0.85-1.00]) and dapagliflozin was associated with a lower rate of HHF than finerenone (OR 0.64 [0.41-0.98]). No other statistical differences were found between interventions. However, the SGLT2 inhibitors showed numerically better efficacy than finerenone for most included outcomes, with generally similar SGLT2 inhibitor treatment effects.	NR	Assessments of heterogeneity were undertaken; all but one of these tests yielded non-significant results. Across studies, definitions of target population differed. Studies included patients with and without T2D and HF. Patients were broadly similar in terms of the distribution of age, sex, BMI but the proportion of Asian patients varied widely across studies. The baseline distribution of eGFR and uACR varied widely between studies, reflecting different study inclusion criteria.	Compared to finerenone, empagliflozin was associated with a significantly lower rate of ACH admissions and dapagliflozin was associated with a significantly lower rate of HHF. Limitations included that the definitions of CKD varied across included studies for inclusion criteria and subgroups. In addition, estimation of relative treatment effects for ACH was limited by a lack of reported data for canagliflozin and dapagliflozin.

Study	Study selection criteria	No. of studies & synthesis method	Main results	CKD subpopulation	Heterogeneity	Conclusions and uncertainties
Qiu (2021)[18]	**Population:** Patients with type 2 diabetes, chronic heart failure, and chronic kidney disease. **Intervention:** SGLT2 inhibitors – dapagliflozin, empagliflozin, ertugliflozin, and canagliflozin. Comparator: Placebo. **Outcome:** Fracture, diabetic ketoacidosis, amputation, urinary tract infection, genital infection, acute kidney injury, severe hypoglycaemia, and volume depletion. **Study design:** Pair-wise meta-analysis.	Total: 8 Dapagliflozin: 3 Empagliflozin: 2	Compared with placebo, SGLT2 inhibitors significantly reduced the risk of acute kidney injury (RR 0.75, 95% CI 0.66–0.85) while showing the reduced trend in the risk of severe hypoglycaemia (RR 0.86, 0.71–1.03). SGLT2 inhibitors significantly increased the risks of diabetic ketoacidosis (RR 2.57, 1.53 – 4.31), genital infection (RR 3.75, 3.00–4.67), and volume depletion (RR 1.14, 1.05–1.24). SGLT2 inhibitors showed increased trends in the risks of fracture (RR 1.07, 0.99–1.16), amputation (RR 1.21, 0.97–1.51), and urinary tract infection (RR 1.07, 0.99–1.15). Effects of SGLT2 inhibitors on the safety outcomes were consistent across disease types and across the four SGLT2 inhibitors.	Fracture risk: RR = 1.23 (0.99, 1.16) Diabetic ketoacidosis: RR = 0.20 (0.01, 4.16) Amputation risk: RR = 0.90 (0.57, 1.41) Urinary tract infection risk: RR = 1.33 (0.68, 2.60) Genital infection: RR = 3.00 (0.12, 73.60) Acute kidney injury: RR = 0.75 (0.50, 1.13) Severe hypoglycaemia: RR = 0.50 (0.26, 0.95) Volume depletion: RR = 1.41 (1.08, 1.84)	Heterogeneity tests found no statistically significant heterogeneity except amputation risk (I^2=58.9%, p=0.017).	SGLT2 inhibitors significantly reduce the risk of acute kidney injury and show the reduced trend in the risk of severe hypoglycaemia. The SGLT2 drug class significantly increases the risks of diabetic ketoacidosis, genital infection, and volume depletion, and show the increased trends in the risks of fracture, amputation, and urinary tract infection, regardless of type of underlying diseases and type of SGLT2 inhibitors.

Source: Baigent (2022)[17], TA942 (2024)[4] and Qiu (2021)[18]
Abbreviations: ACH= all-cause hospitalisations; BMI = body mass index; CKD = chronic kidney disease; CV= cardiovascular; eGFR = estimated glomerular filtration rate; ESKD = end-stage kidney disease; ESRD = end stage renal disease; HF= heart failure; HHF = hospitalisation for heart failure RR= risk ratio; RCT = randomised controlled trial; SGLT2=Sodium-glucose cotransporter-2; T2D = type 2 diabetes; uACR = urinary albumin-creatinine ratio

APPENDIX 2. CHARACTERISTICS OF PATIENTS WITH CHRONIC KIDNEY DISEASE IN ENGLAND[29]

Table 18. Baseline Characteristics of CKD population (eGFR 25-75, all uACR; T2D, no T2D and overall)

Variable		All	T2D	No T2D
Prevalent CKD: n(%)		[redacted]	[redacted]	[redacted]
Age (years)	n (missing)	[redacted]	[redacted]	[redacted]
	Mean (SD)			
	Median (IQR)			
	Min - Max			
Gender	n (missing)			
	Male			
	Female			
BMI	n (missing)			
	Mean (SD)			
	Median (IQR)			
	Min - Max			
Ethnicity	n (missing)			
	White			
	Asian			
	Black			
	Mixed			
	Other			
Smoking Status	n (missing)			
	Never			
	Former			
	Current			
CKD stages using most recent eGFR measure	n (missing)			
	G2 (60-89)			
	G3a (45-59)			
	G3b (30-44)			
	G4 (15-29)			
uACR	n (missing)			
	<30 mg/g			
	30-300 mg/g			
	>=300 mg/g			
uACR	n (missing)			
	<30 mg/g			
	30-200 mg/g			
	>=200 mg/g			
T2D (CPRD diagnosis)				
Glomerulonephritis				
ACEi				
ARB				
MRA				
Diuretics				
Serum Potassium (mmol/L)	n (missing)			
	Mean (SD)			
	Median (IQR)			
	Min - Max			
SBP	n (missing)			
	Mean (SD)			
	Median (IQR)			
	Min - Max			
Haemoglobin (g/L)	n (missing)			
	Mean (SD)			
	Median (IQR)			
	Min - Max			
HF				

Variable		All	T2D	No T2D
MI		[redacted]	[redacted]	[redacted]
Stroke				
ARB or ACEi treatment				
Statins				
Antiplatelet or anticoagulant				
Beta blockers		[redacted]	[redacted]	[redacted]
Dapagliflozin				
Empagliflozin				
Canagliflozin				
K binders				
Phosphate binders				
CKD diagnosis				

Source: Data on file. ID: REF-135938 December 2021,AstraZeneca UK Ltd [29]

Abbreviations: ACEi = angiotensin converting enzyme inhibitor; ARB = angiotensin-receptor blocker; BMI = body mass index; CKD = chronic kidney disease; CPRD = clinical practice research datalink; eGFR = estimated glomerular filtration rate; G2 = eGFR of 60-89 ml/min/1.73m^2 ; G3a = eGFR of 45-59 ml/min/1.73m^2; G3b = eGFR of 30-44 ml/min/1.73m^2 ; G4 = eGFR of 15-29 ml/min/1.73m^2; HF = heart failure; IQR = interquartile range; K = potassium; MI = myocardial infarction; MRA = mineralocorticoid receptor antagonists; SBP = systolic blood pressure; SD = standard deviation; T2D = type 2 diabetes; uACR = urinary albumin-creatinine ratio

Table 19 Baseline Characteristics of CKD population (eGFR 25-75, uACR<22.6mg/mmol; T2D, no T2D and overall)

Variable		All	T2D	No T2D
Prevalent CKD: n(%)		[redacted]	[redacted]	[redacted]
Age (years)	n (missing)	[redacted]	[redacted]	[redacted]
	Mean (SD)			
	Median (IQR)			
	Min - Max			
Gender	n (missing)			
	Male			
	Female			
BMI	n (missing)			
	Mean (SD)			
	Median (IQR)			
	Min - Max			
Ethnicity	n (missing)			
	White			
	Asian			
	Black			
	Mixed			
	Other			
Smoking Status	n (missing)			
	Never			
	Former			
	Current			
CKD stages using most recent eGFR measure	n (missing)			
	G2 (60-89)			
	G3a (45-59)			
	G3b (30-44)			
	G4 (15-29)			
uACR	n (missing)			
	<30 mg/g			
	30-300 mg/g			
	>=300 mg/g			
uACR	n (missing)			
	<30 mg/g			
	30-200 mg/g			
	>=200 mg/g			
T2D (CPRD diagnosis)				
Glomerulonephritis				
ACEi				
ARB				
MRA				
Diuretics				
Serum Potassium (mmol/L)	n (missing)			
	Mean (SD)			
	Median (IQR)			
	Min - Max			
SBP	n (missing)			
	Mean (SD)			
	Median (IQR)			
	Min - Max			
Haemoglobin (g/L)	n (missing)			
	Mean (SD)			
	Median (IQR)			
	Min - Max			
HF				
MI				
Stroke				
ARB or ACEi treatment				
Statins				

Variable		All	T2D	No T2D
Antiplatelet or anticoagulant		[redacted]	[redacted]	[redacted]
Beta blockers		[redacted]	[redacted]	[redacted]
Dapagliflozin		[redacted]	[redacted]	
Empagliflozin		[redacted]	[redacted]	
Canalgliflozin		[redacted]	[redacted]	
K binders		[redacted]	[redacted]	[redacted]
Phosphate binders		[redacted]	[redacted]	[redacted]
CKD diagnosis		[redacted]	[redacted]	[redacted]

Source: Data on file. ID: REF-135938 December 2021,AstraZeneca UK Ltd [29]

Abbreviations: ACEi = angiotensin converting enzyme inhibitor; ARB = angiotensin-receptor blocker; BMI = body mass index; CKD = chronic kidney disease; CPRD = clinical practice research datalink; eGFR = estimated glomerular filtration rate; G2 = eGFR of 60-89 ml/min/1.73m^2 ; G3a = eGFR of 45-59 ml/min/1.73m^2; G3b = eGFR of 30-44 ml/min/1.73m^2 ; G4 = eGFR of 15-29 ml/min/1.73m^2; HF = heart failure; IQR = interquartile range; K = potassium; MI = myocardial infarction; MRA = mineralocorticoid receptor antagonists; SBP = systolic blood pressure; SD = standard deviation; T2D = type 2 diabetes; uACR = urinary albumin-creatinine ratio

Table 20 Baseline Characteristics of CKD population (eGFR 25-75, uACR>22.6mg/mmol; T2D, no T2D and overall

Variable		All	T2D	No T2D
Prevalent CKD: n(%)		[redacted]	[redacted]	[redacted]
Age (years)	n (missing)			
	Mean (SD)			
	Median (IQR)			
	Min - Max			
Gender	n (missing)			
	Male			
	Female			
BMI	n (missing)			
	Mean (SD)			
	Median (IQR)			
	Min - Max			
Ethnicity	n (missing)			
	White			
	Asian			
	Black			
	Mixed			
	Other			
Smoking Status	n (missing)			
	Never			
	Former			
	Current			
CKD stages using most recent eGFR measure	n (missing)			
	G2 (60-89)			
	G3a (45-59)			
	G3b (30-44)			
	G4 (15-29)			
uACR	n (missing)			
	<30 mg/g			
	30-300 mg/g			
	>=300 mg/g			
uACR	n (missing)			
	<30 mg/g			
	30-200 mg/g			
	>=200 mg/g			
T2D (CPRD diagnosis)				
Glomerulonephritis				
ACEi				
ARB				
MRA				
Diuretics				
Serum Potassium (mmol/L)	n (missing)			
	Mean (SD)			
	Median (IQR)			
	Min - Max			
SBP	n (missing)			
	Mean (SD)			
	Median (IQR)			
	Min - Max			
Haemoglobin (g/L)	n (missing)			
	Mean (SD)			
	Median (IQR)			
	Min - Max			
HF				
MI				
Stroke				
ARB or ACEi treatment				
Statins				
Antiplatelet or anticoagulant				[redacted]

Variable		All	T2D	No T2D
Beta blockers		[redacted]	[redacted]	
Dapagliflozin				
Empagliflozin				[redacted]
Canalgliflozin				
K binders				
Phosphate binders				
CKD diagnosis				

Source: Data on file. ID: REF-135938 December 2021,AstraZeneca UK Ltd [29]

Abbreviations: ACEi = angiotensin converting enzyme inhibitor; ARB = angiotensin-receptor blocker; BMI = body mass index; CKD = chronic kidney disease; CPRD = clinical practice research datalink; eGFR = estimated glomerular filtration rate; G2 = eGFR of 60-89 ml/min/1.73m^2 ; G3a = eGFR of 45-59 ml/min/1.73m^2; G3b = eGFR of 30-44 ml/min/1.73m^2 ; G4 = eGFR of 15-29 ml/min/1.73m^2; HF = heart failure; IQR = interquartile range; K = potassium; MI = myocardial infarction; MRA = mineralocorticoid receptor antagonists; SBP = systolic blood pressure; SD = standard deviation; T2D = type 2 diabetes; uACR = urinary albumin-creatinine ratio

APPENDIX 3. SUMMARY OF ADVERSE EVENT DATA FOR DAPAGLIFLOZIN

Table 21 AEs in participants with stage A2 albuminuria (uACR 3.4 to <33.9 mg/mmol) from the DAPA-CKD trial

Characteristic	Dapagliflozin (n=72)	Placebo (n=64)
Drug discontinuation due to AE	2/72	1/64
Serious AE	18/72	14/64
Source: CS Document B, Table 29 Abbreviations: AE = adverse event; uACR = urinary albumin creatinine ratio		

Table 22 AEs in participants with stage A3 albuminuria (uACR ≥33.9 mg/mmol) from the DAPA-CKD trial

Characteristic	Dapagliflozin (n=624)	Placebo (n=635)
Drug discontinuation due to AE	34/624	28/ 635
SAE	132	153
Source: CS Document B, Table 30 Abbreviations: AE = adverse event; SAE = serious adverse event; uACR = urinary albumin creatinine ratio		

Table 23 Safety of dapagliflozin across baseline eGFR subgroups – DAPA-HF

	eGFR <60 ml/min/1.73 m^2			eGFR ≥60 ml/min/1.73 m^2		
	Dapagliflozin	Placebo	*P* value	Dapagliflozin	Placebo	
AEs, n (%)	n=960	n=962		n=1407	n=1,405	*P* value
Volume depletion	97 (10.1)	86 (8.9)	0.39	81 (5.8)	76 (5.4)	0.74
Renal events	97 (10.1)	115 (12.0)	0.22	56 (4.0)	55 (3.9)	1
Amputation	8 (0.8)	9 (0.9)	1	5 (0.4)	3 (0.2)	0.73
Major hypoglycaemia	3 (0.3)	0 (0.0)	0.12	1 (0.1)	4 (0.3)	0.22
Fracture	28 (2.9)	25 (2.6)	0.68	21 (1.5)	25 (1.8)	0.56
Permanent treatment discontinuation	121 (12.6)	130 (13.5)	0.59	128 (9.1)	128 (9.1)	1
Any serious AE	417 (43.4)	482 (50.1)	0.003	478 (34.0)	512 (36.4)	0.18
Source: Company response to clarification question A2, Table 4 Abbreviations: AE = adverse event; eGFR = estimated glomerular filtration rate						

Table 24 Adverse events reported in SmPC for dapagliflozin, based on placebo-controlled clinical studies and post-marketing experience across all licensed indications

System organ class	Very common	Common*	Uncommon**	Rare	Very rare
Infections and infestations		Vulvovaginitis, balanitis and related genital infections; Urinary tract infections	Fungal infection		Necrotising fasciitis of the perineum (Fournier's gangrene)
Metabolism and nutrition disorders	Hypoglycaemia (when used with SU or insulin)		Volume depletion; Thirst	Diabetic ketoacidosis (when used in T2D)	
Nervous system disorders		Dizziness			
Gastrointestinal disorders			Constipation; Dry mouth		
Skin and subcutaneous disorders		Rash			Angioedema
Musculoskeletal and connective tissue disorders		Back pain			
Renal and urinary disorders		Dysuria; Polyuria	Nocturia		Tubulointerstitial nephritis
Reproductive system and breast disorders			Vulvovaginal pruritis; Pruritis genital		
Investigations		Haematocrit increased; Creatinine renal clearance decreased during initial treatment Dyslipidaemia	Blood creatinine increased during initial treatment; Blood urea increased; Weight decreased		

Source: Company response to clarification question A2, Table 3
Further information on selected AEs is presented in the SmPC for dapagliflozin. * Reported in ≥2% of patients and ≥1% more and at least 3 more patients treated with dapagliflozin 10 mg compared with placebo. ** reported by the investigator as possible related, probably related or related to study treatment and reported in ≥0.2% of patients and ≥0.1% more and at least 3 more patients treated with dapagliflozin 10 mg compared with placebo.
Abbreviations: SmPC = Summary of Product Characteristics; T2D = type 2 diabetes.

Single Technology Appraisal

Dapagliflozin for treating chronic kidney disease [ID6411]

EAG report – factual accuracy check and confidential information check

"Data owners may be asked to check that confidential information is correctly marked in documents created by others in the evaluation before release." (Section 5.4.9, NICE health technology evaluations: the manual).

You are asked to check the EAG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on 17 September 2024** using the below comments table.

All factual errors will be highlighted in a report and presented to the appraisal committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and information that is submitted as 'confidential' should be highlighted in turquoise and all information submitted as 'depersonalised data' in pink.

Issue 1 Incorrect understanding of decision problem and aim of targeted review

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
The external assessment group (EAG) state that evidence is required for all populations across the National Institute for Health and Care Excellence (NICE) scope, including those that empagliflozin and dapagliflozin are already recommended in, stating that these populations have been omitted by the Company. For example: P. 8: "[the Company] omits the subpopulations from the NICE scope where both dapagliflozin and empagliflozin are recommended" P. 8: "Robust evidence is required to show equivalence in effectiveness and safety between dapagliflozin and empagliflozin to inform a cost comparison across the entire NICE scope population."	All statements that the Company has omitted the populations in which dapagliflozin is already recommended should be amended to acknowledge that these populations have already been evaluated in Technology Appraisal (TA)775. In addition, the Company requests that all statements indicating that evidence is required to show equivalence of dapagliflozin and empagliflozin in the populations in which both treatments are already recommended are removed. Based on the above, the Company kindly requests that the EAG re-consider the appropriateness of Issue 1 and all related discussion throughout the EAG report.	It was agreed with NICE at the Decision Problem Meeting that the aim of the review is to expand the dapagliflozin recommendation to align with that of empagliflozin, by evaluating dapagliflozin in the populations in which it is not currently recommended, but in whom empagliflozin is. It is incorrect to state that the dapagliflozin recommendation from TA775 should be re-evaluated as part of this review as it is not relevant to the decision problem. In addition, NICE recently made a positive recommendation in TA942 for empagliflozin where there is an overlap in the populations in the relevant randomised controlled trials (RCTs).[1] This part of the recommendation was made based on a cost comparison between the two medicines.[1] As such, a reassessment of the recommendations in these populations is inappropriate. The NICE scope population has already partly been addressed in TA775, so data in this review are only presented for the remaining	Issue 1 and related discussion in the EAG report reflect the EAG's interpretation of the alignment of the submitted evidence to the NICE Scope and is not a factual inaccuracy. No amendments made to the EAG report Please also see the response to Issue 2 regarding the EAG's interpretation of the relevance of the network meta-analysis (NMA) and cost comparison conducted in TA942 to the two omitted subgroups [1) people with T2D and eGFR range between 25 and 75 mL/min/1.73 m2 irrespective of uACR and 2) people without T2D, between 25 and 75 mL/min/1.73 m2 and uACR ≥22.6 mg/mmol] in this review.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
		populations (i.e., those that are recommended for empagliflozin but not for dapagliflozin).[2] It is inaccurate to state that the Company has omitted these populations without acknowledging that they have already been evaluated in TA775; it is, therefore, incorrect to state that evidence is required to demonstrate clinical and cost-equivalence of dapagliflozin and empagliflozin in the populations in which both are already recommended. Based on the aims of this review, Issue 1 in the EAG report is not accurate and should be removed, along with all associated discussion.	
The EAG report states: P.20 "The aim of this review is to compare costs between dapagliflozin and empagliflozin in the NICE scope population" P.14 "proposes an alignment via a cost comparison of the populations for which dapagliflozin and empagliflozin are recommended for."	The company kindly requests that the aim of the review is updated to reflect that agreed with NICE and the EAG during the Decision Problem Meeting. Suggested amended text is provided below: "The aim of this review is to compare costs between dapagliflozin and empagliflozin in the ~~**NICE scope**~~ population**s for which empagliflozin is**	It was agreed with NICE prior to this review that the aim of this review is to evaluate dapagliflozin in the populations in which it is not currently recommended but empagliflozin is to allow the alignment of the dapagliflozin and empagliflozin recommendations. It is incorrect to state that the aim is to simply compare costs between dapagliflozin and empagliflozin in the NICE scope population.	As stated above, the EAG's interpretation of the alignment of the submitted evidence to the NICE scope is not a factual inaccuracy. First proposed amendment not made. However, the second proposed amendment is made to p14 of the EAG report to reflect the company aim of the review.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
	recommended but dapagliflozin is not." "proposes ~~**an alignment via**~~ a cost comparison of the populations for which **empagliflozin is recommended but** dapagliflozin **is not** ~~**and empagliflozin are recommended for**~~"		
The EAG refer to: Pp. 20, 25, 52, 54, 61 "the company defined CKD subpopulations"	The Company kindly requests that the following is amended in all instances in the EAG report as per: "the ~~**company defined**~~ CKD subpopulations"	The subgroups of interest have not been defined by the Company in this review. The subgroups of interest are identified based on the populations that are recommended by NICE for empagliflozin but not dapagliflozin, which are a result of the subgroups defined by NICE within each recommendation.	This is not a factual inaccuracy. The subgroups in the company decision problem are defined by the company, rather than by NICE scope (CS, Document B, Table 1 and EAG report, Table 1). No amendments made to the EAG report.

Issue 2 Inaccurate interpretation of indirect treatment comparison (ITC), NICE Committee conclusions, and methodology used in TA942

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
The EAG state that the ITC and NICE Committee assumptions/conclusions in TA942 have limited applicability to this review. For example:	The Company believes that all statements outlining the conclusions of the ITC presented in TA942 and the NICE Committee assumptions/conclusions are not valid, and kindly request that they	The network meta-analysis (NMA) presented in TA942 was accepted by the NICE Committee as demonstrating similar clinical efficacy and safety for empagliflozin and dapagliflozin in the populations in which dapagliflozin was already recommended (in TA775).[3]	The EAG's interpretation of the relevance of the NMA and cost-comparison conducted in TA942 is not

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
P. 23 “The EAG does not consider that it is valid to assume clinical similarity and cost equivalence in the populations for which dapagliflozin and empagliflozin are both recommended based on the NMA and the committee recommendations made within TA942”. P. 23 “The EAG notes that several aspects limit the applicability of the indirect comparison presented in TA942, and the conclusions made within TA942, to this appraisal”. P. 24 “For this reason, the empagliflozin recommendation made by the NICE committee cannot have been based on the cost comparison presented in the TA942 CS, rather the NICE committee accepted the TA942 NMA conclusion of clinical similarity between dapagliflozin and empagliflozin and	are removed from the EAG report.	There is no reason why the NMA in TA942 would be accepted in TA942 but not considered suitable to demonstrate the same conclusion in this review. It is, therefore, inaccurate to state this. In TA942, a cost-comparison approach was deemed suitable for empagliflozin versus dapagliflozin in the populations for which dapagliflozin is already recommended (based on TA775) on the basis of the presented NMA.[3] As such, the EAG and NICE Committee accepted that the NMA demonstrated equivalent efficacy and safety of dapagliflozin and empagliflozin in the overlapping populations. The EAG incorrectly state that the NICE Committee did not make the empagliflozin recommendation in TA942 on the basis of the cost-comparison versus dapagliflozin. Based on the committee papers and NICE methods, the NICE committee have recommended empagliflozin versus dapagliflozin on the basis of the cost-comparison where there is an overlap in the populations.[3] NICE also recommended empagliflozin in the populations that dapagliflozin is not recommended in based on the cost-effectiveness analysis versus standard of care alone. Moreover, NICE	a factual inaccuracy. No amendments made to the EAG report The EAG reiterates that the cost comparison in TA942 was not valid for decision making because the dapagliflozin and empagliflozin populations included within the TA942 NMA were different, and so cannot have been the basis for any empagliflozin recommendation. Instead, the NICE committee accepted the TA942 NMA conclusion that dapagliflozin and empagliflozin were clinically similar, and recommended empagliflozin based on the cost-effectiveness analysis between empagliflozin and standard of care treatment.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
recommended empagliflozin based upon a cost-effectiveness analysis between empagliflozin and SoC alone within a population which broadly aligns with the direct evidence provided by the EMPA-KIDNEY trial." P. 64 "the EAG does not consider that it is valid to assume clinical similarity and cost-equivalence in the populations for which dapagliflozin and empagliflozin are both recommended, based on the conclusions of TA942"		subsequently developed a combined resource impact report for both treatments.[4]	
Page 23 of the EAG report states: "The company assume that cost-equivalence between dapagliflozin and empagliflozin in these two subpopulations has already been shown in TA942"	The Company kindly requests that this is amended as follows: "~~The company assume that~~ cost-equivalence between dapagliflozin and empagliflozin in these two subpopulations has already been shown in TA942"	It is not a Company assumption that cost-equivalence has been demonstrated in TA942; this was the conclusion of the NICE Committee.[1] It is inaccurate to state that this was an assumption of the Company.	Please see response above. This is not a factual inaccuracy, and no amendments made to the EAG report.
The EAG highlight that one reason for the limited	The Company kindly requests that the EAG report	In line with this review, only the comparison of empagliflozin versus	This is not a factual inaccuracy. The EAG considers that the inclusion of

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
applicability of the NMA from TA942 is "the inclusion of additional SGLT2 inhibitors" beyond dapagliflozin and empagliflozin.	acknowledges that issues associated with the inclusion of additional sodium-glucose co-transporter-2 inhibitors (SGLT2i's) in the NMA were not identified by the EAG or NICE Committee in TA942, or at least did not introduce considerable uncertainty to make the conclusions invalid.	dapagliflozin was of interest in TA942. The EAG or NICE Committee did not identify the inclusion of additional SGLT2i's in the NMA as a source of concern in TA942 and the NMA was accepted as demonstrating similar clinical efficacy and safety for dapagliflozin and empagliflozin in the included populations.[1] This is to be clearly acknowledged in the EAG report.	additional treatments reduces applicability of the NMA findings. No amendments made to the EAG report.
Page 55 of the EAG report states: "The company acknowledge that the relevance of the results of this NMA to the five CKD subpopulations is very limited, only partially including populations which meet the definition of Subpopulation 1 but with no comparative data available for the populations defined in Subpopulations 2 to 5 (response to clarification question A10)."	The Company kindly requests that this is amended as follows: "The company acknowledge that the relevance of the results of this NMA to the five CKD subpopulations **specifically** is very limited, only partially including populations which meet the definition of Subpopulation 1 but with no comparative data available for the populations defined in Subpopulations 2 to 5 (response to clarification question A10). **However, the conclusions of the NMA (that empagliflozin and dapagliflozin are clinically similar) support the overall similarity of the two SGLT2 inhibitors across CKD subgroups.**"	The Company acknowledges the limited relevance of the NMA from TA942 to estimating the relative efficacy of dapagliflozin versus empagliflozin in the specific subgroups in this review, however, the relevance of the NMA in supporting the overall clinical similarity of dapagliflozin and empagliflozin as treatments for chronic kidney disease (CKD) should be acknowledged. It is inaccurate to simply state that the NMA has limited relevance without including the wider context.	This is not a factual inaccuracy. The text on p55 of the EAG report clearly refers to the relevance of the TA942 NMA to the five CKD subgroups defined within the company decision problem (i.e. CKD subgroups Dapagliflozin is not currently recommended for). The relevance of the TA942 NMA to CKD subgroups Dapagliflozin is recommended for is discussed elsewhere in the EAG report (pp 24-25). Therefore, such an amendment is not appropriate on p55 of the EAG report

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 23 of the EAG report states: "their aim within this review is to align the populations that dapagliflozin and empagliflozin are recommended for, rather than to re-evaluate the population which was recommended within TA775 (company response to clarification question A1) and state that dapagliflozin and empagliflozin have already been evaluated in TA942 (CS Document B, Table 1)."	The Company kindly requests that this statement is amended as follows: "their aim within this review is to align the populations that dapagliflozin and empagliflozin are recommended for, rather than to re-evaluate the population which was recommended **for dapagliflozin** within TA775 (company response to clarification question A1) and state that ~~**dapagliflozin and**~~ empagliflozin **was** ~~**have already been**~~ evaluated in TA942 **via a cost-comparison versus dapagliflozin in the dapagliflozin recommended populations** (CS Document B, Table 1)."	Suggested amendment to improve clarity regarding the NICE evaluations that have already taken place. It is currently unclear that dapagliflozin was first recommended (regardless of empagliflozin) and empagliflozin was subsequently recommended via a cost-comparison versus dapagliflozin in the populations in which dapagliflozin was already recommended.	Proposed amendment made to p23 of the EAG report to accurately reflect the company's aim of the review. However, the EAG reiterates that the evaluation of empagliflozin and dapagliflozin in TA942 "*via a cost-comparison versus dapagliflozin in the dapagliflozin recommended populations*" is an incorrect statement and empagliflozin was not evaluated via a cost-comparison versus dapagliflozin in the recommended dapagliflozin recommended populations in TA942. Please see first response to Issue 2 and pp 24-25 of the EAG report for further details.

Issue 3 Inaccurate representation of Company assumptions and empirical evidence of similar efficacy, safety and costs between empagliflozin and dapagliflozin

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
The EAG make several statements that the Company assumes clinical	Statements on the Company's assumptions of equal efficacy, safety and costs for dapagliflozin	It is inaccurate to state that the Company assumed similar efficacy, safety and costs of empagliflozin and	This is not a factual inaccuracy, no empirical data, nor direct evidence have been provided within this

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
similarity in terms of efficacy and safety between empagliflozin and dapagliflozin, or that there are no empirical data or robust evidence to conclude similar effectiveness and efficacy between dapagliflozin and empagliflozin: P.13 “the company assumes that there is no scientific or clinical rationale to believe that dapagliflozin incurs different resource use” and “No empirical data were provided to support these assumptions. The evidence provided to support the same efficacy and safety profile is uncertain.” p. 25 “These assumptions were based on the company’s expectations due to similar mechanism of action, efficacy and safety profiles and were not supported by any direct evidence.”	and empagliflozin should acknowledge the evidence that these are based on, rather than implying that these assumptions are not evidence-based. Likewise, statements on the available evidence are to acknowledge all evidence provided. The company kindly requests that such statements are amended as follows: “the company assumes that there is no scientific or clinical rationale to believe that dapagliflozin incurs different resource use, **based on the conclusions of TA942 and the combined resource impact report of both treatments created by NICE, published ITCs and meta-analyses, UK clinical expert opinion and UK treatment guidelines**.” “~~**No empirical data were provided to support these assumptions**~~. The evidence provided to support the same efficacy and safety profile, **including published ITCs and meta-analyses, clinical expert opinion and UK treatment**	dapagliflozin, without acknowledging the body of evidence that these assumptions are based on. The evidence provided to support the similarity of efficacy and safety between dapagliflozin and empagliflozin include empirical data, while statements in the EAG report currently suggest that these assumptions are not evidence-based. This body of evidence includes: • Both NICE and EAG conclusions in TA942 forming the basis of the recommendation of empagliflozin versus dapagliflozin via cost-comparison in this population in TA942, and the subsequent combined resource impact report of both treatments;[1, 2, 4] • The consistent conclusion of similar clinical efficacy of dapagliflozin and empagliflozin as evidenced by ITCs, including the NMA in TA942 and other published meta-analyses, for CKD and other indications such as ITCs conducted to support the cost-comparison appraisal of empagliflozin versus	submission to inform the parameters of the economic analysis. The proposed amendments have not been made, however, for accuracy, we have updated the statement on p64 of the EAG report to clarify that “no empirical data were provided to support this assumption” rather than “no empirical data exist to support this assumption.”

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
P. 63 “Although this assumption was based on the similar mechanism of action of the two drugs, their expected clinical efficacy equivalency and similar safety profile, no empirical data exist to support this assumption.“	**guidelines,** is **considered as** uncertain **by the EAG**.” “These assumptions were based on the company’s expectations due to similar mechanism of action, efficacy and safety profiles, **based on the conclusions of TA942 and the subsequent combined resource impact report of both treatments, published ITCs and meta-analyses, clinical expert opinion and UK treatment guidelines ~~and were not supported by any direct evidence~~**” “Although this assumption was based on the similar mechanism of action of the two drugs, their expected clinical efficacy equivalency and similar safety profile, **the EAG considers** that **limited ~~no~~** empirical data exist to support this assumption.”	dapagliflozin in heart failure (TA929);[1, 5, 6] • Clinical expert opinion, including comments from United Kingdom (UK) clinical societies on the draft scope for this review and UK clinical experts consulted by AstraZeneca;[7] • Non-differentiation between SGLT2i’s as a class within clinical guidelines such as the UK Kidney Association (UKKA);[8] • The similar mechanism of action of dapagliflozin and empagliflozin, specifically the similar high selectivity for SGLT2 over SGLT1 versus phlorizin demonstrated in pre-clinical studies.[9, 10]	

Issue 4 Inaccurate statement regarding absence of systematic literature review (SLR) conducted for this review

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 26 of the EAG report states: "The company did not update these searches using systematic search methods, therefore there is potential for missing unpublished and published studies, particularly for the comparator drug empagliflozin."	The Company kindly requests that the following statement specifies that the NICE methods do not always require an SLR, which was confirmed by NICE for this review: "the company **was not required by NICE to ~~did not~~** update these searches using systematic search methods **nor to run any systematic literature search**, therefore there is potential for missing unpublished and published studies, particularly for the comparator drug empagliflozin."	An SLR is not always required for a cost-comparison submission as outlined in the *User guide for company evidence submission appendices,* which states that "In exceptional circumstances a systematic literature search may not be necessary". NICE confirmed that an SLR is not required for this appraisal. As explained in the Company Submission (CS) Addendum, studies were included based on the key and relevant studies in TA775 and TA942. Furthermore, as the appraisal of empagliflozin in CKD was conducted recently (published December 2023), it was not deemed necessary to conduct systemic searches to identify any new data for empagliflozin that may have been published in the six months between publication of TA942 and submission of this review.[1] Moreover, due to the timelines associated with this review, it was not feasible to conduct an updated SLR.	This is not a factual inaccuracy, regardless of any requirement to perform an SLR, the EAG considers that the potential for missing relevance evidence remains. No amendments made to the EAG report.

Issue 5 Incorrect explanation for the exclusion of studies included within the SLRs conducted for TA775/TA942

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 26 of the EAG report states: "In response to clarification question A3, the company explained that Kohan (2014),[11] Fioretto (2018),[12] and Pollock (2019)[13] were not included because the populations within these studies do not align with the subpopulations of interest to the review. However, the EAG notes that studies that were included in the CS (e.g., OPTIMISE-CKD included participants with eGFR<20 mL/min/1.73 m^2) were also not aligned with the subpopulations of interest to the review."	The Company kindly requests that this text is amended as follows: "In response to clarification question A3, the company explained that Kohan (2014),[11] Fioretto (2018),[12] and Pollock (2019)[13] were not included because the populations within these studies do not **overlap** ~~**align**~~ with the subpopulations of interest to the review. ~~**However, the EAG notes that studies that were included in the CS (e.g., OPTIMISE-CKD included participants with eGFR<20 mL/min/1.73 m^2) were also not aligned with the subpopulations of interest to the review**~~."	This statement has misinterpreted the Company's response to clarification question A3 which explains why the studies identified in the SLR for TA775 were not included in this review. Kohan (2014), Fioretto (2018), and Pollock (2019) were not included in this review as the populations included with these studies do not overlap with the specific subpopulations of interest within this review. These studies do not include any patients that would fall within any of the five subgroups in this review so do not provide any relevant evidence for this review. This is different from the studies that were included within this review which do not completely align with the subgroups of interest as they may contain broader populations than the subpopulations of interest in this review, but they do overlap with these subpopulations. The example cited by the EAG of OPTIMISE-CKD is not the same as the excluded studies; OPTIMISE-CKD included some patients that fall outside of the subgroups of interest (e.g., estimated glomerular filtration rate [eGFR] <20 ml/min/1.73m^2 as noted by the EAG),	Proposed amendments made to p26 of the EAG report.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
		but also included a large proportion of patients that do overlap with the subgroups of interest.	
Page 9 of the EAG report states: "The CS did not include a systematic review. Whilst the key CKD trials for dapagliflozin and empagliflozin were included in the CS, several studies included in TA775 and TA942 were excluded, and it is uncertain whether all relevant evidence to inform the decision problem has been accounted for."	The Company kindly requests that this is amended as follows: "The CS did not include a systematic review. Whilst the key CKD trials for dapagliflozin and empagliflozin were included in the CS, ~~several studies included in TA775 and TA942 were excluded, and~~ it is uncertain whether all relevant evidence to inform the decision problem has been accounted for."	In response to clarification question A3, and as outlined above, the Company explained why some studies included in the TA775 and TA942 were excluded. As such, it is inaccurate to state that the exclusion of some studies included in TA775 and TA942 results in uncertainty regarding whether all relevant evidence has been included. Alternatively, if the EAG still deem there is uncertainty despite the Company's explanations, it should be acknowledged that the Company did explain why studies included in TA775 and TA942 were not included in this review.	Proposed amendment made to p9 of the EAG report.

Issue 6 Incorrect reporting and interpretation of real-world evidence (RWE) studies

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
The EAG report incorrectly describes the studies by Svensson et *al.* (2024) and Tangri et *al.* (2024) as	The Company kindly requests that all statements regarding the OPTIMISE-CKD studies are amended to not call them retrospective or single-armed.	It is incorrect to state that OPTIMISE-CKD is a retrospective study. Patients in OPTIMISE-CKD were identified retrospectively but followed prospectively. As such, studies in the OPTIMISE-CKD	The use of the term 'retrospective' is not a factual inaccuracy, and no amendments made to the EAG report. The term refers to a 'retrospective" was used in reference to the analysis

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
retrospective and single-arm. For example: P. 30: "Svensson et al. (2024) is a single arm, retrospective analysis of dapagliflozin initiators while Tangri et al. (2024) is a retrospective analysis comparing dapagliflozin initiators and non-initiators using propensity score matching." P. 30: "Svensson et al. (2024) retrospectively analysed claims data for 10,805 CKD patients from the USA who initiated dapagliflozin 10mg once daily and had a baseline uACR measurement between April 2021 and March 2023. The study was a single arm (dapagliflozin), observational cohort study with 12-month follow-up. Comparisons were made between subgroups defined by high uACR (>22.6 mg/mmol) and low uACR (3–22.6 mg/mmol). Differences in eGFR	Suggested amendments are included below: "Svensson *et al.* (2024) is a ~~single~~ **two**-armed ~~retrospective~~ analysis of dapagliflozin initiators **with low versus high uACR,** while Tangri *et.al* (2024) is a**n** ~~retrospective~~ analysis comparing dapagliflozin initiators and non-initiators using propensity score matching." "Svensson *et al.* (2024) ~~retrospectively~~ analysed claims data for 10,805 CKD patients from the USA who initiated dapagliflozin 10 mg once daily and had a baseline uACR measurement between April 2021 and March 2023. The study was a**n** ~~single arm (dapagliflozin),~~ observational cohort study with 12-month follow-up **comparing** ~~were made between subgroups defined~~ **dapagliflozin initiators with** high uACR (>22.6 mg/mmol) ~~and~~ **versus** low uACR (3–22.6 mg/mmol). Differences in eGFR slopes between the uACR subgroups were not subject to inferential statistical analysis. eGFR slopes for each separate	program are observational studies, not retrospective studies.[14, 15] In addition, it is incorrect to call the OPTIMISE-CKD studies single-arm. Both studies from the OPTIMISE-CKD program have two treatment arms; Svensson et *al.* (2024) compares dapagliflozin initiators with low versus high urine albumin-creatinine ratio (uACR) and Tangri et *al.* (2024) compares dapagliflozin initiators and non-initiators.[14, 15]	approach in these studies, in which the full dataset was analysed retrospectively, even though the data were prospectively *collected* for another purpose (such as insurance claim recording). Svensson (2024) does not have a comparator treatment group, which means that inferences regarding treatment efficacy versus placebo or another treatment cannot be made However, the term 'single arm' has been removed on pp 31-32 of the EAG report and replaced with more accurate wording relating to the lack of comparison with another treatment, given that the analysis within Svensson (2024) compared two groups defined by population characteristics.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
slopes between the uACR subgroups were not subject to inferential statistical analysis. eGFR slopes for each separate uACR subgroup were adjusted for baseline eGFR, age, sex, HF and RASi. Hospitalisation data were formally analysed between uACR subgroups, using Cox regression models, adjusting for age, sex, HF, CKD diagnosis, MI, stroke and peripheral arterial disease." P. 31 "Tangri et al. (2024) retrospectively analysed electronic health records and claims data from Japan and the USA in patients with CKD stages 3-4 with/without T2D and uACR <22.6 mg/mmol." P. 32 "Svensson et al. (2024) did not include a control group and made comparisons only of subgroups defined by uACR, which limits the applicability of the results to the NICE scope."	uACR subgroup were adjusted for baseline eGFR, age, sex, HF and RASi. Hospitalisation **and mortality** data were formally analysed between uACR subgroups, using Cox regression models, adjusting for age, sex, HF, CKD diagnosis, MI, stroke and peripheral arterial disease." "Tangri et al. (2024) ~~**retrospectively**~~ analysed electronic health records and claims data from Japan and the USA in patients with CKD stages 3-4 with/without T2D and uACR <22.6 mg/mmol." "Svensson et al. (2024) ~~**did not include a control group and**~~ made comparisons only of subgroups defined by uACR, which limits the applicability of the results to the NICE scope."		

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
The EAG report states that the results of Nakhleh et *al.* (2024) have limited applicability to the decision problem as dapagliflozin and empagliflozin were not evaluated separately. P. 34 "The EAG also notes that analyses did not evaluate the effect of dapagliflozin and empagliflozin separately, which limits the applicability of the results to the company decision problem and to the NICE scope."	The Company requests that the sentence stating that the results of Nakhleh et *al*. (2024) have limited applicability to the decision problem is removed. Suggested amendment is included below: "The EAG also notes that analyses did not evaluate the effect of dapagliflozin and empagliflozin separately~~, which limits the applicability of the results to the company decision problem and to the NICE scope~~."	Considering the consistency of the results of Nakhleh et *al*. (2024) with DAPA-CKD, it is not scientifically plausible for the proportion of patients receiving empagliflozin (~25%) to have substantially impacted the results of this study.[16] To observe a difference in effect between dapagliflozin and empagliflozin, the treatment effect of empagliflozin in ~25% of patients would have to greatly exceed the treatment effect of dapagliflozin in the remaining ~75% of patients. As this is scientifically implausible based on the available data, it is inaccurate to state that the results of Nakhleh et *al*. (2024) have limited applicability to the decision problem.	The EAG's interpretation of the relevance of the Nakhleh et al. 2024 study to the NICE scope is not a factual inaccuracy and no amendments made to the EAG report.
The EAG report states that the results of the OPTIMISE-CKD studies have limited applicability to the decision problem. P.11 "Both have significant design limitations and limited applicability to UK practice." P. 32 "The EAG notes some differences between the characteristics of the	The Company requests that the arguments around the limited applicability of the OPTIMISE-CKD studies based on biological sex and background renin–angiotensin system inhibitor (RASi) therapies are removed or at least amended as outlined below. Moreover, any statements on the limited applicability of the	The proportion of female patients included in OPTIMISE-CKD is higher than the proportion of female patients in DAPA-CKD and EMPA-KIDNEY.[14, 15, 17, 18] DAPA-CKD was already deemed generalisable to UK clinical practice and suitable for decision-making by NICE in TA775 and TA942.[1, 2] Likewise, EMPA-KIDNEY was deemed suitable for decision-making by NICE in TA942.[1] As such, it is incorrect to state that the proportion of females in	The EAG interpretation of the relevance of the OPTIMISE-CKD studies' populations to the CKD population treated within UK NHS practice is not a factual inaccuracy and no amendments made to the EAG report.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
patients within the OPTIMISE-CKD studies and the UK CKD population, for example, the proportion of females (with uACR >3.4mg/mmol) recruited into the Svensson et al. (2024) study is lower than the UK CKD population (see Appendix 2). Furthermore, the OPTIMISE-CKD data were collected in USA and Japan where clinical practice and ethnicity mix will likely differ from that in the UK. In addition, only 62% to 80% of the OPTIMISE-CKD participants received RASi therapy, which does not align with the current UK recommendation dapagliflozin should be added to optimised RASi therapy (unless contra-indicated). Overall, the applicability of the OPTIMISE-CKD study population to the NICE scope is limited."	OPTIMISE-CKD studies to UK clinical practice is to be removed. "Both have ~~**significant**~~ design limitations~~ **and limited applicability to UK practice**~~." "The EAG notes some differences between the characteristics of the patients within the OPTIMISE-CKD studies and the UK CKD population, for example, the proportion of females (with uACR >3.4mg/mmol) recruited into the Svensson et al.(2024) study is lower than the UK CKD population (see Appendix 2). **However, the proportion of female patients in the OPTIMISE-CKD studies is higher than in DAPA-CKD and EMPA-KIDNEY trials, which were deemed suitable for decision-making by the NICE Committees in TA775 and TA942. Moreover, biological sex was not identified as a treatment effect modifier in either of these trials.** Furthermore, the OPTIMISE-CKD data were collected in USA and Japan where clinical practice and ethnicity mix will likely differ	OPTIMISE-CKD limits the generalisability of this study to the UK and the prior conclusions of the NICE Committee regarding DAPA-CKD and EMPA-KIDNEY should be acknowledged. Furthermore, forest plots from DAPA-CKD and EMPA-KIDNEY demonstrate that there is no statistically significant difference in the treatment effect of dapagliflozin in males versus females, hereby, that biological sex is not a treatment effect modifier based on DAPA-CKD and EMPA-KIDNEY.[17, 18] As such, it is inaccurate to state that a difference in the proportion of females would impact the applicability of the study results. Likewise, RASi therapies in EMPA-KIDNEY were received by 85.7% of patients on empagliflozin versus 84.6% in placebo.[18] In DAPA-CKD, 31.3% of patients on dapagliflozin were on an angiotensin-converting enzyme inhibitor (ACEi) versus 31.6% on placebo, and 67.1% received an angiotensin receptor blockers (ARB) in the dapagliflozin arm versus 66.3% in the placebo arm.[17] As DAPA-CKD was already deemed generalisable to UK clinical	

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
	from that in the UK. In addition, only 62% to **~~80%~~ 85%** of the OPTIMISE-CKD participants received RASi therapy, which does not align with the current UK recommendation dapagliflozin should be added to optimised RASi therapy (unless contra-indicated). **However, the proportion of patients on RASi in the OPTIMISE-CKD studies is broadly aligned to DAPA-CKD and EMPA-KIDNEY trials, which were deemed suitable for decision-making by the NICE Committees in TA775 and TA942~~. Overall, the applicability of the OPTIMISE-CKD study population to the NICE scope is limited.”~~	practice and suitable for decision-making by NICE in TA775 and TA942, and EMPA-KIDNEY in TA942, it is inaccurate to state that the proportion of patients on background RASi therapies would impact the applicability of the OPTIMISE-CKD study results.[1, 2] Moreover, in Tangri et *al.* (2024), up to 85% of patients on dapagliflozin were on RASi therapies, rather than 80% as stated by the EAG.[14] The prior conclusions of the NICE Committee regarding DAPA-CKD and EMPA-KIDNEY should be acknowledged. Consequently, statements on the limited applicability of the OPTIMISE-CKD studies to UK clinical practice and the limitations being significant should be removed as they cannot solely be substantiated with the data being from the USA and Japan as opposed to the UK.	

Issue 7 Inaccurate description of clinical data presented in the submission

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 20 of the EAG report states: "This appraisal conducts a naïve comparison of the primary endpoints in the two pivotal clinical trials for dapagliflozin and empagliflozin, DAPA-CKD and EMPA-KIDNEY, respectively."	The Company kindly requests that this text is amended to acknowledge the additional clinical evidence presented by the Company in the submission documents, including additional endpoints from the pivotal clinical trials for dapagliflozin and empagliflozin, additional RCTs for dapagliflozin, and a variety of endpoints from two RWE studies. Suggested amended text is provided below: "This appraisal conducts a naïve comparison of the ~~**primary endpoints in**~~ two pivotal clinical trials for dapagliflozin and empagliflozin, DAPA-CKD and EMPA-KIDNEY, respectively. **Data from other non-CKD RCTs for dapagliflozin and two RWE studies are also included.**"	The Company presented evidence from numerous sources to demonstrate the clinical efficacy and safety of dapagliflozin across CKD subgroups, including data from DAPA-CKD, other non-CKD specific RCTs (DAPA-HF and DECLARE TIMI-58) and two RWE studies. It is inaccurate to state that this review only conducts a naïve comparison of the primary endpoints on DAPA-CKD and EMPA-KIDNEY without acknowledging the additional evidence provided.	The text on p20 (Table 1) of the EAG report was copied directly from the CS (Document B, Table 1). While this is not a factual inaccuracy, the EAG accepts the company update to the outcomes addressed in the company decision problem and has made the amendment on p20 of the EAG report as proposed.

Issue 8 Inaccurate discussion regarding heterogeneity in amputation risk across SGLT2i's

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 18 of the EAG report states: "Visual inspection of forest plots indicated potential variation in the risk of amputation across trials (a significantly increased risk of amputation with canagliflozin in T2D). Although no tests for heterogeneity were reported, a sensitivity analysis showed that the canagliflozin trial in T2D (CANVAS program) had a notable impact on the pooled estimates for amputation risk (see CS addendum, Figure 18)."	The Company requests that this text is amended to acknowledge that variation in amputation risk associated with canagliflozin is not relevant to the discussion of the similar safety profile of dapagliflozin and empagliflozin.	The SGLT2i's of interest in this review are dapagliflozin and empagliflozin. When discussing heterogeneity in amputation risk introduced by canagliflozin, it should be acknowledged that dapagliflozin is not being compared with canagliflozin in this review. It is misleading to imply that variation in the risk of amputation is observed for empagliflozin and dapagliflozin, or that the variation observed for canagliflozin is of significance.	This is not a factual inaccuracy, and no amendments made to the EAG report. The reference to the heightened risk of amputation for canagliflozin is relevant in the context of the existence of a 'class effect' for SGLT2 inhibitors.
Page 19 of the EAG report states: "Whilst there is no evidence of a significant variation across SGLT2 inhibitor trials for most evaluated safety outcomes across SGLT2 inhibitors, evidence of heterogeneity in amputation risk means	The Company kindly requests that this sentence is removed or amended to state that the heterogeneity in amputation risk is in relation to canagliflozin.	The difference in amputation risk between SLGT2i's is due to increased risk for canagliflozin (as acknowledged by the EAG on page 18 of the report, and documented in the Summary of Product Characteristics [SmPC] for canagliflozin).[19] As this review relates to dapagliflozin and empagliflozin, differences in the safety profiles of other SGLT2i's are not relevant. As such, this sentence should be removed	Please see above response. This is not a factual inaccuracy. To modify the strength of the statement, the term "even" was removed from the sentence p19.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
that the strength of evidence for the equivalence in safety across SGLT2 inhibitors is even more uncertain."		or amended to clearly state that this heterogeneity relates to canagliflozin.	

Issue 9 Misinterpretation of discussion on complexities in prescribing dapagliflozin and empagliflozin in clinical practice

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 14 of the EAG report states: "The company argues that the current differences within the recommendations for dapagliflozin and empagliflozin for CKD lead to difficulties in prescribing"	The Company kindly requests that this is amended as follows: "**Supported by comments on the draft scope from clinical groups (e.g., UK Kidney Association and Kidney Research UK),** the company **highlights** ~~**argues**~~ that the current differences within the recommendations for dapagliflozin and empagliflozin for CKD lead to difficulties in prescribing"	It is inaccurate and misleading to state that the Company argues that current differences in the empagliflozin and dapagliflozin recommendations cause complexities in prescribing without highlighting the evidence supporting this. The text should be amended to accurately state that the Company highlights these complexities, based on comments from stakeholders on the draft scope.	This is not a factual inaccuracy, and no amendments made to the EAG report. The EAG's statement is immediately followed by a reference to the CS addendum, page 25, where the company's supporting evidence is cited.
Page 19 of the EAG report states: "Clinical advisors to the EAG do not believe that there are significant	The Company kindly requests that the following is amended to acknowledge that the advice received from the two EAG's clinical advisors is contradictory	The discussion regarding complexities associated with prescribing is currently misleading and should be fair and balanced. It should be acknowledged that the advice received from the two	Clinical advice to the EAG is not a factual inaccuracy and no amendments made to the EAG report. Reference to the CS addendum, page 25, where the company's counterarguments are

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
complexities in prescribing due to the different recommended populations for the two drugs, and noted that in practice, prescribing empagliflozin was simpler due to its broader indication."	to comments on the draft scope received by numerous UK clinical societies (e.g., UK Kidney Association and Kidney Research UK). Moreover, the statement whether prescribing empagliflozin based on its indication would be simpler is to be either removed or specified. Suggested amendment is included below: "Clinical advisors to the EAG do not believe that there are significant complexities in prescribing due to the different recommended populations for the two drugs~~**, and noted that in practice, prescribing empagliflozin was simpler due to its broader indication**~~. **This advice is contradictory to comments received on the draft scope from clinical societies (e.g., UK Kidney Association and Kidney Research UK), which stated alignment of the dapagliflozin and empagliflozin recommendations would remove complexities**."	EAG's clinical advisors regarding the lack of complexities in prescribing is contradictory to comments received on the draft scope from UK clinical societies. Moreover, both dapagliflozin and empagliflozin are "indicated in adults for the treatment of chronic kidney disease" as per their respective SmPC.[20, 21] Therefore, it is factual inaccurate to state that empagliflozin is simpler to prescribe in practice based on its broader indication (compared with dapagliflozin).	provided is made on p14 of the EAG report.

Issue 10 Misleading discussion regarding the use of individual patient data (IPD) from dapagliflozin RCTs

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 65 of the EAG report states: "In the absence of an RCT in the relevant populations, IPD from existing dapagliflozin studies may be used, where available, to inform conclusions on the effectiveness and safety of dapagliflozin in the five CKD subpopulations against placebo and empagliflozin."	The Company kindly requests that this text is amended as follows: "In the absence of an RCT in the relevant populations, IPD from existing dapagliflozin studies may be used, where available, to inform conclusions on the effectiveness and safety of dapagliflozin in the five CKD subpopulations against placebo and empagliflozin. **However, as these analyses would be post-hoc against placebo only and conducted in small subgroups not stratified at randomisation, this additional evidence would likely be uncertain**."	It is misleading to suggest that IPD from the dapagliflozin RCTs could be used to reliably inform conclusions regarding the efficacy and safety of dapagliflozin versus placebo. As acknowledged by the EAG on page 10 of the report, these analyses would likely be insufficient to resolve these issues. This should be acknowledged when stating that IPD could be used in the concluding paragraphs.	This is not a factual inaccuracy, and no amendments made to the EAG report. The EAG states that IPD may provide more relevant information to inform conclusions than is currently available, and did not imply that it would be free from limitations.

Issue 11 Typographical, referencing, and data errors

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Reference 17 is listed on page 17 as "Herrington (2022)" and on pages 18 and 19 as "Baigent (2022)".	The Company kindly requests that this reference in the text is updated to "Nuffield Department of Population Health Renal Studies Group (2022)", which is to reflect reference 17 from the	Reference error. Incorrect referencing is misleading and should, therefore, be amended to reflect the associated source.	Reference 17 has been amended as proposed.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
	bibliography list: Nuffield Department of Population Health Renal Studies Group, SGLT inhibitor Meta-Analysis Cardio-Renal Trialists' Consortium. Impact of diabetes on the effects of sodium glucose co-transporter-2 inhibitors on kidney outcomes: collaborative meta-analysis of large placebo-controlled trials. *Lancet* 2022;400:1788-801.		
Page 17 of the EAG report states: "The company also cites evidence showing how both empagliflozin and dapagliflozin show similar high selectivity for SGLT2 inhibitors over SGLT1 inhibitors versus phlorizin, which might contribute to shared patterns of efficacy and safety."	The Company requests that this statement is amended as follows: "The company also cites evidence showing how both empagliflozin and dapagliflozin show similar high selectivity for SGLT2 **receptors** ~~**inhibitors**~~ over SGLT1 **receptors** ~~**inhibitors**~~ versus phlorizin, which might contribute to shared patterns of efficacy and safety."	Typographical error. Empagliflozin and dapagliflozin have high selectivity for SGLT2 receptors, not SGLT2 inhibitors.	Thank you. This has been amended on p17 of the EAG report
Page 24 of the EAG report states: "Both the NICE scope and decision problem agree that the intervention is empagliflozin."	The Company requests that this statement is amended as follows: "Both the NICE scope and decision problem agree that the **comparator** ~~**intervention**~~ is empagliflozin."	Typographical error. It is incorrectly stated that empagliflozin is the intervention, rather than the comparator.	Thank you. This has been amended on p24 of the EAG report

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 25 of the EAG report states: "No evidence relating to empagliflozin for any clinical efficacy outcomes specified in the NICE scope are provided in the provided in the CS documents and AE data are not available for the five CKD subpopulations."	The Company requests that this statement is amended as follows: "No evidence relating to empagliflozin for any clinical efficacy outcomes specified in the NICE scope are provided ~~in the provided~~ in the CS documents and AE data are not available for the five CKD subpopulations."	Typographical error.	Thank you. This has been amended on p25 of the EAG report
Page 36 of the EAG report states: "The DAPA-HF RCT compared dapagliflozin to placebo comparing dapagliflozin to placebo in 4744 patients with NYHA II-IV HF and an ejection fraction <40%, over a follow up of 8 months."	The Company kindly requests this is amended as follows: "The DAPA-HF RCT compared dapagliflozin to placebo comparing dapagliflozin to placebo in 4744 patients with NYHA II-IV HF and an ejection fraction <40%, over a follow up of 18 months."	Data error. The median follow-up in DAPA-HF is 18 months, as reported in McMurray *et al.* (2019), rather than 8 months.[22]	Thank you. This has been amended on p36 of the EAG report
Page 55 of the EAG report states: "Secondly, no evidence relating to empagliflozin for any outcomes specified in the NICE scope are provided in the provided in the CS documents."	The Company kindly requests this is amended as follows: "Secondly, no evidence relating to empagliflozin for any outcomes specified in the NICE scope are provided in ~~the provided in~~ the CS documents."	Typographical error.	Thank you. This has been amended on p55 of the EAG report

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 62 of the EAG report states: "However, the company included only serious AEs from DAP-CKD in their base-case cost comparison analysis and did not provide comparative estimates from EMPA-KIDNEY."	The Company kindly requests this is amended as follows: "However, the company included only serious AEs from DAP**A**-CKD in their base-case cost comparison analysis and did not provide comparative estimates from EMPA-KIDNEY."	Typographical error.	Thank you. This has been amended on p62 of the EAG report

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal: cost-comparison

Dapagliflozin for the treatment of adults with chronic kidney disease – Review of TA775 [ID6411]

Additional Data

Company evidence submission

November 2024

File name	Version	Contains confidential information	Date
ID6411_Dapagliflozin_CKD_TA775 review_Additional data [CON]	Final	Yes	8th November 2024

Contents

1 Executive summary

Introduction and aim

The aim of this submission is to review the current National Institute for Health and Care Excellence (NICE) recommendation for dapagliflozin in chronic kidney disease (CKD; TA775) and align it with the NICE recommendation for empagliflozin as a treatment for CKD.[1, 2] The empagliflozin recommendation covers a broader population of patients with CKD as an option for the treatment of CKD in adults with:[2]

- An estimated glomerular filtration rate (eGFR) of 20 to less than 45 ml/min/1.73m^2 *or*
- An eGFR of 45 to 90 ml/min/1.73m^2 *and either:*
    - A urine albumin-creatinine ratio (uACR) of 22.6 mg/mmol or more
    - Type 2 diabetes (T2D)

Throughout this appraisal, an abundance of evidence has been presented which supports the clinical equivalence of dapagliflozin and empagliflozin across all CKD subgroups of relevance. This includes data from randomised controlled trials for dapagliflozin in CKD and other indications of relevance (DAPA-CKD, DAPA-HF and DECLARE-TIMI 58), data from real-world evidence (RWE) studies (OPTIMISE–CKD [Svensson *et al.* 2024; Tangri *et al.* 2024] and Nakhleh *et al.* 2024), and discussion of the mechanism of action and biological similarity of dapagliflozin and empagliflozin.[3-8]

Despite the evidence presented demonstrating the consistent treatment effect of dapagliflozin across CKD subgroups and the clinical equivalence of dapagliflozin and empagliflozin, NICE and the External Assessment Group (EAG) deemed that uncertainty remained regarding the relative efficacy of dapagliflozin and empagliflozin across the whole CKD population. As such, AstraZeneca have conducted additional analyses to evaluate the relative effectiveness of dapagliflozin versus empagliflozin across the total CKD population using RWE from Optum Clinformatics Data Mart (CDM).

Methodology

All data were sourced from Optum CDM, which was used to inform the OPTIMISE-CKD study. Data within the database from 24th February 2022 to the latest available date in the database (i.e., 31st March 2024) were used.

Analyses of the relative effectiveness of dapagliflozin and empagliflozin in patients with CKD are presented for four endpoints: 1) eGFR slope, 2) time to hospitalisation for heart failure [HF], 3) time to hospitalisation for CKD and 4) time to death within hospital (all-cause death). These endpoints provide a robust overview of the clinical impact of dapagliflozin and empagliflozin on CKD.

The inclusion criteria applied to Optum CDM align with the EMPA-KIDNEY population as EMPA-KIDNEY was previously deemed generalisable to UK clinical practice. As such, the patient population included from Optum CDM is reflective of UK clinical practice. Data are presented for the overall CKD population included within the Optum CDM database, which aligns with the population included in EMPA-KIDNEY and the NICE recommendation for empagliflozin.

Population subgroup analyses were also conducted on clinically relevant CKD subpopulations, including with/without T2D and high (≥200 mg/g)/low (<200 mg/g) uACR. Sensitivity analyses were conducted further varying the population included within the analyses from Medicare patients only, to 1) the inclusion of commercial insurance patients and 2) the inclusion of patients with missing baseline uACR.

All analyses have been repeated over two time periods. The 'main period' represents the time during which both empagliflozin and dapagliflozin were both approved for use in patients with CKD in the US, as well as T2D and HF. The 'pooled period' represents time periods during which dapagliflozin and empagliflozin were licensed for T2D and/or HF, but not both for CKD.

The primary analysis uses the overall population, Medicare patients only and the 'main period'. Further details on the methodology, and the subgroup and sensitivity analyses conducted are provided in Section 2.

Summary of data presented

The analysis on the overall population, Medicare only patients and the 'main period' represents the primary analysis and these results are presented in Section 3; the 'pooled period' sensitivity analysis using the overall population, Medicare only patients is presented in Section 4. All population subgroup analyses are presented in Section 5, with the remaining sensitivity analyses presented in Section 6. Baseline characteristics and propensity score (PS) weighting plots are presented in the Appendices.

A summary of all analyses conducted and presented within this document is provided in Section 2.8.

Results and conclusion

For the primary analysis, [redacted]

Based on the presented analyses of dapagliflozin versus empagliflozin in patients with CKD, [redacted]

2 Methodology

2.1 Objectives and outcomes

The objective of these analyses was to estimate the relative treatment effect of dapagliflozin versus empagliflozin in patients with CKD, and demonstrate the consistency of treatment effect between treatments. In these analyses, CKD was defined as follows, in line with the enrolment criteria of the EMPA-KIDNEY study:

- Baseline eGFR ≥20 and <45 mL/min/m^2 **and** any uACR; **or**
- Baseline eGFR ≥45 and <90 mL/min/m^2 **and** uACR ≥200 mg/g

The treatment effect was assessed using the following endpoints:

- eGFR slope
- Time to first hospitalisation for CKD
- Time to first hospitalisation for HF
- Time to death within hospital

Data on time to all-cause death within hospital are presented in the absence of data on all-cause mortality in all settings, as these data were not available within the Optum CDM database.

2.2 Data sources – Optum Clinformatics Data Mart (CDM)

All data were sourced from Optum CDM, which was used to inform the OPTIMISE-CKD study. Data within the database across the period 30th April 2021 to the 31st March 2024 (the latest available date within the database) were available. As discussed further in Section 2.4, data from 24th February 2022 to the latest available date in the database (i.e., 31st March 2024) were ultimately used.

Optum CDM is a US claims database, which contains patient-level data from claims submitted for all medical and pharmacy health care services for more than 78 million people across all 50 US states since January 2007. The population covered include privately insured patients with commercial or Medicare Advantage coverage. Optum CDM contains outcomes data for patients with CKD after initiation of empagliflozin and dapagliflozin, so it was deemed feasible to conduct an analysis to determine the relative treatment effect of dapagliflozin versus empagliflozin in patients with CKD.

2.3 Populations

The relative treatment effect for dapagliflozin and empagliflozin was evaluated in the overall population, which aligns with the population included in EMPA-KIDNEY and NICE recommendation for empagliflozin. Identification of patients included within the overall population corresponds broadly with OPTIMISE-CKD. The inclusion and exclusion criteria applied are presented in Table 1.

The primary analysis was conducted in the 'complete case' overall population, which consisted of patients with eGFR measurement and uACR measurements in the 122 days

prior to or at index date, and age and sex known at index date. For the population informing the primary analysis (described further in Section 2.4), [redacted] patients receiving dapagliflozin were included and [redacted] patients receiving empagliflozin were included (total patients: [redacted]; overall population, Medicare only).

Table 1: Inclusion and exclusion criteria applied to Optum CDM to identify eligible patients with CKD

Inclusion criteria	Exclusion criteria

• Patients prescribed with dapagliflozin 10 mg OR empagliflozin 10 mg in the period 30th April 2021 – 31st March 2024 (day of prescription = "index date")[a]	• Patients without 365 days of continuous enrolment in Optum CDM prior to index date
	• Patients without:
	  • Two eGFR measurements ≤60 mL/min/1.73m^2 taken ≥90 days apart at any time prior or equal to index OR
	  • eGFR ≤90 mL/min/1.73m^2 followed by a CKD diagnosis at any time prior or equal to index
	• Patients with T1D or gestational diabetes
	• Patients with known eGFR <20 mL/min/1.73m^2 in 365 days prior to or at index date
	• Patients with use of any SGLT2i prior to index date
	• Patients with known eGFR ≥45 mL/min/1.73m^2 and known UACR <200 mg/g at index
	• Patients with known eGFR ≥90 mL/min/1.73m^2 at index

[a] Based on the feasibility assessment, only patients in Periods 3 to 5 (24th February 2022 to the latest available date in the database) were included (Section 2.4).
Abbreviations: CDM: Clinformatics Data Mart; CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; SGLT2i: sodium-glucose co-transporter-2 inhibitor; T1D: type 1 diabetes mellitus; uACR: urinary abumin-creatinine ratio

2.3.1 Subgroup analyses

In addition to the overall population, the following additional subgroups were explored:

- **With T2D:** Patients with a diagnosis of T2D at any time prior to or at index
- **Without T2D:** Patients without a diagnosis of T2D at any time prior to or at index
- **Low uACR (<200 mg/g):** Patients with last uACR prior to index <200 mg/g
- **High uACR (≥200 mg/g):** Patients with last uACR prior to index ≥200 mg/g
- **uACR <200 mg/g and T2DM**: Patients with a diagnosis of type 2 diabetes at any time prior to or at index and last uACR prior to index <200 mg/g
- **uACR <200 mg/g and no T2DM**: Patients without a diagnosis of type 2 diabetes at any time prior to or at index and last uACR prior to index <200 mg/g
- **uACR ≥200 mg/g and T2DM**: Patients with a diagnosis of type 2 diabetes at any time prior to or at index and last uACR prior to index ≥200 mg/g
- **uACR ≥200 mg/g and no T2DM**: Patients without a diagnosis of type 2 diabetes at any time prior to or at index and last uACR prior to index ≥200 mg/g

Due to the definitions of CKD used in these analyses (Section 2.1), patients included in the low uACR (<200 mg/g) subgroup analyses also needed a baseline eGFR measurement of <45 mL/min/1.73m^2.

2.4 Time period

All analyses have been repeated over two time periods. The 'main period' represents the time during which both empagliflozin and dapagliflozin were both approved for use in patients with CKD in the US, as well as T2D and HF (i.e., period 5 in Table 2). This period is 22nd September 2023 to the latest available date in the database (i.e., 31st March 2024). The 'pooled period' represents time periods during which dapagliflozin and empagliflozin were licensed for T2D and/or HF, but not both for CKD. As patients with T2D and HF may have comorbid CKD, data are available within Optum CDM that show outcomes relevant to CKD from these patients. This period is 24th February 2022 to the latest available date in the database (i.e., 31st March 2024; Periods 3 to 5 in Table 2).

The primary analysis uses the 'main period' and the 'pooled period' is a sensitivity analysis. The 'pooled period' includes a larger population and greater number of events; based on a feasibility analysis showing comparable eGFR declines for dapagliflozin and empagliflozin in period 3 to 5, these periods were used for the 'pooled period'. However, the approved indications for the two treatments differ which may result in one population being more or less enriched with patients with HF or T2D versus the other population. For the subgroup of patients without T2D and low uACR (<200 mg/g), there were insufficient events to run analyses using the 'main period' so results are only available using the 'pooled period'.

An overview of the timeline for approval of dapagliflozin and empagliflozin in relevant indications in the US is presented in Table 2.

Table 2: Timeline of approved populations in the US for dapagliflozin and empagliflozin

Period		T2D		CKD		HFrEF		HFpEF	
		Dapa	Empa	Dapa	Empa	Dapa	Empa	Dapa	Empa
1	30th April 2021–17th August 2021	Yes	Yes	Yes	No	Yes	No	No	No
2	18th August 2021–23rd February 2022	Yes	Yes	Yes	No	Yes	Yes	No	No
3	24th February 2022–8th May 2023	Yes	Yes	Yes	No	Yes	Yes	No	Yes
4	9th May 2023–21st September 2023	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes
5	22nd September 2023–April 2024	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

Period 5 only is hereafter referred to as the 'main period'. Periods 3 to 5 are hereafter referred to as the 'pooled period'.
Abbreviations: CKD: chronic kidney disease; HFpEF: heart failure with preserved ejection fraction; HFrEF: heart failure with reduced ejection fraction; T2D: type 2 diabetes.

2.5 Sensitivity analyses

The primary analysis only included patients from Optum CDM who were Medicare recipients. Moreover, the primary analysis was conducted in the 'complete case' population, which included patients that had uACR measurements in the 122 days prior to or at index date.

The following sensitivity analyses were conducted varying the population included within the analyses: 1) inclusion of commercial insurance patients and 2) inclusion of patients with missing baseline uACR.

2.5.1 Inclusion of commercial insurance patients

While the vast majority of patients receiving dapagliflozin in the US are expected to be Medicare recipients, analyses were conducted to explore the sensitivity of the results to a broader population by including patients with commercial insurance as well as those with Medicare. This population is hereafter referred to as 'Medicare plus commercial'.

2.5.2 Inclusion of patients with missing baseline uACR

The 'complete case' overall population requires that patients have both a uACR and eGFR measurement at baseline to assess inclusion criteria. However, for those with a baseline eGFR <45 mL/min/1.73 m^2, there were no uACR requirements for empagliflozin. Therefore, sensitivity analyses were conducted in which individuals with a baseline eGFR of <45 mL/min/1.73 m^2 and any uACR (including missing) were included. This population is hereafter referred to as 'Medicare plus missing uACR'.

2.6 Propensity score analysis

2.6.1 Weighting

The 'complete case' population in the 'main period' prescribed empagliflozin were considered the target population, as this population was deemed most likely to be representative of the contemporary overall CKD population.

Outcomes weighting was conducted using inverse probability of treatment weights given by the PS models which are discussed below. Weights were used to generate estimates of the average treatment effect on the treated.

2.6.2 Propensity score model

A PS model was fitted to the patients within the period identified as plausible for comparison to the 'main period' for empagliflozin. Further discussion of the time periods is provided in Section 2.4. The covariables included were those used in Tangri *et al.* (2024),[9] excluding nationality covariables:

- Sex
- Age (modelled as a continuous variable with 10 knot splines)
- Race {Asian, Black, Hispanic, White, Other/unknown}
- CKD aetiology {Diabetic, Hypertensive, Glomerular disease, Renal tubulo-interstitial disease, Other/unknown}
- Hx Angina pectoris
- Hx Atrial fibrillation
- Hx Bradycardia
- Hx Heart failure
- Hx Hypertension
- Hx Myocardial infarction
- Hx Stroke
- Hx Other cardiovascular disease
- Hx Anaemia
- Hx Hyperkalaemia
- Hx Type 2 diabetes

- RASi treatment
- ARNI treatment
- Beta-blocker treatment
- Calcium channel blocker treatment
- Diuretic treatment
- Antithrombotic agent treatment
- Statin treatment
- Antihyperkalaemic treatment
- Antidiabetic treatment
- eGFR (categorical) {<30, 30-44, 45-60, 60-75, 75+}
- eGFR (continuous with 4 knot splines)
- UACR (categorical) {0-29, 30-199, 200+}
- UACR ((continuous with 4 knot splines)

The interaction term between angiotensin receptor/neprilysin inhibitor (ARNI) and HF described in Tangri (2024)[9] was included.

2.6.3 Propensity score weighting

Inverse probability weights[10] generated by the PS models were used to weight individuals within the overlapping regions by the inverse of the probability of the patients occurring in the population first prescribed empagliflozin in the 'main period'. This is preferred to a matching analysis, as the number of patients prescribed empagliflozin was larger than the number of patients prescribed dapagliflozin (in the same time period), and so matching would either have to compensate for sampling with replacement of the dapagliflozin subgroup, or would have to thin the empagliflozin subgroup. The weighting process was repeated for each subgroup analyses to ensure balance between subgroups.

In order to estimate the average treatment effect on the treated (ATT), the weights for the patients within the empagliflozin subgroup are assigned as "1", and those outside are given a weight of $\frac{\pi(x_i)}{1-\pi(x_i)}$ where $\pi(x_i)$ is the PS for patient i.

Standardised mean difference of covariables between the weighted population receiving dapagliflozin and the weighted population receiving empagliflozin was evaluated to demonstrate comparability of populations. A threshold of ±0.1 was used to evaluate imbalance.

2.7 Statistical analyses

In the primary analysis, predictions of the average treatment effect on the treated considered the 'complete case' overall population. In addition to PS weighting, further adjustments were conducted by a quantile regression model, adjusting for piecewise $\log_{10}$uACR, piecewise eGFR, T2D, and body mass index (BMI). This additional adjustment included variables identified as important. Further reasons for including BMI were that it was not able to be included within the propensity score model due to missingness of data but showed some residual imbalance between treatment groups after weighting. Further details on this are provided in the following sections by endpoint.

2.7.1 eGFR slope between dapagliflozin and empagliflozin

For the analysis of difference in median eGFR slope between dapagliflozin and empagliflozin, the empagliflozin data in the eligible earlier periods were augmented by inverse probability weighting to the 'main period' cohort. The dapagliflozin data consisted of

two cohorts, the ‘main period’ cohort (i.e., Period 5) and the Period <5 cohort, which were independently weighted to the empagliflozin ‘main period’ cohort. Eligible patients required at least two eGFR measurements (excluding baseline) at least 30 days apart for a valid eGFR slope to be calculated.

Comparison of median eGFR slope was conducted by a quantile regression model adjusting for piecewise log_{10}uACR, piecewise eGFR, T2D, and BMI. This regression model was weighted by the inverse probability of treatment weights. Results are presented for both with (‘PS weighted and adjusted’) and without (‘PS weighted’) adjustment.

2.7.2 Time to event outcomes

Using the same inverse probability of treatment weights described above, weighted Kaplan-Meier (KM) estimators of time to event outcomes were generated. Cumulative numbers of events and patients remaining at risk are reported at regular timepoints. Unadjusted Cox proportional hazards models upon the weighted data (‘PS weighted’) and a log-rank test upon the weighted data are reported along with adjustment for piecewise log_{10}uACR, piecewise eGFR, T2D, and BMI (‘PS weighted and adjusted’).

2.8 Summary of analyses conducted

A summary of all analyses conducted and presented within this document is provided in Table 3.

Table 3: Analyses conducted on the Optum database and presented within this document

Population subgroup	Endpoint				Sensitivity analyses				
					Time period		Patients included		
	Difference in median eGFR slope	Hospitalisation for HF	Hospitalisation for CKD	Death within hospital[a]	Main period	Pooled period	Medicare only	Medicare plus commercial	Medicare plus missing uACR
Overall population	✓	✓	✓	✓	✓	✓	✓	✓	✓
With T2D	✓	✓	✓	×	✓	✓	✓	✓	✓
Without T2D	✓	✓	✓	×	✓	✓	✓	✓	✓
Low uACR (<200 mg/g)	✓	✓	✓	×	✓	✓	✓	✓	×[c]
High uACR (≥200 mg/g)	✓	✓	✓	×	✓	✓	✓	✓	×[c]
With T2D, low uACR	✓	✓	✓	×	✓	✓	✓	✓	×[c]
With T2D, high uACR	✓	✓	✓	×	✓	✓	✓	✓	×[c]
Without T2D, low uACR	✓	✓	✓	×	×[b]	✓	✓	✓	×[c]
Without T2D, high uACR	✓	✓	✓	×	×[b]	✓	✓	✓	×[c]

For all analyses, results using both the PS weighted and adjusted model and the PS weighting only are presented. [a] There were insufficient events to run analyses for death within hospital in the population subgroups. [b] For the without T2D, low uACR and the without T2D, high uACR subgroups, there were insufficient events in the 'main period' for analyses to be run; results for these subgroups are only presented using the 'pooled period'. [c] For the population subgroup analyses with uACR requirements, the Medicare plus missing uACR sensitivity analyses were not run as results would be the same as the primary results and therefore redundant.
Abbreviations: CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; HF: heart failure; T2D: type 2 diabetes; uACR: urine albumin-creatinine ratio.

3 Results – Primary analysis (overall population, Medicare patients only, 'main period')

3.1 Baseline characteristics

A table presenting the baseline characteristics of patients receiving dapagliflozin and empagliflozin in the overall population (being 'complete case' and Medicare only, see Section 2) from the 'main period' is presented in Table 4, before and after weighting. The inclusion criteria applied to Optum CDM align with the EMPA-KIDNEY population as EMPA-KIDNEY was deemed generalisable to UK clinical practice. As such, the patient population included from Optum CDM is reflective of UK clinical practice.

As demonstrated by the standardised mean difference (SMD) for each variable, the treatment arms were well balanced before and after weighting. [redacted]. This variable was also included in the adjusted analyses (Section 2.7).

Table 4: Baseline characteristics of patients in the overall population ('complete case') during the 'main period', Medicare only

	Before weighting			After weighting		
Characteristic	**Dapagliflozin (n=[redacted])**	**Empagliflozin (n=[redacted])**	**SMD**	**Dapagliflozin (n=[redacted])**	**Empagliflozin (n=[redacted])**	**SMD**
Age, years, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BMI, kg/m^2						
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Categorical						
<25	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
25.0-29.9	[redacted]	[redacted]		[redacted]	[redacted]	
≥30	[redacted]	[redacted]		[redacted]	[redacted]	
Missing	[redacted]	[redacted]		[redacted]	[redacted]	
Baseline eGFR, mL/min/1.73m^2 [a]						
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Categorical						
60-89 (G2), n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
45-59 (G3a), n (%)	[redacted]	[redacted]		[redacted]	[redacted]	
30-44 (G3b), n (%)	[redacted]	[redacted]		[redacted]	[redacted]	
15-29 (G4), n (%)	[redacted]	[redacted]		[redacted]	[redacted]	
Baseline uACR, mg/g[a]						
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Categorical						
0-29, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
30-199, n (%)	[redacted]	[redacted]		[redacted]	[redacted]	
≥200, n (%)	[redacted]	[redacted]		[redacted]	[redacted]	
ln_uacr, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Female, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age, n (%)						
<40	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

40-49	[redacted]	[redacted]		[redacted]	[redacted]	
50-59	[redacted]	[redacted]		[redacted]	[redacted]	
60-69	[redacted]	[redacted]		[redacted]	[redacted]	
70-79	[redacted]	[redacted]		[redacted]	[redacted]	
≥80	[redacted]	[redacted]		[redacted]	[redacted]	
Race, n (%)						
Asian	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Black	[redacted]	[redacted]		[redacted]	[redacted]	
Unknown/Other	[redacted]	[redacted]		[redacted]	[redacted]	
White	[redacted]	[redacted]		[redacted]	[redacted]	
Medicare, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cause of CKD, n (%)						
Diabetic kidney disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypertensive disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Glomerular disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Renal tubolo-interstitial disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other/unknown	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Comorbidities						
Angina	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Atrial fibrillation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bradycardia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Heart failure	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Myocardial infarction	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stroke	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other cardiovascular disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hyperkalaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

T2D	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Medications, n (%)						
RASi	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ARNI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Beta-blocker	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Calcium channel blocker	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Diuretics	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Antithrombotic agent	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Statins	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anti-hyperkaliaemic treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anti-diabetic treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[a] Patients in the 'complete case' had an eGFR and uACR measurement within 122 days prior to or at the index date.
Abbreviations: ARNI: angiotensin receptor/neprilysin inhibitor; BMI: body mass index; CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; RASi: renin-angiotensin system inhibitor; SD: standard deviation; SMD: standardised mean difference; T2D: type 2 diabetes; uACR: urinary albumin-creatinine ratio.

3.2 Propensity score matching

A density plot of the PS and weight distribution are presented in Figure 1 and Figure 2. The PS demonstrate [redacted].

Figure 1: Density plot of PS for dapagliflozin and empagliflozin

[redacted]

'Period 5' refers to the 'main period.
Abbreviations: dapa: dapagliflozin; empa: empagliflozin; PS: propensity score

Figure 2: Weight distribution for dapagliflozin patients following PS weighting

[redacted]

'Period 5' refers to the 'main period.
Abbreviations: dapa: dapagliflozin; PS: propensity score.

3.3 Effectiveness outcomes

3.3.1 Median eGFR slope

The median eGFR slope for patients receiving dapagliflozin and empagliflozin (PS weighted) are presented in Figure 3, with the difference in median eGFR slope presented in Table 5.

These data demonstrate [redacted]

Figure 3: Median eGFR slope for patients receiving dapagliflozin and empagliflozin (PS weighted) – overall population, 'main period'

[redacted]

A higher value indicates a greater treatment benefit. Dapagliflozin patient numbers: 90 days: [redacted]; 180 days: [redacted]. Empagliflozin patient numbers: 90 days: [redacted]; 180 days: [redacted].
Abbreviations: dapa: dapagliflozin; eGFR: estimated glomerular filtration rate; empa: empagliflozin.

Table 5: Difference in median eGFR slope for patients receiving dapagliflozin versus empagliflozin – overall population, 'main period'

Follow-up duration	PS weighted		PS weighted and adjusted[a]	
	Difference (mL/min/1.73m^2 [95% CIs])	P-value	Difference (mL/min/1.73m^2 [95% CIs])	P-value
90 days slope	[redacted]	[redacted]	[redacted]	[redacted]
180 days slope	[redacted]	[redacted]	[redacted]	[redacted]
Total slope	[redacted]	[redacted]	[redacted]	[redacted]

A positive value indicates a treatment benefit of dapagliflozin versus empagliflozin. [a] Adjusted for baseline ln(uACR), uACR category, baseline eGFR, eGFR category, T2D, and BMI class.
Abbreviations: BMI: body mass index; CIs: confidence intervals; eGFR: estimated glomerular filtration rate; PS: propensity score; T2D: type 2 diabetes; uACR: urine albumin-creatinine ratio.

3.3.2 Time to hospitalisation for HF

A KM plot of time to hospitalisation for HF for dapagliflozin and empagliflozin is presented in Figure 4. The total number of events observed (both treatment arms) was [redacted] (n=[redacted]). The hazard ratio (HR) following PS weighting and adjustment for time to hospitalisation for HF for

dapagliflozin versus empagliflozin was [redacted] (95% CIs: [redacted]), with a PS weighted HR of [redacted] (95% CIs: [redacted]).
[redacted].

Figure 4: KM plot for time to hospitalisation for HF for dapagliflozin and empagliflozin (PS weighted) – overall population, 'main period'

[redacted]

Abbreviations: HF: heart failure.

3.3.3 Time to hospitalisation for CKD

A KM curve of time to hospitalisation for CKD for dapagliflozin and empagliflozin is presented in Figure 5. The total number of events observed (both treatment arms) was [redacted] (n=[redacted]). The PS weighted and adjusted HR for dapagliflozin versus empagliflozin for time to hospitalisation for CKD was [redacted] (95% CIs: [redacted]), with a PS weighted HR of [redacted] (95% CIs: [redacted]).
[redacted].

Figure 5: KM plot for time to hospitalisation for CKD for dapagliflozin and empagliflozin (PS weighted) – overall population, 'main period'

[redacted]

Abbreviations: CKD: chronic kidney disease; KM: Kaplan–Meier.

3.3.4 Time to death within hospital

A KM curve of time to death within hospital for dapagliflozin and empagliflozin is presented in Figure 6. The total number of events observed (both treatment arms) was [redacted] (n=[redacted]). The PS weighted and adjusted HR for dapagliflozin versus empagliflozin for time to death within hospital was [redacted] (95% CIs: [redacted]), with a PS weighted HR of [redacted] (95% CIs: [redacted]).
[redacted].

Figure 6: KM plot for time to death within hospital for dapagliflozin and empagliflozin (PS weighted) – overall population, 'main period'

[redacted]

Abbreviations: KM: Kaplan–Meier.

4 Additional analysis (overall population, Medicare only, 'pooled period', subgroups) – Effectiveness results

4.1 Median eGFR slope

The median eGFR slope for patients receiving dapagliflozin and empagliflozin (PS weighted) are presented in Figure 7, with the difference in median eGFR slope presented in Table 7.

[redacted].

Figure 7: Median eGFR slope for patients receiving dapagliflozin and empagliflozin (PS weighted) – overall population, 'pooled period'

[redacted]

A higher value indicates a greater treatment benefit. Dapagliflozin patient numbers: 90 days: [redacted]; 180 days: [redacted]; total: [redacted]. Empagliflozin patient numbers: 90 days: [redacted]; 180 days: [redacted]; total: [redacted].
Abbreviations: dapa: dapagliflozin; eGFR: estimated glomerular filtration rate; empa: empagliflozin.

Table 6: Difference in median eGFR slope for patients receiving dapagliflozin versus empagliflozin – overall population, 'pooled period'

Follow-up duration	PS weighted		PS weighted and adjusted	
	Difference (mL/min/1.73m^2 [95% CIs])	P-value	Difference (mL/min/1.73m^2 [95% CIs])	P-value
90 days slope	[redacted]	[redacted]	[redacted]	[redacted]
180 days slope	[redacted]	[redacted]	[redacted]	[redacted]
Total slope	[redacted]	[redacted]	[redacted]	[redacted]

A positive value indicates a treatment benefit of dapagliflozin versus empagliflozin. [a] Adjusted for baseline ln(uACR), uACR category, baseline eGFR, eGFR category, T2D, and BMI class.
Abbreviations: BMI: body mass index; CIs: confidence intervals; eGFR: estimated glomerular filtration rate; T2D: type 2 diabetes; uACR: urine albumin-creatinine ratio.

4.2 Time to hospitalisation for HF

A KM plot of time to hospitalisation for HF for dapagliflozin and empagliflozin is presented in Figure 8. [redacted]

The total number of events observed (both treatment arms) was [redacted] (n=[redacted]). The PS weighted and adjusted HR for time to hospitalisation for HF for dapagliflozin versus empagliflozin was [redacted] (95% CIs: [redacted]), with a PS weighted HR of [redacted] (95% CIs: [redacted]

Figure 8: KM plot for time to hospitalisation for HF for dapagliflozin and empagliflozin (PS weighted) – overall population, 'pooled period'

[redacted]
Abbreviations: HF: heart failure.

4.3 Time to hospitalisation for CKD

A KM curve of time to hospitalisation for CKD for dapagliflozin and empagliflozin is presented in Figure 9.
[redacted]

The total number of events observed (both treatment arms) was [redacted] (n=[redacted]). The PS weighted and adjusted HR for dapagliflozin versus empagliflozin for time to hospitalisation for CKD was [redacted] (95% CIs: [redacted]), with a PS weighted HR of [redacted] (95% CIs:
[redacted]

Figure 9: KM plot for time to hospitalisation for CKD for dapagliflozin and empagliflozin (PS weighted) – overall population, 'pooled period'

Abbreviations: CKD: chronic kidney disease; KM: Kaplan–Meier.

4.4 Time to death within hospital

A KM curve of time to death within hospital for dapagliflozin and empagliflozin is presented in Figure 10.

The total number of events observed (both treatment arms) was (n=). The PS weighted and adjusted HR for dapagliflozin versus empagliflozin for time to death within hospital was (95% CIs:), with a PS weighted HR of (95% CIs:

Figure 10: KM plot for time to death within hospital for dapagliflozin and empagliflozin (PS weighted) – overall population, 'pooled period'

Abbreviations: KM: Kaplan–Meier.

5 Population subgroup analyses – Effectiveness results

Full effectiveness results for the population subgroup analyses are presented in the following sections. Baseline characteristics and PS weighting plots are presented in Appendix A and Appendix B, respectively.

5.1 Overview of population subgroup analyses

An overview of the results across populations for time to hospitalisation for HF and time to hospitalisation for CKD is presented in Figure 11 and Figure 12, respectively. It was not possible to produce visual representations of difference in median eGFR slope due to the measurement scale. Detailed results on median eGFR slope are presented in the following sections.

In terms of time to hospitalisation for HF,

.

Figure 11: Population subgroup forest plot for dapagliflozin versus empagliflozin for time to hospitalisation for HF

A HR below 1.0 indicates a treatment benefit of dapagliflozin over empagliflozin.

Abbreviations: CI: confidence interval; HF: heart failure; HR: hazard ratio; uACR: urine albumin-creatinine ratio.

Figure 12: Population subgroup forest plot for dapagliflozin versus empagliflozin for time to hospitalisation for CKD

[redacted]

A HR below 1.0 indicates a treatment benefit of dapagliflozin over empagliflozin.
Abbreviations: CI: confidence interval; HF: heart failure; HR: hazard ratio; uACR: urine albumin-creatinine ratio.

5.2 Patients with T2D

5.2.1 Medicare only, 'main period'

5.2.1.1 Median eGFR slope

The median eGFR slope for patients receiving dapagliflozin and empagliflozin (PS weighted) are presented in Figure 13, with the difference in median eGFR slope presented in Table 8.

[redacted]

Figure 13: Median eGFR slope for patients receiving dapagliflozin and empagliflozin (PS weighted) – with T2D, 'main period'

[redacted]

A higher value indicates a greater treatment benefit. Dapagliflozin patient numbers: 90 days: [redacted]; 180 days: [redacted]. Empagliflozin patient numbers: 90 days: [redacted]; 180 days: [redacted].
Abbreviations: dapa: dapagliflozin; eGFR: estimated glomerular filtration rate; empa: empagliflozin.

Table 7: Difference in median eGFR slope for patients receiving dapagliflozin versus empagliflozin – with T2D, 'main period'

Follow-up duration	PS weighted		PS weighted and adjusted[a]	
	Difference (mL/min/1.73m^2 [95% CIs])	P-value	Difference (mL/min/1.73m^2 [95% CIs])	P-value
90 days slope	[redacted]	[redacted]	[redacted]	[redacted]
180 days slope	[redacted]	[redacted]	[redacted]	[redacted]
Total slope	[redacted]	[redacted]	[redacted]	[redacted]

A positive value indicates a treatment benefit of dapagliflozin versus empagliflozin. [a] Adjusted for baseline ln(uACR), uACR category, baseline eGFR, eGFR category, T2D, and BMI class.
Abbreviations: BMI: body mass index; CIs: confidence intervals; eGFR: estimated glomerular filtration rate; T2D: type 2 diabetes; uACR: urine albumin-creatinine ratio.

5.2.1.2 Time to hospitalisation for HF

A KM plot of time to hospitalisation for HF for dapagliflozin and empagliflozin is presented in Figure 14. [redacted]

The total number of events observed (both treatment arms) was [redacted] (n=[redacted]). The PS weighted and adjusted HR for time to hospitalisation for HF for dapagliflozin versus empagliflozin was [redacted] (95% CIs: [redacted]), with a PS weighted HR of [redacted] (95% CIs: [redacted]

Figure 14: KM plot for time to hospitalisation for HF for dapagliflozin and empagliflozin (PS weighted) – with T2D, 'main period'

[redacted]

Abbreviations: HF: heart failure.

5.2.1.3 Time to hospitalisation for CKD

A KM curve of time to hospitalisation for CKD for dapagliflozin and empagliflozin is presented in Figure 15.

[redacted]

The total number of events observed (both treatment arms) was [redacted] (n=[redacted]). The PS weighted and adjusted HR for dapagliflozin versus empagliflozin for time to hospitalisation for CKD was [redacted] (95% CIs: [redacted]), with a PS weighted HR of [redacted] (95% CIs: [redacted]

Figure 15: KM plot for time to hospitalisation for CKD for dapagliflozin and empagliflozin (PS weighted) – with T2D, 'main period'

[redacted]

Abbreviations: CKD: chronic kidney disease; KM: Kaplan–Meier.

5.2.2 Medicare only, 'pooled period'

5.2.2.1 Median eGFR slope

The median eGFR slope for patients receiving dapagliflozin and empagliflozin (PS weighted) are presented in Figure 16, with the difference in median eGFR slope presented in Table 8.

[redacted]

Figure 16: Median eGFR slope for patients receiving dapagliflozin and empagliflozin (PS weighted) – with T2D, 'pooled period'

[redacted]

A higher value indicates a greater treatment benefit. Dapagliflozin patient numbers: 90 days: [redacted]; 180 days: [redacted]; total: [redacted]. Empagliflozin patient numbers: 90 days: [redacted]; 180 days: [redacted]; total: [redacted].

Abbreviations: dapa: dapagliflozin; eGFR: estimated glomerular filtration rate; empa: empagliflozin.

Table 8: Difference in median eGFR slope for patients receiving dapagliflozin versus empagliflozin – with T2D, 'pooled period'

	PS weighted	PS weighted and adjusted[a]

Follow-up duration	Difference (mL/min/1.73m^2 [95% CIs])	P-value	Difference (mL/min/1.73m^2 [95% CIs])	P-value
90 days slope	[redacted]	[redacted]	[redacted]	[redacted]
180 days slope	[redacted]	[redacted]	[redacted]	[redacted]
Total slope	[redacted]	[redacted]	[redacted]	[redacted]

A positive value indicates a treatment benefit of dapagliflozin versus empagliflozin. [a] Adjusted for baseline ln(uACR), uACR category, baseline eGFR, eGFR category, T2D, and BMI class.
Abbreviations: BMI: body mass index; CIs: confidence intervals; eGFR: estimated glomerular filtration rate; T2D: type 2 diabetes; uACR: urine albumin-creatinine ratio.

5.2.2.2 Time to hospitalisation for HF

A KM plot of time to hospitalisation for HF for dapagliflozin and empagliflozin is presented in Figure 17. [redacted]

The total number of events observed (both treatment arms) was [redacted] (n=[redacted]). The PS weighted and adjusted HR for time to hospitalisation for HF for dapagliflozin versus empagliflozin was [redacted] (95% CIs: [redacted]), with a PS weighted HR of [redacted] (95% CIs: [redacted].

Figure 17: KM plot for time to hospitalisation for HF for dapagliflozin and empagliflozin (PS weighted) – with T2D, 'pooled period'

[redacted]
Abbreviations: HF: heart failure.

5.2.2.3 Time to hospitalisation for CKD

A KM curve of time to hospitalisation for CKD for dapagliflozin and empagliflozin is presented in Figure 18.
[redacted]

The total number of events observed (both treatment arms) was [redacted] (n=[redacted]). The PS weighted and adjusted HR for dapagliflozin versus empagliflozin for time to hospitalisation for CKD was [redacted] (95% CIs: [redacted]), with a PS weighted HR of [redacted] (95% CIs: [redacted].

Figure 18: KM plot for time to hospitalisation for CKD for dapagliflozin and empagliflozin (PS weighted) – with T2D, 'pooled period'

[redacted]
Abbreviations: CKD: chronic kidney disease; KM: Kaplan–Meier.

5.3 Patients without T2D

5.3.1 Medicare only, 'main period'

5.3.1.1 Median eGFR slope

The median eGFR slope for patients receiving dapagliflozin and empagliflozin (PS weighted) are presented in Figure 19, with the difference in median eGFR slope presented in Table 8.

[redacted].

Figure 19: Median eGFR slope for patients receiving dapagliflozin and empagliflozin (PS weighted) – without T2D, 'main period'

[redacted]

A higher value indicates a greater treatment benefit. Dapagliflozin patient numbers: 90 days: [redacted]; 180 days: [redacted]. Empagliflozin patient numbers: 90 days: [redacted]; 180 days: [redacted]
Abbreviations: dapa: dapagliflozin; eGFR: estimated glomerular filtration rate; empa: empagliflozin.

Table 9: Difference in median eGFR slope for patients receiving dapagliflozin versus empagliflozin – without T2D, 'main period'

Follow-up duration	PS weighted		PS weighted and adjusted[a]	
	Difference (mL/min/1.73m^2 [95% CIs])	P-value	Difference (mL/min/1.73m^2 [95% CIs])	P-value
90 days slope	[redacted]	[redacted]	[redacted]	[redacted]
180 days slope	[redacted]	[redacted]	[redacted]	[redacted]
Total slope	[redacted]	[redacted]	[redacted]	[redacted]

A positive value indicates a treatment benefit of dapagliflozin versus empagliflozin. [a] Adjusted for baseline ln(uACR), uACR category, baseline eGFR, eGFR category, T2D, and BMI class.
Abbreviations: BMI: body mass index; CIs: confidence intervals; eGFR: estimated glomerular filtration rate; T2D: type 2 diabetes; uACR: urine albumin-creatinine ratio.

5.3.1.2 Time to hospitalisation for HF

A KM plot of time to hospitalisation for HF for dapagliflozin and empagliflozin is presented in Figure 20. [redacted]

The total number of events observed (both treatment arms) was [redacted] (n=[redacted]). The PS weighted and adjusted HR for time to hospitalisation for HF for dapagliflozin versus empagliflozin was [redacted] (95% CIs: [redacted]), with a PS weighted HR of [redacted] (95% CIs: [redacted]). Following adjustment, [redacted]

Figure 20: KM plot for time to hospitalisation for HF for dapagliflozin and empagliflozin (PS weighted) – without T2D, 'main period'

[redacted]

Abbreviations: HF: heart failure.

5.3.1.3 Time to hospitalisation for CKD

A KM curve of time to hospitalisation for CKD for dapagliflozin and empagliflozin is presented in Figure 21.

[redacted]

The total number of events observed (both treatment arms) was [redacted] (n=[redacted]). The PS weighted and adjusted HR for dapagliflozin versus empagliflozin for time to hospitalisation for CKD was [redacted] (95% CIs: [redacted]), with a PS weighted HR of [redacted] (95% CIs: [redacted]

Figure 21: KM plot for time to hospitalisation for CKD for dapagliflozin and empagliflozin (PS weighted) – without T2D, 'main period'

[redacted]

Abbreviations: CKD: chronic kidney disease; KM: Kaplan–Meier.

5.3.2 Medicare only, 'pooled period'

5.3.2.1 Median eGFR slope

The median eGFR slope for patients receiving dapagliflozin and empagliflozin (PS weighted) are presented in Figure 22, with the difference in median eGFR slope presented in Table 10.

[redacted]

Figure 22: Median eGFR slope for patients receiving dapagliflozin and empagliflozin (PS weighted) – without T2D, 'pooled period'

[redacted]

A higher value indicates a greater treatment benefit. Dapagliflozin patient numbers: 90 days: [redacted]; 180 days: [redacted]; total: [redacted]. Empagliflozin patient numbers: 90 days: [redacted]; 180 days: [redacted]; total: [redacted].
Abbreviations: dapa: dapagliflozin; eGFR: estimated glomerular filtration rate; empa: empagliflozin.

Table 10: Difference in median eGFR slope for patients receiving dapagliflozin versus empagliflozin – without T2D, 'pooled period'

Follow-up duration	PS weighted		PS weighted and adjusted[a]	
	Difference (mL/min/1.73m^2 [95% CIs])	P-value	Difference (mL/min/1.73m^2 [95% CIs])	P-value
90 days slope	[redacted]	[redacted]	[redacted]	[redacted]
180 days slope	[redacted]	[redacted]	[redacted]	[redacted]

Total slope	[redacted]	[redacted]	[redacted]	[redacted]

A positive value indicates a treatment benefit of dapagliflozin versus empagliflozin. [a] Adjusted for baseline ln(uACR), uACR category, baseline eGFR, eGFR category, T2D, and BMI class.
Abbreviations: BMI: body mass index; CIs: confidence intervals; eGFR: estimated glomerular filtration rate; T2D: type 2 diabetes; uACR: urine albumin-creatinine ratio.

5.3.2.2 Time to hospitalisation for HF

A KM plot of time to hospitalisation for HF for dapagliflozin and empagliflozin is presented in Figure 23. [redacted]

The total number of events observed (both treatment arms) was [redacted] (n=[redacted]). The PS weighted and adjusted HR for time to hospitalisation for HF for dapagliflozin versus empagliflozin was [redacted] (95% CIs: [redacted]), with a PS weighted HR of [redacted] (95% CIs: [redacted]

Figure 23: KM plot for time to hospitalisation for HF for dapagliflozin and empagliflozin (PS weighted) – without T2D, 'pooled period'

[redacted]
Abbreviations: HF: heart failure.

5.3.2.3 Time to hospitalisation for CKD

A KM curve of time to hospitalisation for CKD for dapagliflozin and empagliflozin is presented in Figure 23. [redacted]

The total number of events observed (both treatment arms) was [redacted] (n=[redacted]). The PS weighted and adjusted HR for dapagliflozin versus empagliflozin for time to hospitalisation for CKD was [redacted] (95% CIs: [redacted]), with a PS weighted HR of [redacted] (95% CIs: [redacted]

Figure 24: KM plot for time to hospitalisation for CKD for dapagliflozin and empagliflozin (PS weighted) – without T2D, 'pooled period'

[redacted]
Abbreviations: CKD: chronic kidney disease; KM: Kaplan–Meier.

5.4 Patients with low uACR (<200 mg/g)

5.4.1 Medicare only, 'main period'

5.4.1.1 Median eGFR slope

The median eGFR slope for patients receiving dapagliflozin and empagliflozin (PS weighted) are presented in Figure 25, with the difference in median eGFR slope presented in Table 8.

[redacted]

Figure 25: Median eGFR slope for patients receiving dapagliflozin and empagliflozin (PS weighted) – low uACR, 'main period'

[redacted]

A higher value indicates a greater treatment benefit. Dapagliflozin patient numbers: 90 days: [redacted]; 180 days: [redacted]. Empagliflozin patient numbers: 90 days: [redacted]; 180 days: [redacted].
Abbreviations: dapa: dapagliflozin; eGFR: estimated glomerular filtration rate; empa: empagliflozin.

Table 11: Difference in median eGFR slope for patients receiving dapagliflozin versus empagliflozin – low uACR, 'main period'

Follow-up duration	PS weighted		PS weighted and adjusted[a]	
	Difference (mL/min/1.73m^2 [95% CIs])	P-value	Difference (mL/min/1.73m^2 [95% CIs])	P-value
90 days slope	[redacted]	[redacted]	[redacted]	[redacted]
180 days slope	[redacted]	[redacted]	[redacted]	[redacted]
Total slope	[redacted]	[redacted]	[redacted]	[redacted]

A positive value indicates a treatment benefit of dapagliflozin versus empagliflozin. [a] Adjusted for baseline ln(uACR), uACR category, baseline eGFR, eGFR category, T2D, and BMI class.
Abbreviations: BMI: body mass index; CIs: confidence intervals; eGFR: estimated glomerular filtration rate; T2D: type 2 diabetes; uACR: urine albumin-creatinine ratio.

5.4.1.2 Time to hospitalisation for HF

A KM plot of time to hospitalisation for HF for dapagliflozin and empagliflozin is presented in Figure 26. [redacted]

The total number of events observed (both treatment arms) was [redacted] (n=[redacted]). The PS weighted and adjusted HR for time to hospitalisation for HF for dapagliflozin versus empagliflozin was [redacted] (95% CIs: [redacted]), with a PS weighted HR of [redacted] (95% CIs: [redacted]

Figure 26: KM plot for time to hospitalisation for HF for dapagliflozin and empagliflozin (PS weighted) – low uACR, 'main period'

[redacted]

Abbreviations: HF: heart failure.

5.4.1.3 Time to hospitalisation for CKD

A KM curve of time to hospitalisation for CKD for dapagliflozin and empagliflozin is presented in Figure 27.

[redacted]

The total number of events observed (both treatment arms) was [redacted] (n=[redacted]). The PS weighted and adjusted HR for dapagliflozin versus empagliflozin for time to hospitalisation for CKD was [redacted] (95% CIs: [redacted]), with a PS weighted HR of [redacted] (95% CIs: [redacted]

[redacted]

Figure 27: KM plot for time to hospitalisation for CKD for dapagliflozin and empagliflozin (PS weighted) – low uACR, 'main period'

[redacted]

Abbreviations: CKD: chronic kidney disease; KM: Kaplan–Meier.

5.4.2 Medicare only, 'pooled period'

5.4.2.1 Median eGFR slope

The median eGFR slope for patients receiving dapagliflozin and empagliflozin (PS weighted) are presented in Figure 28, with the difference in median eGFR slope presented in Table 12.

[redacted]

Figure 28: Median eGFR slope for patients receiving dapagliflozin and empagliflozin (PS weighted) – low uACR, 'pooled period'

[redacted]

A higher value indicates a greater treatment benefit. Dapagliflozin patient numbers: 90 days: [redacted]; 180 days: [redacted]; total: [redacted]. Empagliflozin patient numbers: 90 days: [redacted]; 180 days: [redacted]; total: [redacted].
Abbreviations: dapa: dapagliflozin; eGFR: estimated glomerular filtration rate; empa: empagliflozin.

Table 12: Difference in median eGFR slope for patients receiving dapagliflozin versus empagliflozin – low uACR, 'pooled period'

Follow-up duration	PS weighted		PS weighted and adjusted[a]	
	Difference (mL/min/1.73m^2 [95% CIs])	P-value	Difference (mL/min/1.73m^2 [95% CIs])	P-value
90 days slope	[redacted]	[redacted]	[redacted]	[redacted]
180 days slope	[redacted]	[redacted]	[redacted]	[redacted]
Total slope	[redacted]	[redacted]	[redacted]	[redacted]

A positive value indicates a treatment benefit of dapagliflozin versus empagliflozin. [a] Adjusted for baseline ln(uACR), uACR category, baseline eGFR, eGFR category, T2D, and BMI class.
Abbreviations: BMI: body mass index; CIs: confidence intervals; eGFR: estimated glomerular filtration rate; T2D: type 2 diabetes; uACR: urine albumin-creatinine ratio.

5.4.2.2 Time to hospitalisation for HF

A KM plot of time to hospitalisation for HF for dapagliflozin and empagliflozin is presented in Figure 29. [redacted]

The total number of events observed (both treatment arms) was [redacted] (n=[redacted]). The PS weighted and adjusted HR for time to hospitalisation for HF for dapagliflozin versus empagliflozin was [redacted] (95% CIs: [redacted]), with a PS weighted HR of [redacted] (95%

CIs: [redacted]).

[redacted]

Figure 29: KM plot for time to hospitalisation for HF for dapagliflozin and empagliflozin (PS weighted) – low uACR, 'pooled period'

[redacted]

Abbreviations: HF: heart failure.

5.4.2.3 Time to hospitalisation for CKD

A KM curve of time to hospitalisation for CKD for dapagliflozin and empagliflozin is presented in Figure 30.

[redacted]

The total number of events observed (both treatment arms) was [redacted] (n=[redacted]). The PS weighted and adjusted HR for dapagliflozin versus empagliflozin for time to hospitalisation for CKD was [redacted] (95% CIs: [redacted]), with a PS weighted HR of [redacted] (95% CIs: [redacted]

Figure 30: KM plot for time to hospitalisation for CKD for dapagliflozin and empagliflozin (PS weighted) – low uACR, 'pooled period'

[redacted]

Abbreviations: CKD: chronic kidney disease; KM: Kaplan–Meier.

5.5 Patients with high uACR (≥200 mg/g)

5.5.1 Medicare only, 'main period'

5.5.1.1 Median eGFR slope

The median eGFR slope for patients receiving dapagliflozin and empagliflozin (PS weighted) are presented in Figure 31, with the difference in median eGFR slope presented in Table 8.

[redacted]

Figure 31: Median eGFR slope for patients receiving dapagliflozin and empagliflozin (PS weighted) – high uACR, 'main period'

[redacted]

A higher value indicates a greater treatment benefit. Dapagliflozin patient numbers: 90 days: 43; 180 days: 98. Empagliflozin patient numbers: 90 days: 36; 180 days: 83.
Abbreviations: dapa: dapagliflozin; eGFR: estimated glomerular filtration rate; empa: empagliflozin.

Table 13: Difference in median eGFR slope for patients receiving dapagliflozin versus empagliflozin – high uACR, 'main period'

	PS weighted	PS weighted and adjusted[a]

Follow-up duration	Difference (mL/min/1.73m^2 [95% CIs])	P-value	Difference (mL/min/1.73m^2 [95% CIs])	P-value
90 days slope	[redacted]	[redacted]	[redacted]	[redacted]
180 days slope	[redacted]	[redacted]	[redacted]	[redacted]
Total slope	[redacted]	[redacted]	[redacted]	[redacted]

A positive value indicates a treatment benefit of dapagliflozin versus empagliflozin. A positive value indicates a treatment benefit of dapagliflozin versus empagliflozin. [a] Adjusted for baseline ln(uACR), uACR category, baseline eGFR, eGFR category, T2D, and BMI class.
Abbreviations: BMI: body mass index; CIs: confidence intervals; eGFR: estimated glomerular filtration rate; T2D: type 2 diabetes; uACR: urine albumin-creatinine ratio.

5.5.1.2 Time to hospitalisation for HF

A KM plot of time to hospitalisation for HF for dapagliflozin and empagliflozin is presented in Figure 32. [redacted]

The total number of events observed (both treatment arms) was [redacted] (n=[redacted]). The PS weighted and adjusted HR for time to hospitalisation for HF for dapagliflozin versus empagliflozin was [redacted] (95% CIs: [redacted]), with a PS weighted HR of [redacted] (95% CIs: [redacted]

Figure 32: KM plot for time to hospitalisation for HF for dapagliflozin and empagliflozin (PS weighted) – high uACR, 'main period'

[redacted]
Abbreviations: HF: heart failure.

5.5.1.3 Time to hospitalisation for CKD

A KM curve of time to hospitalisation for CKD for dapagliflozin and empagliflozin is presented in Figure 33.

[redacted]

The total number of events observed (both treatment arms) was [redacted] (n=[redacted]). The PS weighted and adjusted HR for dapagliflozin versus empagliflozin for time to hospitalisation for CKD was [redacted] (95% CIs: [redacted]), with a PS weighted HR of [redacted] (95% CIs: [redacted]

Figure 33: KM plot for time to hospitalisation for CKD for dapagliflozin and empagliflozin (PS weighted) – high uACR, 'main period'

[redacted]
Abbreviations: CKD: chronic kidney disease; KM: Kaplan–Meier.

5.5.2 Medicare only, 'pooled period'

5.5.2.1 Median eGFR slope

The median eGFR slope for patients receiving dapagliflozin and empagliflozin (PS weighted) are presented in Figure 34, with the difference in median eGFR slope presented in Table 14.

[redacted]

Figure 34: Median eGFR slope for patients receiving dapagliflozin and empagliflozin (PS weighted) – high uACR, 'pooled period'

[redacted]

A higher value indicates a greater treatment benefit. Dapagliflozin patient numbers: 90 days: [redacted]; 180 days: [redacted]; total: [redacted]. Empagliflozin patient numbers: 90 days: [redacted]; 180 days: [redacted]; total: [redacted].
Abbreviations: dapa: dapagliflozin; eGFR: estimated glomerular filtration rate; empa: empagliflozin.

Table 14: Difference in median eGFR slope for patients receiving dapagliflozin versus empagliflozin – high uACR, 'pooled period'

Follow-up duration	PS weighted		PS weighted and adjusted[a]	
	Difference (mL/min/1.73m^2 [95% CIs])	P-value	Difference (mL/min/1.73m^2 [95% CIs])	P-value
90 days slope	[redacted]	[redacted]	[redacted]	[redacted]
180 days slope	[redacted]	[redacted]	[redacted]	[redacted]
Total slope	[redacted]	[redacted]	[redacted]	[redacted]

A positive value indicates a treatment benefit of dapagliflozin versus empagliflozin. A positive value indicates a treatment benefit of dapagliflozin versus empagliflozin. [a] Adjusted for baseline ln(uACR), uACR category, baseline eGFR, eGFR category, T2D, and BMI class.
Abbreviations: BMI: body mass index; CIs: confidence intervals; eGFR: estimated glomerular filtration rate; T2D: type 2 diabetes; uACR: urine albumin-creatinine ratio.

5.5.2.2 Time to hospitalisation for HF

A KM plot of time to hospitalisation for HF for dapagliflozin and empagliflozin is presented in Figure 35. [redacted]

The total number of events observed (both treatment arms) was [redacted] (n=[redacted]). The PS weighted and adjusted HR for time to hospitalisation for HF for dapagliflozin versus empagliflozin was [redacted] (95% CIs: [redacted]), with a PS weighted HR of [redacted] (95% CIs:

[redacted]

Figure 35: KM plot for time to hospitalisation for HF for dapagliflozin and empagliflozin (PS weighted) – high uACR, 'pooled period'

[redacted]

Abbreviations: HF: heart failure.

5.5.2.3 Time to hospitalisation for CKD

A KM curve of time to hospitalisation for CKD for dapagliflozin and empagliflozin is presented in Figure 36.

[redacted]

The total number of events observed (both treatment arms) was [redacted] (n=[redacted]). The PS weighted and adjusted HR for dapagliflozin versus empagliflozin for time to hospitalisation for CKD was [redacted] (95% CIs: [redacted]), with a PS weighted HR of [redacted] (95% CIs: [redacted]

Figure 36: KM plot for time to hospitalisation for CKD for dapagliflozin and empagliflozin (PS weighted) – high uACR, 'pooled period'

[redacted]

Abbreviations: CKD: chronic kidney disease; KM: Kaplan–Meier.

5.6 Patients with T2D and low uACR (<200 mg/g)

5.6.1 Medicare only, 'main period'

5.6.1.1 Median eGFR slope

The median eGFR slope for patients receiving dapagliflozin and empagliflozin (PS weighted) are presented in Figure 37, with the difference in median eGFR slope presented in Table 8.

[redacted]

Figure 37: Median eGFR slope for patients receiving dapagliflozin and empagliflozin (PS weighted) – with T2D and low uACR, 'main period'

[redacted]

A higher value indicates a greater treatment benefit. Dapagliflozin patient numbers: 90 days: [redacted]; 180 days: [redacted]. Empagliflozin patient numbers: 90 days: [redacted]; 180 days: [redacted].

Abbreviations: dapa: dapagliflozin; eGFR: estimated glomerular filtration rate; empa: empagliflozin.

Table 15: Difference in median eGFR slope for patients receiving dapagliflozin versus empagliflozin – with T2D and low uACR, 'main period'

Follow-up duration	PS weighted		PS weighted and adjusted[a]	
	Difference (mL/min/1.73m^2 [95% CIs])	P-value	Difference (mL/min/1.73m^2 [95% CIs])	P-value
90 days slope	[redacted]	[redacted]	[redacted]	[redacted]
180 days slope	[redacted]	[redacted]	[redacted]	[redacted]
Total slope	[redacted]	[redacted]	[redacted]	[redacted]

A positive value indicates a treatment benefit of dapagliflozin versus empagliflozin. [a] Adjusted for baseline ln(uACR), uACR category, baseline eGFR, eGFR category, T2D, and BMI class.

Abbreviations: BMI: body mass index; CIs: confidence intervals; eGFR: estimated glomerular filtration rate; T2D: type 2 diabetes; uACR: urine albumin-creatinine ratio.

5.6.1.2 Time to hospitalisation for HF

A KM plot of time to hospitalisation for HF for dapagliflozin and empagliflozin is presented in Figure 38. [redacted]

The total number of events observed (both treatment arms) was [redacted] (n=[redacted]). The PS weighted and adjusted HR for time to hospitalisation for HF for dapagliflozin versus empagliflozin was [redacted] (95% CIs: [redacted]), with a PS weighted HR of [redacted] (95% CIs:
[redacted]

Figure 38: KM plot for time to hospitalisation for HF for dapagliflozin and empagliflozin (PS weighted) – with T2D and low uACR, 'main period'
[redacted]
Abbreviations: HF: heart failure.

5.6.1.3 Time to hospitalisation for CKD

A KM curve of time to hospitalisation for CKD for dapagliflozin and empagliflozin is presented in Figure 39.
[redacted]

The total number of events observed (both treatment arms) was [redacted] (n=[redacted]). The PS weighted and adjusted HR for dapagliflozin versus empagliflozin for time to hospitalisation for CKD was [redacted] (95% CIs: [redacted]), with a PS weighted HR of [redacted] (95% CIs:
[redacted]

Figure 39: KM plot for time to hospitalisation for CKD for dapagliflozin and empagliflozin (PS weighted) – with T2D and low uACR, 'main period'
[redacted]
Abbreviations: CKD: chronic kidney disease; KM: Kaplan–Meier.

5.6.2 Medicare only, 'pooled period'

5.6.2.1 Median eGFR slope

The median eGFR slope for patients receiving dapagliflozin and empagliflozin (PS weighted) are presented in Figure 40, with the difference in median eGFR slope presented in Table 16.

[redacted]

Figure 40: Median eGFR slope for patients receiving dapagliflozin and empagliflozin (PS weighted) – with T2D and low uACR, 'pooled period'
[redacted]

A higher value indicates a greater treatment benefit. Dapagliflozin patient numbers: 90 days: [redacted]; 180 days: [redacted]; total: [redacted]. Empagliflozin patient numbers: 90 days: [redacted]; 180 days: [redacted]; total: [redacted].
Abbreviations: dapa: dapagliflozin; eGFR: estimated glomerular filtration rate; empa: empagliflozin.

Table 16: Difference in median eGFR slope for patients receiving dapagliflozin versus empagliflozin – with T2D and low uACR, 'pooled period'

Follow-up duration	PS weighted		PS weighted and adjusted[a]	
	Difference (mL/min/1.73m^2 [95% CIs])	P-value	Difference (mL/min/1.73m^2 [95% CIs])	P-value
90 days slope	[redacted]	[redacted]	[redacted]	[redacted]
180 days slope	[redacted]	[redacted]	[redacted]	[redacted]
Total slope	[redacted]	[redacted]	[redacted]	[redacted]

A positive value indicates a treatment benefit of dapagliflozin versus empagliflozin. [a] Adjusted for baseline ln(uACR), uACR category, baseline eGFR, eGFR category, T2D, and BMI class.
Abbreviations: BMI: body mass index; CIs: confidence intervals; eGFR: estimated glomerular filtration rate; T2D: type 2 diabetes; uACR: urine albumin-creatinine ratio.

5.6.2.2 Time to hospitalisation for HF

A KM plot of time to hospitalisation for HF for dapagliflozin and empagliflozin is presented in Figure 41. [redacted]

The total number of events observed (both treatment arms) was [redacted] (n=[redacted]). The PS weighted and adjusted HR for time to hospitalisation for HF for dapagliflozin versus empagliflozin was [redacted] (95% CIs: [redacted]), with a PS weighted HR of [redacted] (95% CIs: [redacted]).
[redacted].

Figure 41: KM plot for time to hospitalisation for HF for dapagliflozin and empagliflozin (PS weighted) – with T2D and low uACR, 'pooled period'
[redacted]
Abbreviations: HF: heart failure.

5.6.2.3 Time to hospitalisation for CKD

A KM curve of time to hospitalisation for CKD for dapagliflozin and empagliflozin is presented in Figure 42.
[redacted]

The total number of events observed (both treatment arms) was [redacted] (n=[redacted]). The PS weighted and adjusted HR for dapagliflozin versus empagliflozin for time to hospitalisation for CKD was [redacted] (95% CIs: [redacted]), with a PS weighted HR of [redacted] (95% CIs: [redacted]

Figure 42: KM plot for time to hospitalisation for CKD for dapagliflozin and empagliflozin (PS weighted) – with T2D and low uACR, 'pooled period'

[redacted]

Abbreviations: CKD: chronic kidney disease; KM: Kaplan–Meier.

5.7 Patients with T2D and high uACR (≥200 mg/g)

5.7.1 Medicare only, 'main period'

5.7.1.1 Median eGFR slope

The median eGFR slope for patients receiving dapagliflozin and empagliflozin (PS weighted) are presented in Figure 43, with the difference in median eGFR slope presented in Table 8.

[redacted]

Figure 43: Median eGFR slope for patients receiving dapagliflozin and empagliflozin (PS weighted) – with T2D and high uACR, 'main period'

[redacted]

A higher value indicates a greater treatment benefit. Dapagliflozin patient numbers: 90 days: [redacted]; 180 days: [redacted]. Empagliflozin patient numbers: 90 days: [redacted]; 180 days: [redacted].
Abbreviations: dapa: dapagliflozin; eGFR: estimated glomerular filtration rate; empa: empagliflozin.

Table 17: Difference in median eGFR slope for patients receiving dapagliflozin versus empagliflozin – with T2D and high uACR, 'main period'

Follow-up duration	PS weighted		PS weighted and adjusted[a]	
	Difference (mL/min/1.73m^2 [95% CIs])	P-value	Difference (mL/min/1.73m^2 [95% CIs])	P-value
90 days slope	[redacted]	[redacted]	[redacted]	[redacted]
180 days slope	[redacted]	[redacted]	[redacted]	[redacted]
Total slope	[redacted]	[redacted]	[redacted]	[redacted]

A positive value indicates a treatment benefit of dapagliflozin versus empagliflozin. [a] Adjusted for baseline ln(uACR), uACR category, baseline eGFR, eGFR category, T2D, and BMI class.
Abbreviations: BMI: body mass index; CIs: confidence intervals; eGFR: estimated glomerular filtration rate; T2D: type 2 diabetes; uACR: urine albumin-creatinine ratio.

5.7.1.2 Time to hospitalisation for HF

A KM plot of time to hospitalisation for HF for dapagliflozin and empagliflozin is presented in Figure 44. [redacted]

The total number of events observed (both treatment arms) was [redacted] (n=[redacted]). The PS weighted and adjusted HR for time to hospitalisation for HF for dapagliflozin versus empagliflozin was [redacted] (95% CIs: [redacted]), with a PS weighted HR of [redacted] (95% CIs:

[redacted]

Figure 44: KM plot for time to hospitalisation for HF for dapagliflozin and empagliflozin (PS weighted) – with T2D and high uACR, 'main period'

[redacted]

Abbreviations: HF: heart failure.

5.7.1.3 Time to hospitalisation for CKD

A KM curve of time to hospitalisation for CKD for dapagliflozin and empagliflozin is presented in Figure 45.

[redacted]

The total number of events observed (both treatment arms) was [redacted] (n=[redacted]). The PS weighted and adjusted HR for dapagliflozin versus empagliflozin for time to hospitalisation for CKD was [redacted] (95% CIs: [redacted]), with a PS weighted HR of [redacted] (95% CIs: [redacted]

Figure 45: KM plot for time to hospitalisation for CKD for dapagliflozin and empagliflozin (PS weighted) – with T2D and high uACR, 'main period'

[redacted]

Abbreviations: CKD: chronic kidney disease; KM: Kaplan–Meier.

5.7.2 Medicare only, 'pooled period'

5.7.2.1 Median eGFR slope

The median eGFR slope for patients receiving dapagliflozin and empagliflozin (PS weighted) are presented in Figure 46, with the difference in median eGFR slope presented in Table 18.

[redacted]

Figure 46: Median eGFR slope for patients receiving dapagliflozin and empagliflozin (PS weighted) – with T2D and high uACR, 'pooled period'

[redacted]

A higher value indicates a greater treatment benefit. Dapagliflozin patient numbers: 90 days: [redacted]; 180 days: [redacted]; total: [redacted]. Empagliflozin patient numbers: 90 days: [redacted]; 180 days: [redacted]; total: [redacted].

Abbreviations: dapa: dapagliflozin; eGFR: estimated glomerular filtration rate; empa: empagliflozin.

Table 18: Difference in median eGFR slope for patients receiving dapagliflozin versus empagliflozin – with T2D and high uACR, 'pooled period'

Follow-up duration	PS weighted		PS weighted and adjusted[a]	
	Difference (mL/min/1.73m^2 [95% CIs])	P-value	Difference (mL/min/1.73m^2 [95% CIs])	P-value
90 days slope	[redacted]	[redacted]	[redacted]	[redacted]

180 days slope	[redacted]	[redacted]	[redacted]	[redacted]
Total slope	[redacted]	[redacted]	[redacted]	[redacted]

A positive value indicates a treatment benefit of dapagliflozin versus empagliflozin. [a] Adjusted for baseline ln(uACR), uACR category, baseline eGFR, eGFR category, T2D, and BMI class.
Abbreviations: BMI: body mass index; CIs: confidence intervals; eGFR: estimated glomerular filtration rate; T2D: type 2 diabetes; uACR: urine albumin-creatinine ratio.

5.7.2.2 Time to hospitalisation for HF

A KM plot of time to hospitalisation for HF for dapagliflozin and empagliflozin is presented in Figure 47. [redacted]

The total number of events observed (both treatment arms) was [redacted] (n=[redacted]). The PS weighted and adjusted HR for time to hospitalisation for HF for dapagliflozin versus empagliflozin was [redacted] (95% CIs: [redacted]), with a PS weighted HR of [redacted] (95% CIs: [redacted]

Figure 47: KM plot for time to hospitalisation for HF for dapagliflozin and empagliflozin (PS weighted) – with T2D and high uACR, 'pooled period'
[redacted]
Abbreviations: HF: heart failure.

5.7.2.3 Time to hospitalisation for CKD

A KM curve of time to hospitalisation for CKD for dapagliflozin and empagliflozin is presented in Figure 48.
[redacted]

The total number of events observed (both treatment arms) was [redacted] (n=[redacted]). The PS weighted and adjusted HR for dapagliflozin versus empagliflozin for time to hospitalisation for CKD was [redacted] (95% CIs: [redacted]), with a PS weighted HR of [redacted] (95% CIs: [redacted]

Figure 48: KM plot for time to hospitalisation for CKD for dapagliflozin and empagliflozin (PS weighted) – with T2D and high uACR, 'pooled period'
[redacted]
Abbreviations: CKD: chronic kidney disease; KM: Kaplan–Meier.

5.8 Patients without T2D and low uACR (<200 mg/g)

Note: analyses for the without T2D and low uACR subgroup are only presented for the 'pooled period'; there were insufficient events in the 'main period' for the analyses to be run.

5.8.1 Medicare only, 'pooled period'

5.8.1.1 Median eGFR slope

The median eGFR slope for patients receiving dapagliflozin and empagliflozin (PS weighted) are presented in Figure 49, with the difference in median eGFR slope presented in Table 19.

[redacted]

Figure 49: Median eGFR slope for patients receiving dapagliflozin and empagliflozin (PS weighted) – without T2D and low uACR, 'pooled period'

[redacted]

A higher value indicates a greater treatment benefit. Dapagliflozin patient numbers: 90 days: [redacted]; 180 days: [redacted]; total: [redacted]. Empagliflozin patient numbers: 90 days: [redacted]; 180 days: [redacted]; total: [redacted].
Abbreviations: dapa: dapagliflozin; eGFR: estimated glomerular filtration rate; empa: empagliflozin.

Table 19: Difference in median eGFR slope for patients receiving dapagliflozin versus empagliflozin – without T2D and low uACR, 'pooled period'

Follow-up duration	PS weighted		PS weighted and adjusted[a]	
	Difference (mL/min/1.73m^2 [95% CIs])	P-value	Difference (mL/min/1.73m^2 [95% CIs])	P-value
90 days slope	[redacted]	[redacted]	[redacted]	[redacted]
180 days slope	[redacted]	[redacted]	[redacted]	[redacted]
Total slope	[redacted]	[redacted]	[redacted]	[redacted]

A positive value indicates a treatment benefit of dapagliflozin versus empagliflozin. [a] Adjusted for baseline ln(uACR), uACR category, baseline eGFR, eGFR category, T2D, and BMI class.
Abbreviations: BMI: body mass index; CIs: confidence intervals; eGFR: estimated glomerular filtration rate; T2D: type 2 diabetes; uACR: urine albumin-creatinine ratio.

5.8.1.1 Time to hospitalisation for HF

A KM plot of time to hospitalisation for HF for dapagliflozin and empagliflozin is presented in Figure 50. [redacted].

The total number of events observed (both treatment arms) was 44 (n=[redacted]). The PS weighted and adjusted HR for time to hospitalisation for HF for dapagliflozin versus empagliflozin was [redacted] (95% CIs: [redacted]), with a PS weighted HR of [redacted] (95% CIs:

[redacted]

Figure 50: KM plot for time to hospitalisation for HF for dapagliflozin and empagliflozin (PS weighted) – without T2D and low uACR, 'pooled period'

[redacted]

Abbreviations: HF: heart failure.

5.8.1.2 Time to hospitalisation for CKD

A KM curve of time to hospitalisation for CKD for dapagliflozin and empagliflozin is presented in Figure 51

[redacted]

The total number of events observed (both treatment arms) was [redacted] (n=[redacted]). The PS weighted and adjusted HR for dapagliflozin versus empagliflozin for time to hospitalisation for CKD was [redacted] (95% CIs: [redacted]), with a PS weighted HR of [redacted] (95% CIs: [redacted]

Figure 51: KM plot for time to hospitalisation for CKD for dapagliflozin and empagliflozin (PS weighted) – without T2D and low uACR, 'pooled period'

[redacted]

Abbreviations: CKD: chronic kidney disease; KM: Kaplan–Meier.

5.9 Patients without T2D and high uACR (≥200 mg/g)

Note: analyses for the without T2D and high uACR subgroup are only presented for the 'pooled period'; there were insufficient events in the 'main period' for the analyses to be run.

5.9.1 Medicare only, 'pooled period'

5.9.1.1 Median eGFR slope

The median eGFR slope for patients receiving dapagliflozin and empagliflozin (PS weighted) are presented in Figure 52, with the difference in median eGFR slope presented in Table 20.

[redacted]

Figure 52: Median eGFR slope for patients receiving dapagliflozin and empagliflozin (PS weighted) – without T2D and high uACR, 'pooled period'

[redacted]

A higher value indicates a greater treatment benefit. Dapagliflozin patient numbers: 90 days: [redacted]; 180 days: [redacted]; total: [redacted]. Empagliflozin patient numbers: 90 days: [redacted]; 180 days: [redacted]; total: [redacted].
Abbreviations: dapa: dapagliflozin; eGFR: estimated glomerular filtration rate; empa: empagliflozin.

Table 20: Difference in median eGFR slope for patients receiving dapagliflozin versus empagliflozin – without T2D and high uACR, 'pooled period'

Follow-up duration	PS weighted		PS weighted and adjusted[a]	
	Difference (mL/min/1.73m^2 [95% CIs])	P-value	Difference (mL/min/1.73m^2 [95% CIs])	P-value
90 days slope	[redacted]	[redacted]	[redacted]	[redacted]
180 days slope	[redacted]	[redacted]	[redacted]	[redacted]

Total slope	[redacted]	[redacted]	[redacted]	[redacted]

A positive value indicates a treatment benefit of dapagliflozin versus empagliflozin. [a] Adjusted for baseline ln(uACR), uACR category, baseline eGFR, eGFR category, T2D, and BMI class.
Abbreviations: BMI: body mass index; CIs: confidence intervals; eGFR: estimated glomerular filtration rate; T2D: type 2 diabetes; uACR: urine albumin-creatinine ratio.

5.9.1.2 Time to hospitalisation for HF

A KM plot of time to hospitalisation for HF for dapagliflozin and empagliflozin is presented in Figure 53. [redacted]

The total number of events observed (both treatment arms) was [redacted] (n=[redacted]). The PS weighted and adjusted HR for time to hospitalisation for HF for dapagliflozin versus empagliflozin was [redacted] (95% CIs: [redacted]), with a PS weighted HR of [redacted] (95% CIs: [redacted]

Figure 53: KM plot for time to hospitalisation for HF for dapagliflozin and empagliflozin (PS weighted) – without T2D and high uACR, 'pooled period'
[redacted]
Abbreviations: HF: heart failure.

5.9.1.3 Time to hospitalisation for CKD

A KM curve of time to hospitalisation for CKD for dapagliflozin and empagliflozin is presented in Figure 54.
[redacted]

The total number of events observed (both treatment arms) was [redacted] (n=[redacted]). The PS weighted and adjusted HR for dapagliflozin versus empagliflozin for time to hospitalisation for CKD was [redacted] (95% CIs: [redacted]), with a PS weighted HR of [redacted] (95% CIs: [redacted]

Figure 54: KM plot for time to hospitalisation for CKD for dapagliflozin and empagliflozin (PS weighted) – without T2D and high uACR, 'pooled period'
[redacted]
Abbreviations: CKD: chronic kidney disease; KM: Kaplan–Meier.

6 Additional sensitivity analyses – Effectiveness results

Forest plots of the HR for dapagliflozin versus empagliflozin for time to hospitalisation for HF and time to hospitalisation for CKD including Medicare plus commercial patients are presented in Figure 55, with the corresponding Medicare plus missing uACR results presented in Figure 56. The HRs for time to death within hospital are presented for the Medicare plus commercial and Medicare plus missing uACR sensitivity analyses in Table 21 (overall population only).

The difference in eGFR slope for all analyses is presented in Table 22; it was not possible to produce visual representations of eGFR slope due to the measurement scale. **Bold**

highlighting is used to indicate any results which show a statistically significant difference in the treatment effect of dapagliflozin and empagliflozin.

Baseline characteristics and PS weighting plots are presented in Appendix C and Appendix D, respectively.

Figure 55: Sensitivity analysis forest plot for A) time to hospitalisation for HF and B) time to hospitalisation for CKD – Medicare plus commercial

A

[redacted]

B

[redacted]

A: time to hospitalisation for HF; B: time to hospitalisation for CKD. PS weighted and adjusted model (adjusted for baseline ln(uACR), uACR category, baseline eGFR, eGFR category, T2D, and BMI class).
Abbreviations: BMI: body mass index; CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; uACR: urine albumin-creatinine ratio; T2D: type 2 diabetes

Figure 56: Sensitivity analysis forest plot for A) time to hospitalisation for HF and B) time to hospitalisation for CKD – Medicare plus missing uACR

A

[redacted]

B

[redacted]

A: time to hospitalisation for HF; B: time to hospitalisation for CKD. PS weighted and adjusted model (adjusted for baseline ln(uACR), uACR category, baseline eGFR, eGFR category, T2D, and BMI class). The Medicare plus missing uACR sensitivity analyses were not run for subgroups with uACR requirements, as results would be the same as the primary results and therefore redundant.
Abbreviations: BMI: body mass index; CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; uACR: urine albumin-creatinine ratio; T2D: type 2 diabetes

Table 21: HRs for dapagliflozin versus empagliflozin for time to death within hospital – Sensitivity analyses on overall population

Analysis	Dapagliflozin versus empagliflozin, HR (95% CIs; p-value)	
	PS weighted	PS weighted and adjusted[a]
Medicare plus commercial, 'main period'	[redacted]	[redacted]
Medicare plus commercial, 'pooled period'	[redacted]	[redacted]
Medicare plus missing uACR, 'main period'	[redacted]	[redacted]
Medicare plus missing uACR, 'pooled period'	[redacted]	[redacted]

Results are only presented for the overall population as there were insufficient events to run analyses for death within hospital in the population subgroups**. Bold** highlighting indicates statistically significant differences. [a] Adjusted for baseline ln(uACR), uACR category, baseline eGFR, eGFR category, T2D, and BMI class.
Abbreviations: BMI: body mass index; CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; HF: heart failure; HR: hazard ratio; PS: propensity score; T2D: type 2 diabetes; uACR: urine albumin-creatinine ratio.

Table 22: Difference in median eGFR slope for dapagliflozin versus empagliflozin – Sensitivity analyses, PS weighted and adjusted model[a]

Analysis	Difference in median eGFR slope, mL/min/1.73m^2 (95% CIs)					
	90 days follow-up		180 days follow-up		Total follow-up	
	Difference	P-value	Difference	P-value	Difference	P-value
Overall population						
Medicare plus commercial, 'main period'	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Medicare plus commercial, 'pooled period'	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Medicare plus missing uACR, 'main period'	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Medicare plus missing uACR, 'pooled period'	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
With T2D						
Medicare plus commercial, 'main period'	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Medicare plus commercial, 'pooled period'	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Medicare plus missing uACR, 'main period'	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Medicare plus missing uACR, 'pooled period'	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Without T2D						
Medicare plus commercial, 'main period'	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Medicare plus commercial, 'pooled period'	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Medicare plus missing uACR, 'main period'	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Medicare plus missing uACR, 'pooled period'	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Low uACR (<200 mg/g)						
Medicare plus commercial, 'main period'	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Medicare plus commercial, 'pooled period'	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
High uACR (≥200 mg/g)						
Medicare plus commercial, 'main period'	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Medicare plus commercial, 'pooled period'	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
With T2D and low uACR (<200 mg/g)						
Medicare plus commercial, 'main period'	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Medicare plus commercial, 'pooled period'	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
With T2D and high uACR (≥200 mg/g)						
Medicare plus commercial, 'main period'	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Medicare plus commercial, 'pooled period'	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Without T2D and low uACR (<200 mg/g)						
Medicare plus commercial, 'pooled period'	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Without T2D and high uACR (≥200 mg/g)						
Medicare plus commercial, 'main period'	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Medicare plus commercial, 'pooled period'	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

A positive value indicates a treatment benefit of dapagliflozin versus empagliflozin. [a] Adjusted for baseline ln(uACR), uACR category, baseline eGFR, eGFR category, T2D, and BMI class.
Abbreviations: BMI: body mass index; CI: confidence interval; CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; HF: heart failure; HR: hazard ratio; PS: propensity score; T2D: type 2 diabetes; uACR: urine albumin-creatinine ratio.

Table 23: Difference in median eGFR slope for dapagliflozin versus empagliflozin – Sensitivity analyses, PS weighted

Analysis	Difference in median eGFR slope, mL/min/1.73m^2 (95% CIs)					
	90 days follow-up		180 days follow-up		Total follow-up	
	Difference	P-value	Difference	P-value	Difference	P-value
Overall population						
Medicare plus commercial, 'main period'	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Medicare plus commercial, 'pooled period'	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Medicare plus missing uACR, 'main period'	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Medicare plus missing uACR, 'pooled period'	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
With T2D						
Medicare plus commercial, 'main period'	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Medicare plus commercial, 'pooled period'	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Medicare plus missing uACR, 'main period'	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Medicare plus missing uACR, 'pooled period'	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Without T2D						
Medicare plus commercial, 'main period'	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Medicare plus commercial, 'pooled period'	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Medicare plus missing uACR, 'main period'	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Medicare plus missing uACR, 'pooled period'	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Low uACR (<200 mg/g)						
Medicare plus commercial, 'main period'	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Medicare plus commercial, 'pooled period'	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
High uACR (≥200 mg/g)						
Medicare plus commercial, 'main period'	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Medicare plus commercial, 'pooled period'	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
With T2D and low uACR (<200 mg/g)						
Medicare plus commercial, 'main period'	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Medicare plus commercial, 'pooled period'	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
With T2D and high uACR (≥200 mg/g)						
Medicare plus commercial, 'main period'	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Medicare plus commercial, 'pooled period'	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Without T2D and low uACR (<200 mg/g)						
Medicare plus commercial, 'pooled period'	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Without T2D and high uACR (≥200 mg/g)						

Medicare plus commercial, ‘main period’	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Medicare plus commercial, ‘pooled period’	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

A positive value indicates a treatment benefit of dapagliflozin versus empagliflozin.
Abbreviations: BMI: body mass index; CI: confidence interval; CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; HF: heart failure; HR: hazard ratio; PS: propensity score; T2D: type 2 diabetes; uACR: urine albumin-creatinine ratio.

7 Discussion and conclusion

Discussion and interpretation of results

This report presents relative effectiveness estimates for dapagliflozin versus empagliflozin in patients with CKD using RWE from Optum CDM. For the primary analysis, [redacted].

For the primary analysis (overall population, 'main period', Medicare only), the difference in median eGFR slope for dapagliflozin versus empagliflozin (PS weighted and adjusted) was [redacted] (95% CIs [redacted] (95% CIs: [redacted] (95% CIs: [redacted]) and [redacted] (95% CIs: [redacted]), respectively (PS weighted, adjusted models). [redacted]

[redacted] when the time period considered was expanded to the 'pooled period', which included a larger population but periods during which dapagliflozin and empagliflozin were licensed for different indications. [redacted]

Alongside the primary analyses, numerous population subgroup analyses and sensitivity analyses were conducted to explore the impact of varying the included populations. The results of all subgroup and sensitivity analyses [redacted]. Of all sensitivity analyses conducted, [redacted]

The analyses presented in this report employed robust methodology to minimise any bias in the comparison conducted, including the use of PS weighting which accounts for observed prognostic factors and treatment effect modifiers in line with the list used in Tangri *et al.* (2024). Despite this, as is the case for any non-randomised comparison, some residual confounding and unobserved confounding may be present, which introduces some uncertainty. However, as data in this comparison are all sourced from patients in the same geographic region, from Medicare only patients (in the primary analysis) in the same calendar period, and empagliflozin and dapagliflozin are seen as equivalent by clinicians, homogeneity of the source population is expected to minimise any bias introduced by residual or unobserved confounding. Furthermore, the use of the 'main period' minimises the possibility of either population being influenced by underlying factors for prescribing

empagliflozin or dapagliflozin and therefore being enriched with patients with other conditions (i.e., HF or T2D).

Optum CDM is a US-based database which includes data on more than 78 million people across all 50 US states. After application of appropriate inclusion/exclusion criteria, a total of [redacted] patients were included in the primary analysis (dapagliflozin: [redacted]; empagliflozin: [redacted]), within whom [redacted] heart failure hospitalisations, [redacted] CKD hospitalisations and [redacted] deaths were observed across both treatment arms. Despite being US-based, data from Optum CDM are expected to be generalisable to patients with CKD in the UK; subgroup analyses of CKD randomised controlled trials (e.g., DAPA-CKD), show that there is no significant variation in treatment effect between geographical regions, including Europe and North America.[1] Optum CDM also includes patients across the range of clinically relevant CKD subgroups. The consistency of the results across subgroup analyses demonstrates the robustness of the results to variation in the baseline characteristics of the populations included.

Conclusion

Based on the presented analyses of dapagliflozin versus empagliflozin in patients with CKD, using the Optum CDM database,

[redacted]

[redacted]

[redacted] aligning the NICE recommendations for the two treatments would simplify the treatment pathway in both primary and secondary care by removing some of the complexities of prescribing dapagliflozin and empagliflozin, as supported by stakeholder comments on the draft scope for this appraisal.[11] By doing so, this would improve access to effective treatments for patients with CKD.

Appendices

Appendix A Subgroup analyses: Baseline characteristics

Baseline characteristics for the overall population ('pooled period') and all population subgroups ('main period' and 'pooled period') are presented in the following section. All populations are the Medicare patients only.

A.1 Overall population

Table 24: Baseline characteristics – overall population, Medicare only, 'pooled period'

	Before weighting			After weighting		
Characteristic	**Dapagliflozin (n=[redacted])**	**Empagliflozin (n=[redacted])**	**SMD**	**Dapagliflozin (n=[redacted])**	**Empagliflozin (n=[redacted])**	**SMD**
Age, years, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BMI, kg/m^2						
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Categorical						
<25, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥30, n (%)	[redacted]	[redacted]		[redacted]	[redacted]	
25.0-29.9, n (%)	[redacted]	[redacted]		[redacted]	[redacted]	
Missing, n (%)	[redacted]	[redacted]		[redacted]	[redacted]	
Baseline eGFR, mL/min/1.73m^2 [a]						
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Categorical						
60-89 (G2), n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
45-59 (G3a), n (%)	[redacted]	[redacted]		[redacted]	[redacted]	
30-44 (G3b), n (%)	[redacted]	[redacted]		[redacted]	[redacted]	
15-29 (G4), n (%)	[redacted]	[redacted]		[redacted]	[redacted]	
Baseline uACR, mg/g[a]						

Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Categorical						
0-29, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
30-199, n (%)	[redacted]	[redacted]		[redacted]	[redacted]	
≥200, n (%)	[redacted]	[redacted]		[redacted]	[redacted]	
ln_uacr, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Female, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age, n (%)						
<40	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
40-49	[redacted]	[redacted]		[redacted]	[redacted]	
50-59	[redacted]	[redacted]		[redacted]	[redacted]	
60-69	[redacted]	[redacted]		[redacted]	[redacted]	
70-79	[redacted]	[redacted]		[redacted]	[redacted]	
≥80	[redacted]	[redacted]		[redacted]	[redacted]	
Race, n (%)						
Asian	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Black	[redacted]	[redacted]		[redacted]	[redacted]	
Unknown/Other	[redacted]	[redacted]		[redacted]	[redacted]	
White	[redacted]	[redacted]		[redacted]	[redacted]	
Medicare, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cause of CKD, n (%)						
Diabetic kidney disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypertensive disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Glomerular disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Renal tubolo-interstitial disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other/unknown	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Comorbidities, n (%)						
Angina	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Atrial fibrillation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Bradycardia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Heart failure	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Myocardial infarction	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stroke	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other cardiovascular disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hyperkalaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
T2D	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Medications, n (%)						
RASi	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ARNI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Beta-blocker	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Calcium channel blocker	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Diuretics	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Antithrombotic agent	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Statins	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anti-hyperkaliaemic treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anti-diabetic treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[a] Patients in the 'complete case' had an eGFR and uACR measurement within 122 days prior to or at the index date.
Abbreviations: ARNI: angiotensin receptor/neprilysin inhibitor; BMI: body mass index; CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; RASi: renin-angiotensin system inhibitor; SD: standard deviation; SMD: standardised mean difference; T2D: type 2 diabetes; uACR: urinary albumin-creatinine ratio.

A.2 With T2D

Table 25: Baseline characteristics – with T2D, Medicare only, 'main period'

	Before weighting			After weighting		
Characteristic	**Dapagliflozin (n=[redacted])**	**Empagliflozin (n=[redacted])**	**SMD**	**Dapagliflozin (n=[redacted])**	**Empagliflozin (n=[redacted])**	**SMD**

Age, years, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BMI, kg/m^2						
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Categorical						
<25, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥30, n (%)	[redacted]	[redacted]		[redacted]	[redacted]	
25.0-29.9, n (%)	[redacted]	[redacted]		[redacted]	[redacted]	
Missing, n (%)	[redacted]	[redacted]		[redacted]	[redacted]	
Baseline eGFR, mL/min/1.73m^2 [a]						
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Categorical						
60-89 (G2), n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
45-59 (G3a), n (%)	[redacted]	[redacted]		[redacted]	[redacted]	
30-44 (G3b), n (%)	[redacted]	[redacted]		[redacted]	[redacted]	
15-29 (G4), n (%)	[redacted]	[redacted]		[redacted]	[redacted]	
Baseline uACR, mg/g[a]						
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Categorical						
0-29, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
30-199, n (%)	[redacted]	[redacted]		[redacted]	[redacted]	
≥200, n (%)	[redacted]	[redacted]		[redacted]	[redacted]	
ln_uacr, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Female, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age, n (%)						
<40	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
40-49	[redacted]	[redacted]		[redacted]	[redacted]	
50-59	[redacted]	[redacted]		[redacted]	[redacted]	
60-69	[redacted]	[redacted]		[redacted]	[redacted]	
70-79	[redacted]	[redacted]		[redacted]	[redacted]	

≥80	[redacted]	[redacted]		[redacted]	[redacted]	
Race, n (%)						
Asian	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Black	[redacted]	[redacted]		[redacted]	[redacted]	
Unknown/Other	[redacted]	[redacted]		[redacted]	[redacted]	
White	[redacted]	[redacted]		[redacted]	[redacted]	
Medicare, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cause of CKD, n (%)						
Diabetic kidney disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypertensive disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Glomerular disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Renal tubolo-interstitial disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other/unknown	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Comorbidities						
Angina	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Atrial fibrillation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bradycardia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Heart failure	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Myocardial infarction	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stroke	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other cardiovascular disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hyperkalaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
T2D	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Medications, n (%)						
RASi	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ARNI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Beta-blocker	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Calcium channel blocker	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Diuretics	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Antithrombotic agent	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Statins	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anti-hyperkaliaemic treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anti-diabetic treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[a] Patients in the 'complete case' had an eGFR and uACR measurement within 122 days prior to or at the index date.
Abbreviations: ARNI: angiotensin receptor/neprilysin inhibitor; BMI: body mass index; CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; RASi: renin-angiotensin system inhibitor; SD: standard deviation; SMD: standardised mean difference; T2D: type 2 diabetes; uACR: urinary albumin-creatinine ratio.

Table 26: Baseline characteristics – with T2D, Medicare only, 'pooled period'

	Before weighting			After weighting		
Characteristic	**Dapagliflozin (n=[redacted])**	**Empagliflozin (n=[redacted])**	**SMD**	**Dapagliflozin (n=[redacted])**	**Empagliflozin (n=[redacted])**	**SMD**
Age, years, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BMI, kg/m^2						
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Categorical						
<25, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥30, n (%)	[redacted]	[redacted]		[redacted]	[redacted]	
25.0-29.9, n (%)	[redacted]	[redacted]		[redacted]	[redacted]	
Missing, n (%)	[redacted]	[redacted]		[redacted]	[redacted]	
Baseline eGFR, mL/min/1.73m^2 [a]						
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Categorical						
60-89 (G2), n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
45-59 (G3a), n (%)	[redacted]	[redacted]		[redacted]	[redacted]	

30-44 (G3b), n (%)	[redacted]	[redacted]		[redacted]	[redacted]	
15-29 (G4), n (%)	[redacted]	[redacted]		[redacted]	[redacted]	
Baseline uACR, mg/g[a]						
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Categorical						
0-29, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
30-199, n (%)	[redacted]	[redacted]		[redacted]	[redacted]	
≥200, n (%)	[redacted]	[redacted]		[redacted]	[redacted]	
ln_uacr, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Female, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age, n (%)						
<40	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
40-49	[redacted]	[redacted]		[redacted]	[redacted]	
50-59	[redacted]	[redacted]		[redacted]	[redacted]	
60-69	[redacted]	[redacted]		[redacted]	[redacted]	
70-79	[redacted]	[redacted]		[redacted]	[redacted]	
≥80	[redacted]	[redacted]		[redacted]	[redacted]	
Race, n (%)						
Asian	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Black	[redacted]	[redacted]		[redacted]	[redacted]	
Unknown/Other	[redacted]	[redacted]		[redacted]	[redacted]	
White	[redacted]	[redacted]		[redacted]	[redacted]	
Medicare, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cause of CKD, n (%)						
Diabetic kidney disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypertensive disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Glomerular disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Renal tubolo-interstitial disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other/unknown	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Comorbidities						
Angina	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Atrial fibrillation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bradycardia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Heart failure	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Myocardial infarction	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stroke	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other cardiovascular disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hyperkalaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
T2D	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Medications, n (%)						
RASi	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ARNI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Beta-blocker	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Calcium channel blocker	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Diuretics	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Antithrombotic agent	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Statins	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anti-hyperkaliaemic treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anti-diabetic treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[a] Patients in the 'complete case' had an eGFR and uACR measurement within 122 days prior to or at the index date.

Abbreviations: ARNI: angiotensin receptor/neprilysin inhibitor; BMI: body mass index; CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; RASi: renin-angiotensin system inhibitor; SD: standard deviation; SMD: standardised mean difference; T2D: type 2 diabetes; uACR: urinary albumin-creatinine ratio.

A.3 Without T2D

Table 27: Baseline characteristics – without T2D, Medicare only, 'main period'

	Before weighting			After weighting		
Characteristic	**Dapagliflozin (n=[redacted])**	**Empagliflozin (n=[redacted])**	**SMD**	**Dapagliflozin (n=[redacted])**	**Empagliflozin (n=[redacted])**	**SMD**
Age, years, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BMI, kg/m^2						
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Categorical						
<25, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥30, n (%)	[redacted]	[redacted]		[redacted]	[redacted]	
25.0-29.9, n (%)	[redacted]	[redacted]		[redacted]	[redacted]	
Missing, n (%)	[redacted]	[redacted]		[redacted]	[redacted]	
Baseline eGFR, mL/min/1.73m^2 [a]						
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Categorical						
60-89 (G2), n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
45-59 (G3a), n (%)	[redacted]	[redacted]		[redacted]	[redacted]	
30-44 (G3b), n (%)	[redacted]	[redacted]		[redacted]	[redacted]	
15-29 (G4), n (%)	[redacted]	[redacted]		[redacted]	[redacted]	
Baseline uACR, mg/g[a]						
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Categorical						
0-29, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
30-199, n (%)	[redacted]	[redacted]		[redacted]	[redacted]	
≥200, n (%)	[redacted]	[redacted]		[redacted]	[redacted]	
ln_uacr, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Female, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age, n (%)						

<40	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
40-49	[redacted]	[redacted]		[redacted]	[redacted]	
50-59	[redacted]	[redacted]		[redacted]	[redacted]	
60-69	[redacted]	[redacted]		[redacted]	[redacted]	
70-79	[redacted]	[redacted]		[redacted]	[redacted]	
≥80	[redacted]	[redacted]		[redacted]	[redacted]	
Race, n (%)						
Asian	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Black	[redacted]	[redacted]		[redacted]	[redacted]	
Unknown/Other	[redacted]	[redacted]		[redacted]	[redacted]	
White	[redacted]	[redacted]		[redacted]	[redacted]	
Medicare, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cause of CKD, n (%)						
Diabetic kidney disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypertensive disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Glomerular disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Renal tubolo-interstitial disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other/unknown	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Comorbidities						
Angina	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Atrial fibrillation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bradycardia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Heart failure	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Myocardial infarction	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stroke	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other cardiovascular disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Hyperkalaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
T2D	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Medications, n (%)						
RASi	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ARNI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Beta-blocker	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Calcium channel blocker	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Diuretics	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Antithrombotic agent	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Statins	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anti-hyperkaliaemic treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anti-diabetic treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[a] Patients in the 'complete case' had an eGFR and uACR measurement within 122 days prior to or at the index date.
Abbreviations: ARNI: angiotensin receptor/neprilysin inhibitor; BMI: body mass index; CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; RASi: renin-angiotensin system inhibitor; SD: standard deviation; SMD: standardised mean difference; T2D: type 2 diabetes; uACR: urinary albumin-creatinine ratio.

Table 28: Baseline characteristics – without T2D, Medicare only, 'pooled period'

	Before weighting			After weighting		
Characteristic	**Dapagliflozin (n=[redacted])**	**Empagliflozin (n=[redacted])**	**SMD**	**Dapagliflozin (n=[redacted])**	**Empagliflozin (n=[redacted])**	**SMD**
Age, years, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BMI, kg/m^2						
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Categorical						
<25, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥30, n (%)	[redacted]	[redacted]		[redacted]	[redacted]	
25.0-29.9, n (%)	[redacted]	[redacted]		[redacted]	[redacted]	
Missing, n (%)	[redacted]	[redacted]		[redacted]	[redacted]	

Baseline eGFR, mL/min/1.73m^2 [a]						
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Categorical						
60-89 (G2), n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
45-59 (G3a), n (%)	[redacted]	[redacted]		[redacted]	[redacted]	
30-44 (G3b), n (%)	[redacted]	[redacted]		[redacted]	[redacted]	
15-29 (G4), n (%)	[redacted]	[redacted]		[redacted]	[redacted]	
Baseline uACR, mg/g[a]						
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Categorical						
0-29, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
30-199, n (%)	[redacted]	[redacted]		[redacted]	[redacted]	
≥200, n (%)	[redacted]	[redacted]		[redacted]	[redacted]	
ln_uacr, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Female, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age, n (%)						
<40	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
40-49	[redacted]	[redacted]		[redacted]	[redacted]	
50-59	[redacted]	[redacted]		[redacted]	[redacted]	
60-69	[redacted]	[redacted]		[redacted]	[redacted]	
70-79	[redacted]	[redacted]		[redacted]	[redacted]	
≥80	[redacted]	[redacted]		[redacted]	[redacted]	
Race, n (%)						
Asian	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Black	[redacted]	[redacted]		[redacted]	[redacted]	
Unknown/Other	[redacted]	[redacted]		[redacted]	[redacted]	
White	[redacted]	[redacted]		[redacted]	[redacted]	
Medicare, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cause of CKD, n (%)						

Diabetic kidney disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypertensive disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Glomerular disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Renal tubolo-interstitial disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other/unknown	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Comorbidities						
Angina	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Atrial fibrillation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bradycardia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Heart failure	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Myocardial infarction	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stroke	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other cardiovascular disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hyperkalaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
T2D	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Medications, n (%)						
RASi	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ARNI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Beta-blocker	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Calcium channel blocker	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Diuretics	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Antithrombotic agent	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Statins	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anti-hyperkaliaemic treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Anti-diabetic treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[a] Patients in the 'complete case' had an eGFR and uACR measurement within 122 days prior to or at the index date.
Abbreviations: ARNI: angiotensin receptor/neprilysin inhibitor; BMI: body mass index; CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; RASi: renin-angiotensin system inhibitor; SD: standard deviation; SMD: standardised mean difference; T2D: type 2 diabetes; uACR: urinary albumin-creatinine ratio.

A.4 Low uACR (<200 mg/g)

Table 29: Baseline characteristics – low uACR (<200 mg/g), Medicare only, 'main period'

	Before weighting			After weighting		
Characteristic	**Dapagliflozin (n=[redacted])**	**Empagliflozin (n=[redacted])**	**SMD**	**Dapagliflozin (n=[redacted])**	**Empagliflozin (n=[redacted])**	**SMD**
Age, years, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BMI, kg/m^2						
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Categorical						
<25, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥30, n (%)	[redacted]	[redacted]		[redacted]	[redacted]	
25.0-29.9, n (%)	[redacted]	[redacted]		[redacted]	[redacted]	
Missing, n (%)	[redacted]	[redacted]		[redacted]	[redacted]	
Baseline eGFR, mL/min/1.73m^2 [a]						
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Categorical[b]						
15-29 (G4), n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline uACR, mg/g[a]						
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Categorical[b]						
30-199, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ln_uacr, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Female, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age, n (%)						

40-49	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
50-59	[redacted]	[redacted]		[redacted]	[redacted]	
60-69	[redacted]	[redacted]		[redacted]	[redacted]	
70-79	[redacted]	[redacted]		[redacted]	[redacted]	
≥80	[redacted]	[redacted]		[redacted]	[redacted]	
Race, n (%)						
Asian	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Black	[redacted]	[redacted]		[redacted]	[redacted]	
Unknown/Other	[redacted]	[redacted]		[redacted]	[redacted]	
White	[redacted]	[redacted]		[redacted]	[redacted]	
Medicare, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cause of CKD, n (%)						
Diabetic kidney disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypertensive disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Glomerular disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Renal tubolo-interstitial disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other/unknown	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Comorbidities						
Angina	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Atrial fibrillation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bradycardia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Heart failure	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Myocardial infarction	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stroke	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other cardiovascular disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hyperkalaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

T2D	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Medications, n (%)						
RASi	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ARNI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Beta-blocker	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Calcium channel blocker	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Diuretics	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Antithrombotic agent	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Statins	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anti-hyperkaliaemic treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anti-diabetic treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[a] Patients in the 'complete case' had an eGFR and uACR measurement within 122 days prior to or at the index date. [b] Reported as binary categories. All remaining patients were in the 30-45 mL/min/1.73 m^2 eGFR category or the 0-29 mg/g uACR category.
Abbreviations: ARNI: angiotensin receptor/neprilysin inhibitor; BMI: body mass index; CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; RASi: renin-angiotensin system inhibitor; SD: standard deviation; SMD: standardised mean difference; T2D: type 2 diabetes; uACR: urinary albumin-creatinine ratio.

Table 30: Baseline characteristics – low uACR (<200 mg/g), Medicare only, 'pooled period'

	Before weighting			After weighting		
Characteristic	**Dapagliflozin (n=[redacted])**	**Empagliflozin (n=[redacted])**	**SMD**	**Dapagliflozin (n=[redacted])**	**Empagliflozin (n=[redacted])**	**SMD**
Age, years, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BMI, kg/m^2						
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Categorical						
<25	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥30	[redacted]	[redacted]		[redacted]	[redacted]	
25.0-29.9	[redacted]	[redacted]		[redacted]	[redacted]	
Missing	[redacted]	[redacted]		[redacted]	[redacted]	
Baseline eGFR, mL/min/1.73m^2 [a]						

Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Categorical[b]						
15-29 (G4), n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline uACR, mg/g[a]						
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Categorical[b]						
30-199, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ln_uacr, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Female, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age, n (%)						
40-49	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
50-59	[redacted]	[redacted]		[redacted]	[redacted]	
60-69	[redacted]	[redacted]		[redacted]	[redacted]	
70-79	[redacted]	[redacted]		[redacted]	[redacted]	
≥80	[redacted]	[redacted]		[redacted]	[redacted]	
Race, n (%)						
Asian	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Black	[redacted]	[redacted]		[redacted]	[redacted]	
Unknown/Other	[redacted]	[redacted]		[redacted]	[redacted]	
White	[redacted]	[redacted]		[redacted]	[redacted]	
Medicare, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cause of CKD, n (%)						
Diabetic kidney disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypertensive disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Glomerular disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Renal tubolo-interstitial disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other/unknown	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Comorbidities						
Angina	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Atrial fibrillation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bradycardia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Heart failure	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Myocardial infarction	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stroke	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other cardiovascular disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hyperkalaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
T2D	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Medications, n (%)						
RASi	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ARNI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Beta-blocker	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Calcium channel blocker	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Diuretics	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Antithrombotic agent	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Statins	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anti-hyperkaliaemic treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anti-diabetic treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[a] Patients in the 'complete case' had an eGFR and uACR measurement within 122 days prior to or at the index date. [b] Reported as binary categories. All remaining patients were in the 30-45 mL/min/1.73 m^2 eGFR category or the 0-29 mg/g uACR category.
Abbreviations: ARNI: angiotensin receptor/neprilysin inhibitor; BMI: body mass index; CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; RASi: renin-angiotensin system inhibitor; SD: standard deviation; SMD: standardised mean difference; T2D: type 2 diabetes; uACR: urinary albumin-creatinine ratio.

A.5 High uACR (≥200 mg/g)

Table 31: Baseline characteristics – high uACR (≥200 mg/g), Medicare only, 'main period'

	Before weighting	After weighting

Characteristic	Dapagliflozin (n=[redacted])	Empagliflozin (n=[redacted])	SMD	Dapagliflozin (n=[redacted])	Empagliflozin (n=[redacted])	SMD
Age, years, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BMI, kg/m^2						
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Categorical						
<25, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥30, n (%)	[redacted]	[redacted]		[redacted]	[redacted]	
25.0-29.9, n (%)	[redacted]	[redacted]		[redacted]	[redacted]	
Missing, n (%)	[redacted]	[redacted]		[redacted]	[redacted]	
Baseline eGFR, mL/min/1.73m^2 [a]						
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Categorical						
60-89 (G2), n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
45-59 (G3a), n (%)	[redacted]	[redacted]		[redacted]	[redacted]	
30-44 (G3b), n (%)	[redacted]	[redacted]		[redacted]	[redacted]	
15-29 (G4), n (%)	[redacted]	[redacted]		[redacted]	[redacted]	
Baseline uACR, mg/g[a]						
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Categorical						
≥200, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ln_uacr, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Female, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age, n (%)						
<40	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
40-49	[redacted]	[redacted]		[redacted]	[redacted]	
50-59	[redacted]	[redacted]		[redacted]	[redacted]	
60-69	[redacted]	[redacted]		[redacted]	[redacted]	
70-79	[redacted]	[redacted]		[redacted]	[redacted]	

≥80	[redacted]	[redacted]		[redacted]	[redacted]	
Race, n (%)						
Asian	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Black	[redacted]	[redacted]		[redacted]	[redacted]	
Unknown/Other	[redacted]	[redacted]		[redacted]	[redacted]	
White	[redacted]	[redacted]		[redacted]	[redacted]	
Medicare, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cause of CKD, n (%)						
Diabetic kidney disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypertensive disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Glomerular disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Renal tubolo-interstitial disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other/unknown	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Comorbidities						
Angina	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Atrial fibrillation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bradycardia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Heart failure	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Myocardial infarction	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stroke	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other cardiovascular disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hyperkalaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
T2D	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Medications, n (%)						
RASi	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ARNI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Beta-blocker	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Calcium channel blocker	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Diuretics	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Antithrombotic agent	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Statins	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anti-hyperkaliaemic treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anti-diabetic treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[a] Patients in the 'complete case' had an eGFR and uACR measurement within 122 days prior to or at the index date.
Abbreviations: ARNI: angiotensin receptor/neprilysin inhibitor; BMI: body mass index; CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; RASi: renin-angiotensin system inhibitor; SD: standard deviation; SMD: standardised mean difference; T2D: type 2 diabetes; uACR: urinary albumin-creatinine ratio.

Table 32: Baseline characteristics – high uACR (≥200 mg/g), Medicare only, 'pooled period'

	Before weighting			After weighting		
Characteristic	**Dapagliflozin (n=[redacted])**	**Empagliflozin (n=[redacted])**	**SMD**	**Dapagliflozin (n=[redacted])**	**Empagliflozin (n=[redacted])**	**SMD**
Age, years, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BMI, kg/m^2						
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Categorical						
<25, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥30, n (%)	[redacted]	[redacted]		[redacted]	[redacted]	
25.0-29.9, n (%)	[redacted]	[redacted]		[redacted]	[redacted]	
Missing, n (%)	[redacted]	[redacted]		[redacted]	[redacted]	
Baseline eGFR, mL/min/1.73m^2 [a]						
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Categorical						
60-89 (G2), n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
45-59 (G3a), n (%)	[redacted]	[redacted]		[redacted]	[redacted]	

30-44 (G3b), n (%)	[redacted]	[redacted]		[redacted]	[redacted]	
15-29 (G4), n (%)	[redacted]	[redacted]		[redacted]	[redacted]	
Baseline uACR, mg/g[a]						
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Categorical						
≥200, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ln_uacr, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Female, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age, n (%)						
<40	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
40-49	[redacted]	[redacted]		[redacted]	[redacted]	
50-59	[redacted]	[redacted]		[redacted]	[redacted]	
60-69	[redacted]	[redacted]		[redacted]	[redacted]	
70-79	[redacted]	[redacted]		[redacted]	[redacted]	
≥80	[redacted]	[redacted]		[redacted]	[redacted]	
Race, n (%)						
Asian	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Black	[redacted]	[redacted]		[redacted]	[redacted]	
Unknown/Other	[redacted]	[redacted]		[redacted]	[redacted]	
White	[redacted]	[redacted]		[redacted]	[redacted]	
Medicare, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cause of CKD, n (%)						
Diabetic kidney disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypertensive disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Glomerular disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Renal tubolo-interstitial disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other/unknown	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Comorbidities						
Angina	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Atrial fibrillation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bradycardia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Heart failure	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Myocardial infarction	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stroke	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other cardiovascular disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hyperkalaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
T2D	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Medications, n (%)						
RASi	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ARNI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Beta-blocker	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Calcium channel blocker	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Diuretics	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Antithrombotic agent	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Statins	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anti-hyperkaliaemic treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anti-diabetic treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[a] Patients in the 'complete case' had an eGFR and uACR measurement within 122 days prior to or at the index date.
Abbreviations: ARNI: angiotensin receptor/neprilysin inhibitor; BMI: body mass index; CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; RASi: renin-angiotensin system inhibitor; SD: standard deviation; SMD: standardised mean difference; T2D: type 2 diabetes; uACR: urinary albumin-creatinine ratio.

A.6 With T2D and low uACR (<200 mg/g)

Table 33: Baseline characteristics – with T2D and low uACR (<200 mg/g), Medicare only, 'main period'

	Before weighting	After weighting

Characteristic	Dapagliflozin (n=[redacted])	Empagliflozin (n=[redacted])	SMD	Dapagliflozin (n=[redacted])	Empagliflozin (n=[redacted])	SMD
Age, years, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BMI, kg/m^2						
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Categorical						
<25, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥30, n (%)	[redacted]	[redacted]		[redacted]	[redacted]	
25.0-29.9, n (%)	[redacted]	[redacted]		[redacted]	[redacted]	
Missing, n (%)	[redacted]	[redacted]		[redacted]	[redacted]	
Baseline eGFR, mL/min/1.73m^2 [a]						
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Categorical[b]						
15-29 (G4), n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline uACR, mg/g[a]						
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Categorical[b]						
30-199, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ln_uacr, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Female, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age, n (%)						
50-59	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
60-69	[redacted]	[redacted]		[redacted]	[redacted]	
70-79	[redacted]	[redacted]		[redacted]	[redacted]	
≥80	[redacted]	[redacted]		[redacted]	[redacted]	
Race, n (%)						
Asian	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Black	[redacted]	[redacted]		[redacted]	[redacted]	
Unknown/Other	[redacted]	[redacted]		[redacted]	[redacted]	

White	[redacted]	[redacted]		[redacted]	[redacted]	
Medicare, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cause of CKD, n (%)						
Diabetic kidney disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypertensive disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Glomerular disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Renal tubolo-interstitial disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other/unknown	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Comorbidities						
Angina	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Atrial fibrillation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bradycardia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Heart failure	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Myocardial infarction	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stroke	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other cardiovascular disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hyperkalaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
T2D	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Medications, n (%)						
RASi	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ARNI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Beta-blocker	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Calcium channel blocker	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Diuretics	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Antithrombotic agent	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Statins	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anti-hyperkaliaemic treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anti-diabetic treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[a] Patients in the 'complete case' had an eGFR and uACR measurement within 122 days prior to or at the index date. [b] Reported as binary categories. All remaining patients were in the 30-45 mL/min/1.73 m^2 eGFR category or the 0-29 mg/g uACR category.
Abbreviations: ARNI: angiotensin receptor/neprilysin inhibitor; BMI: body mass index; CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; RASi: renin-angiotensin system inhibitor; SD: standard deviation; SMD: standardised mean difference; T2D: type 2 diabetes; uACR: urinary albumin-creatinine ratio.

Table 34: Baseline characteristics – with T2D and low uACR (<200 mg/g), Medicare only, 'pooled period'

	Before weighting			After weighting		
Characteristic	**Dapagliflozin (n=[redacted])**	**Empagliflozin (n=[redacted])**	**SMD**	**Dapagliflozin (n=[redacted])**	**Empagliflozin (n=[redacted])**	**SMD**
Age, years, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BMI, kg/m^2						
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Categorical						
<25	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥30	[redacted]	[redacted]		[redacted]	[redacted]	
25.0-29.9	[redacted]	[redacted]		[redacted]	[redacted]	
Missing	[redacted]	[redacted]		[redacted]	[redacted]	
Baseline eGFR, mL/min/1.73m^2 [a]						
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Categorical[b]						
15-29 (G4), n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline uACR, mg/g[a]						
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Categorical[b]						
30-199, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ln_uacr, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Female, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age, n (%)						
40-49	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
50-59	[redacted]	[redacted]		[redacted]	[redacted]	
60-69	[redacted]	[redacted]		[redacted]	[redacted]	
70-79	[redacted]	[redacted]		[redacted]	[redacted]	
≥80	[redacted]	[redacted]		[redacted]	[redacted]	
Race, n (%)						
Asian	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Black	[redacted]	[redacted]		[redacted]	[redacted]	
Unknown/Other	[redacted]	[redacted]		[redacted]	[redacted]	
White	[redacted]	[redacted]		[redacted]	[redacted]	
Medicare, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cause of CKD, n (%)						
Diabetic kidney disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypertensive disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Glomerular disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Renal tubolo-interstitial disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other/unknown	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Comorbidities						
Angina	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Atrial fibrillation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bradycardia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Heart failure	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Myocardial infarction	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stroke	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other cardiovascular disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Anaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hyperkalaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
T2D	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Medications, n (%)						
RASi	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ARNI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Beta-blocker	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Calcium channel blocker	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Diuretics	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Antithrombotic agent	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Statins	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anti-hyperkaliaemic treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anti-diabetic treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[a] Patients in the 'complete case' had an eGFR and uACR measurement within 122 days prior to or at the index date. [b] Reported as binary categories. All remaining patients were in the 30-45 mL/min/1.73 m^2 eGFR category or the 0-29 mg/g uACR category.
Abbreviations: ARNI: angiotensin receptor/neprilysin inhibitor; BMI: body mass index; CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; RASi: renin-angiotensin system inhibitor; SD: standard deviation; SMD: standardised mean difference; T2D: type 2 diabetes; uACR: urinary albumin-creatinine ratio.

A.7 With T2D and high uACR (≥200 mg/g)

Table 35: Baseline characteristics – with T2D and high uACR (≥200 mg/g), Medicare only, 'main period'

	Before weighting			After weighting		
Characteristic	**Dapagliflozin (n=[redacted])**	**Empagliflozin (n=[redacted])**	**SMD**	**Dapagliflozin (n=[redacted])**	**Empagliflozin (n=[redacted])**	**SMD**
Age, years, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BMI, kg/m^2						
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Categorical						
<25	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

≥30	[redacted]	[redacted]		[redacted]	[redacted]	
25.0-29.9	[redacted]	[redacted]		[redacted]	[redacted]	
Missing	[redacted]	[redacted]		[redacted]	[redacted]	
Baseline eGFR, mL/min/1.73m^2 [a]						
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Categorical						
60-89 (G2), n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
45-59 (G3a), n (%)	[redacted]	[redacted]		[redacted]	[redacted]	
30-44 (G3b), n (%)	[redacted]	[redacted]		[redacted]	[redacted]	
15-29 (G4), n (%)	[redacted]	[redacted]		[redacted]	[redacted]	
Baseline uACR, mg/g[a]						
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Categorical						
≥200, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ln_uacr, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Female, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age, n (%)						
<40	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
40-49	[redacted]	[redacted]		[redacted]	[redacted]	
50-59	[redacted]	[redacted]		[redacted]	[redacted]	
60-69	[redacted]	[redacted]		[redacted]	[redacted]	
70-79	[redacted]	[redacted]		[redacted]	[redacted]	
≥80	[redacted]	[redacted]		[redacted]	[redacted]	
Race, n (%)						
Asian	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Black	[redacted]	[redacted]		[redacted]	[redacted]	
Unknown/Other	[redacted]	[redacted]		[redacted]	[redacted]	
White	[redacted]	[redacted]		[redacted]	[redacted]	
Medicare, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cause of CKD, n (%)						

Diabetic kidney disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypertensive disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Glomerular disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Renal tubolo-interstitial disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other/unknown	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Comorbidities						
Angina	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Atrial fibrillation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bradycardia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Heart failure	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Myocardial infarction	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stroke	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other cardiovascular disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hyperkalaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
T2D	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Medications, n (%)						
RASi	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ARNI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Beta-blocker	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Calcium channel blocker	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Diuretics	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Antithrombotic agent	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Statins	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anti-hyperkaliaemic treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Anti-diabetic treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[a] Patients in the 'complete case' had an eGFR and uACR measurement within 122 days prior to or at the index date.
Abbreviations: ARNI: angiotensin receptor/neprilysin inhibitor; BMI: body mass index; CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; RASi: renin-angiotensin system inhibitor; SD: standard deviation; SMD: standardised mean difference; T2D: type 2 diabetes; uACR: urinary albumin-creatinine ratio.

Table 36: Baseline characteristics – withT2D and high uACR (≥200 mg/g), Medicare only, 'pooled period'

	Before weighting			After weighting		
Characteristic	**Dapagliflozin (n=[redacted])**	**Empagliflozin (n=[redacted])**	**SMD**	**Dapagliflozin (n=[redacted])**	**Empagliflozin (n=[redacted])**	**SMD**
Age, years, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BMI, kg/m^2						
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Categorical						
<25	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥30	[redacted]	[redacted]		[redacted]	[redacted]	
25.0-29.9	[redacted]	[redacted]		[redacted]	[redacted]	
Missing	[redacted]	[redacted]		[redacted]	[redacted]	
Baseline eGFR, mL/min/1.73m^2 [a]						
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Categorical						
60-89 (G2), n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
45-59 (G3a), n (%)	[redacted]	[redacted]		[redacted]	[redacted]	
30-44 (G3b), n (%)	[redacted]	[redacted]		[redacted]	[redacted]	
15-29 (G4), n (%)	[redacted]	[redacted]		[redacted]	[redacted]	
Baseline uACR, mg/g[a]						
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Categorical						
≥200, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ln_uacr, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Female, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Age, n (%)						
<40	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
40-49	[redacted]	[redacted]		[redacted]	[redacted]	
50-59	[redacted]	[redacted]		[redacted]	[redacted]	
60-69	[redacted]	[redacted]		[redacted]	[redacted]	
70-79	[redacted]	[redacted]		[redacted]	[redacted]	
≥80	[redacted]	[redacted]		[redacted]	[redacted]	
Race, n (%)						
Asian	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Black	[redacted]	[redacted]		[redacted]	[redacted]	
Unknown/Other	[redacted]	[redacted]		[redacted]	[redacted]	
White	[redacted]	[redacted]		[redacted]	[redacted]	
Medicare, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cause of CKD, n (%)						
Diabetic kidney disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypertensive disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Glomerular disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Renal tubolo-interstitial disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other/unknown	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Comorbidities						
Angina	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Atrial fibrillation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bradycardia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Heart failure	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Myocardial infarction	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stroke	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other cardiovascular disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Anaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hyperkalaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
T2D	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Medications, n (%)						
RASi	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ARNI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Beta-blocker	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Calcium channel blocker	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Diuretics	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Antithrombotic agent	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Statins	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anti-hyperkaliaemic treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anti-diabetic treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[a] Patients in the 'complete case' had an eGFR and uACR measurement within 122 days prior to or at the index date.
Abbreviations: ARNI: angiotensin receptor/neprilysin inhibitor; BMI: body mass index; CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; RASi: renin-angiotensin system inhibitor; SD: standard deviation; SMD: standardised mean difference; T2D: type 2 diabetes; uACR: urinary albumin-creatinine ratio.

A.8 Without T2D and low uACR (<200 mg/g)

Table 37: Baseline characteristics – without T2D and low uACR (<200 mg/g), Medicare only, 'pooled period'

	Before weighting			After weighting		
Characteristic	**Dapagliflozin (n=[redacted])**	**Empagliflozin (n=[redacted])**	**SMD**	**Dapagliflozin (n=[redacted])**	**Empagliflozin (n=[redacted])**	**SMD**
Age, years, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BMI, kg/m^2						
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Categorical						
<25	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥30	[redacted]	[redacted]		[redacted]	[redacted]	

25.0-29.9	[redacted]	[redacted]		[redacted]	[redacted]	
Missing	[redacted]	[redacted]		[redacted]	[redacted]	
Baseline eGFR, mL/min/1.73m^2 [a]						
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Categorical[b]						
15-29 (G4), n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline uACR, mg/g[a]						
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Categorical[b]						
30-199, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ln_uacr, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Female, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age, n (%)						
40-49	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
50-59	[redacted]	[redacted]		[redacted]	[redacted]	
60-69	[redacted]	[redacted]		[redacted]	[redacted]	
70-79	[redacted]	[redacted]		[redacted]	[redacted]	
≥80	[redacted]	[redacted]		[redacted]	[redacted]	
Race, n (%)						
Asian	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Black	[redacted]	[redacted]		[redacted]	[redacted]	
Unknown/Other	[redacted]	[redacted]		[redacted]	[redacted]	
White	[redacted]	[redacted]		[redacted]	[redacted]	
Medicare, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cause of CKD, n (%)						
Diabetic kidney disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypertensive disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Glomerular disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Renal tubolo-interstitial disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Other/unknown	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Comorbidities						
Angina	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Atrial fibrillation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bradycardia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Heart failure	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Myocardial infarction	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stroke	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other cardiovascular disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hyperkalaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
T2D	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Medications, n (%)						
RASi	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ARNI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Beta-blocker	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Calcium channel blocker	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Diuretics	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Antithrombotic agent	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Statins	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anti-hyperkaliaemic treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anti-diabetic treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[a] Patients in the 'complete case' had an eGFR and uACR measurement within 122 days prior to or at the index date. [b] Reported as binary categories. All remaining patients were in the 30-45 mL/min/1.73 m^2 eGFR category or the 0-29 mg/g uACR category.

Abbreviations: ARNI: angiotensin receptor/neprilysin inhibitor; BMI: body mass index; CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; RASi: renin-angiotensin system inhibitor; SD: standard deviation; SMD: standardised mean difference; T2D: type 2 diabetes; uACR: urinary albumin-creatinine ratio.

Table 38: Baseline characteristics – without T2D and low uACR (<200 mg/g), Medicare only, 'main period'

	Before weighting			After weighting		
Characteristic	**Dapagliflozin (n=[redacted])**	**Empagliflozin (n=[redacted])**	**SMD**	**Dapagliflozin (n=[redacted])**	**Empagliflozin (n=[redacted])**	**SMD**
Age, years, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BMI, kg/m^2						
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Categorical						
<25	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥30	[redacted]	[redacted]		[redacted]	[redacted]	
25.0-29.9	[redacted]	[redacted]		[redacted]	[redacted]	
Missing	[redacted]	[redacted]		[redacted]	[redacted]	
Baseline eGFR, mL/min/1.73m^2 [a]						
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Categorical[b]						
15-29 (G4), n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline uACR, mg/g[a]						
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Categorical[b]						
30-199, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ln_uacr, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Female, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age, n (%)						
40-49	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
50-59	[redacted]	[redacted]		[redacted]	[redacted]	
60-69	[redacted]	[redacted]		[redacted]	[redacted]	
70-79	[redacted]	[redacted]		[redacted]	[redacted]	
≥80	[redacted]	[redacted]		[redacted]	[redacted]	
Race, n (%)						

Asian	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Black	[redacted]	[redacted]		[redacted]	[redacted]	
Unknown/Other	[redacted]	[redacted]		[redacted]	[redacted]	
White	[redacted]	[redacted]		[redacted]	[redacted]	
Medicare, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cause of CKD, n (%)						
Diabetic kidney disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypertensive disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Glomerular disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Renal tubolo-interstitial disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other/unknown	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Comorbidities						
Angina	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Atrial fibrillation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bradycardia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Heart failure	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Myocardial infarction	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stroke	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other cardiovascular disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hyperkalaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
T2D	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Medications, n (%)						
RASi	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ARNI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Beta-blocker	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Calcium channel blocker	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Diuretics	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Antithrombotic agent	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Statins	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anti-hyperkaliaemic treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anti-diabetic treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[a] Patients in the 'complete case' had an eGFR and uACR measurement within 122 days prior to or at the index date. [b] Reported as binary categories. All remaining patients were in the 30-45 mL/min/1.73 m^2 eGFR category or the 0-29 mg/g uACR category.
Abbreviations: ARNI: angiotensin receptor/neprilysin inhibitor; BMI: body mass index; CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; RASi: renin-angiotensin system inhibitor; SD: standard deviation; SMD: standardised mean difference; T2D: type 2 diabetes; uACR: urinary albumin-creatinine ratio.

A.9 Without T2D and high uACR (≥200 mg/g)

Table 39: Baseline characteristics – without T2D and high uACR (≥200 mg/g), Medicare only, 'pooled period'

	Before weighting			After weighting		
Characteristic	**Dapagliflozin (n=[redacted])**	**Empagliflozin (n=[redacted])**	**SMD**	**Dapagliflozin (n=[redacted])**	**Empagliflozin (n=[redacted])**	**SMD**
Age, years, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BMI, kg/m^2						
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Categorical						
<25	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥30	[redacted]	[redacted]		[redacted]	[redacted]	
25.0-29.9	[redacted]	[redacted]		[redacted]	[redacted]	
Missing	[redacted]	[redacted]		[redacted]	[redacted]	
Baseline eGFR, mL/min/1.73m^2 [a]						
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Categorical						
60-89 (G2), n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

45-59 (G3a), n (%)	[redacted]	[redacted]		[redacted]	[redacted]	
30-44 (G3b), n (%)	[redacted]	[redacted]		[redacted]	[redacted]	
15-29 (G4), n (%)	[redacted]	[redacted]		[redacted]	[redacted]	
Baseline uACR, mg/g[a]						
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Categorical						
≥200, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ln_uacr, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Female, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age, n (%)						
<40	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
50-59	[redacted]	[redacted]		[redacted]	[redacted]	
60-69	[redacted]	[redacted]		[redacted]	[redacted]	
70-79	[redacted]	[redacted]		[redacted]	[redacted]	
≥80	[redacted]	[redacted]		[redacted]	[redacted]	
Race, n (%)						
Asian	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Black	[redacted]	[redacted]		[redacted]	[redacted]	
Unknown/Other	[redacted]	[redacted]		[redacted]	[redacted]	
White	[redacted]	[redacted]		[redacted]	[redacted]	
Medicare, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cause of CKD, n (%)						
Diabetic kidney disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypertensive disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Glomerular disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Renal tubolo-interstitial disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other/unknown	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Comorbidities						
Angina	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Atrial fibrillation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bradycardia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Heart failure	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Myocardial infarction	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stroke	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other cardiovascular disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hyperkalaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
T2D	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Medications, n (%)						
RASi	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ARNI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Beta-blocker	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Calcium channel blocker	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Diuretics	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Antithrombotic agent	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Statins	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anti-hyperkaliaemic treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anti-diabetic treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[a] Patients in the 'complete case' had an eGFR and uACR measurement within 122 days prior to or at the index date.
Abbreviations: ARNI: angiotensin receptor/neprilysin inhibitor; BMI: body mass index; CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; RASi: renin-angiotensin system inhibitor; SD: standard deviation; SMD: standardised mean difference; T2D: type 2 diabetes; uACR: urinary albumin-creatinine ratio.

Table 26: Baseline characteristics – without T2D and high uACR (≥200 mg/g), Medicare only, 'main period'

	Before weighting			After weighting		
Characteristic	**Dapagliflozin (n=[redacted])**	**Empagliflozin (n=[redacted])**	**SMD**	**Dapagliflozin (n=[redacted])**	**Empagliflozin (n=[redacted])**	**SMD**

Age, years, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BMI, kg/m^2						
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Categorical						
<25	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥30	[redacted]	[redacted]		[redacted]	[redacted]	
25.0-29.9	[redacted]	[redacted]		[redacted]	[redacted]	
Missing	[redacted]	[redacted]		[redacted]	[redacted]	
Baseline eGFR, mL/min/1.73m^2 [a]						
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Categorical						
60-89 (G2), n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
45-59 (G3a), n (%)	[redacted]	[redacted]		[redacted]	[redacted]	
30-44 (G3b), n (%)	[redacted]	[redacted]		[redacted]	[redacted]	
15-29 (G4), n (%)	[redacted]	[redacted]		[redacted]	[redacted]	
Baseline uACR, mg/g[a]						
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Categorical						
≥200, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ln_uacr, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Female, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age, n (%)						
<40	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
50-59	[redacted]	[redacted]		[redacted]	[redacted]	
60-69	[redacted]	[redacted]		[redacted]	[redacted]	
70-79	[redacted]	[redacted]		[redacted]	[redacted]	
≥80	[redacted]	[redacted]		[redacted]	[redacted]	
Race, n (%)						
Asian	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Black	[redacted]	[redacted]		[redacted]	[redacted]	
Unknown/Other	[redacted]	[redacted]		[redacted]	[redacted]	
White	[redacted]	[redacted]		[redacted]	[redacted]	
Medicare, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cause of CKD, n (%)						
Diabetic kidney disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypertensive disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Glomerular disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Renal tubolo-interstitial disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other/unknown	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Comorbidities						
Angina	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Atrial fibrillation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bradycardia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Heart failure	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Myocardial infarction	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stroke	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other cardiovascular disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hyperkalaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
T2D	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Medications, n (%)						
RASi	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ARNI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Beta-blocker	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Calcium channel blocker	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Diuretics	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Antithrombotic agent	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Statins	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anti-hyperkaliaemic treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anti-diabetic treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[a] Patients in the 'complete case' had an eGFR and uACR measurement within 122 days prior to or at the index date.
Abbreviations: ARNI: angiotensin receptor/neprilysin inhibitor; BMI: body mass index; CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; RASi: renin-angiotensin system inhibitor; SD: standard deviation; SMD: standardised mean difference; T2D: type 2 diabetes; uACR: urinary albumin-creatinine ratio.

Appendix B Subgroup analyses: Propensity score matching

B.1 Overall population

B.1.1 Medicare only, 'pooled period'

A density plot of the PS and weight distribution are presented in Figure 57.

Figure 57: Density plot of PS and weight distribution following PS weighting for dapagliflozin and empagliflozin – Overall population, 'pooled period'

[redacted]

Abbreviations: PS: propensity score

B.2 With T2D

B.2.1 Medicare only, 'main period'

A density plot of the PS and weight distribution are presented in Figure 58.

Figure 58: Density plot of PS and weight distribution following PS weighting for dapagliflozin and empagliflozin – with T2D, 'main period'

[redacted]

Abbreviations: PS: propensity score

B.2.2 Medicare only, 'pooled period'

A density plot of the PS and weight distribution are presented in Figure 58.

Figure 59: Density plot of PS and weight distribution following PS weighting for dapagliflozin and empagliflozin – with T2D, 'pooled period'

[redacted]

Abbreviations: PS: propensity score.

B.3 Without T2D

B.3.1 Medicare only, 'main period'

A density plot of the PS and weight distribution are presented in Figure 60.

Figure 60: Density plot of PS and weight distribution following PS weighting for dapagliflozin and empagliflozin – without T2D, 'main period'

[redacted]

Abbreviations: PS: propensity score.

B.3.2 Medicare only, 'pooled period'

A density plot of the PS and weight distribution are presented in Figure 61.

Figure 61: Density plot of PS and weight distribution following PS weighting for dapagliflozin and empagliflozin – without T2D, 'pooled period'

[redacted]

Abbreviations: PS: propensity score.

B.4 Low uACR (<200 mg/g)

B.4.1 Medicare only, 'main period'

A density plot of the PS and weight distribution are presented in Figure 62.

Figure 62: Density plot of PS and weight distribution following PS weighting for dapagliflozin and empagliflozin – low uACR, 'main period'

[redacted]

Abbreviations: PS: propensity score.

B.4.2 Medicare only, 'pooled period'

A density plot of the PS and weight distribution are presented in Figure 63.

Figure 63: Density plot of PS and weight distribution following PS weighting for dapagliflozin and empagliflozin – low uACR, 'pooled period'

[redacted]

Abbreviations: PS: propensity score.

B.5 High uACR (≥200 mg/g)

B.5.1 Medicare only, 'main period'

A density plot of the PS and weight distribution are presented in Figure 64.

Figure 64: Density plot of PS and weight distribution following PS weighting for dapagliflozin and empagliflozin – high uACR, 'main period'

[redacted]

Abbreviations: PS: propensity score.

B.5.2 Medicare only, 'pooled period'

A density plot of the PS and weight distribution are presented in Figure 65.

Figure 65: Density plot of PS and weight distribution following PS weighting for dapagliflozin and empagliflozin – high uACR, 'pooled period'

[redacted]

Abbreviations: PS: propensity score.

B.6 With T2D and low uACR (<200 mg/g)

B.6.1 Medicare only, 'main period'

A density plot of the PS and weight distribution are presented in Figure 66.

Figure 66: Density plot of PS and weight distribution following PS weighting for dapagliflozin and empagliflozin – with T2D and low uACR, 'main period'

[redacted]

Abbreviations: PS: propensity score.

B.6.2 Medicare only, 'pooled period'

A density plot of the PS and weight distribution are presented in Figure 67.

Figure 67: Density plot of PS and weight distribution following PS weighting for dapagliflozin and empagliflozin – with T2D and low uACR, 'pooled period'

[redacted]

Abbreviations: PS: propensity score.

B.7 With T2D and high uACR (≥200 mg/g)

B.7.1 Medicare only, 'main period'

A density plot of the PS and weight distribution are presented in Figure 68.

Figure 68: Density plot of PS and weight distribution following PS weighting for dapagliflozin and empagliflozin – with T2D and high uACR, 'main period'

[redacted]

Abbreviations: PS: propensity score.

B.7.2 Medicare only, 'pooled period'

A density plot of the PS and weight distribution are presented in Figure 69.

Figure 69: Density plot of PS and weight distribution following PS weighting for dapagliflozin and empagliflozin – with T2D and high uACR, 'pooled period'

[redacted]

Abbreviations: PS: propensity score.

B.8 Without T2D and low uACR (<200 mg/g)

B.8.1 Medicare only, 'main period'

A density plot of the PS and weight distribution are presented in Figure 70.

Figure 70: Density plot of PS and weight distribution following PS weighting for dapagliflozin and empagliflozin – without T2D and low UACR, 'main period'

[redacted]

Abbreviations: PS: propensity score.

B.8.2 Medicare only, 'pooled period'

A density plot of the PS and weight distribution are presented in Figure 71.

Figure 71: Density plot of PS and weight distribution following PS weighting for dapagliflozin and empagliflozin – without T2D and low uACR, 'pooled period'

[redacted]

Abbreviations: PS: propensity score.

B.9 Without T2D and high uACR (≥200 mg/g)

B.9.1 Medicare only, 'main period'

A density plot of the PS and weight distribution are presented in Figure 72.

Figure 72: Density plot of PS and weight distribution following PS weighting for dapagliflozin and empagliflozin – without T2D and high uACR, 'main period'

[redacted]

Abbreviations: PS: propensity score.

B.9.2 Medicare only, 'pooled period'

A density plot of the PS and weight distribution are presented in Figure 73.

Figure 73: Density plot of PS and weight distribution following PS weighting for dapagliflozin and empagliflozin – without T2D and high uACR, 'pooled period'

[redacted]

Abbreviations: PS: propensity score.

Appendix C Sensitivity analyses: Baseline characteristics

Baseline characteristics for the Medicare plus commercial and Medicare plus missing uACR populations in all population subgroups ('main period' and 'pooled period') are presented in the following sections.

C.1 Overall population

Table 40: Baseline characteristics – overall population, Medicare plus commercial, 'pooled period'

	Before weighting			After weighting		
Characteristic	**Dapagliflozin (n=[redacted])**	**Empagliflozin (n=[redacted])**	**SMD**	**Dapagliflozin (n=[redacted])**	**Empagliflozin (n=[redacted])**	**SMD**
Age, years, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BMI, kg/m^2						
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Categorical						
<25	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥30	[redacted]	[redacted]		[redacted]	[redacted]	
25.0-29.9	[redacted]	[redacted]		[redacted]	[redacted]	
Missing	[redacted]	[redacted]		[redacted]	[redacted]	
Baseline eGFR, mL/min/1.73m^2 [a]						
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Categorical						
60-89 (G2), n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
45-59 (G3a), n (%)	[redacted]	[redacted]		[redacted]	[redacted]	
30-44 (G3b), n (%)	[redacted]	[redacted]		[redacted]	[redacted]	
15-29 (G4), n (%)	[redacted]	[redacted]		[redacted]	[redacted]	
Baseline uACR, mg/g[a]						
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Categorical						

0-29, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
30-199, n (%)	[redacted]	[redacted]		[redacted]	[redacted]	
≥200, n (%)	[redacted]	[redacted]		[redacted]	[redacted]	
ln_uacr, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Female, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age, n (%)						
<40	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
40-49	[redacted]	[redacted]		[redacted]	[redacted]	
50-59	[redacted]	[redacted]		[redacted]	[redacted]	
60-69	[redacted]	[redacted]		[redacted]	[redacted]	
70-79	[redacted]	[redacted]		[redacted]	[redacted]	
≥80	[redacted]	[redacted]		[redacted]	[redacted]	
Race, n (%)						
Asian	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Black	[redacted]	[redacted]		[redacted]	[redacted]	
Unknown/Other	[redacted]	[redacted]		[redacted]	[redacted]	
White	[redacted]	[redacted]		[redacted]	[redacted]	
Medicare, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cause of CKD, n (%)						
Diabetic kidney disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypertensive disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Glomerular disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Renal tubolo-interstitial disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other/unknown	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Comorbidities						
Angina	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Atrial fibrillation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bradycardia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Heart failure	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Hypertension	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Myocardial infarction	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stroke	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other cardiovascular disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hyperkalaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
T2D	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Medications, n (%)						
RASi	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ARNI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Beta-blocker	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Calcium channel blocker	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Diuretics	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Antithrombotic agent	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Statins	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anti-hyperkaliaemic treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anti-diabetic treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[a] Patients in the 'complete case' had an eGFR and uACR measurement within 122 days prior to or at the index date.
Abbreviations: ARNI: angiotensin receptor/neprilysin inhibitor; BMI: body mass index; CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; RASi: renin-angiotensin system inhibitor; SD: standard deviation; SMD: standardised mean difference; T2D: type 2 diabetes; uACR: urinary albumin-creatinine ratio.

Table 41: Baseline characteristics – overall population, Medicare plus commercial, 'main period'

	Before weighting			After weighting		
Characteristic	**Dapagliflozin (n=[redacted])**	**Empagliflozin (n=[redacted])**	**SMD**	**Dapagliflozin (n=[redacted])**	**Empagliflozin (n=[redacted])**	**SMD**
Age, years, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BMI, kg/m^2						
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Categorical						
<25	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥30	[redacted]	[redacted]		[redacted]	[redacted]	
25.0-29.9	[redacted]	[redacted]		[redacted]	[redacted]	
Missing	[redacted]	[redacted]		[redacted]	[redacted]	
Baseline eGFR, mL/min/1.73m^2 [a]						
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Categorical						
60-89 (G2), n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
45-59 (G3a), n (%)	[redacted]	[redacted]		[redacted]	[redacted]	
30-44 (G3b), n (%)	[redacted]	[redacted]		[redacted]	[redacted]	
15-29 (G4), n (%)	[redacted]	[redacted]		[redacted]	[redacted]	
Baseline uACR, mg/g[a]						
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Categorical						
0-29, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
30-199, n (%)	[redacted]	[redacted]		[redacted]	[redacted]	
≥200, n (%)	[redacted]	[redacted]		[redacted]	[redacted]	
ln_uacr, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Female, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age, n (%)						
<40	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
40-49	[redacted]	[redacted]		[redacted]	[redacted]	
50-59	[redacted]	[redacted]		[redacted]	[redacted]	
60-69	[redacted]	[redacted]		[redacted]	[redacted]	
70-79	[redacted]	[redacted]		[redacted]	[redacted]	
≥80	[redacted]	[redacted]		[redacted]	[redacted]	
Race, n (%)						
Asian	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Black	[redacted]	[redacted]		[redacted]	[redacted]	

Unknown/Other	[redacted]	[redacted]		[redacted]	[redacted]	
White	[redacted]	[redacted]		[redacted]	[redacted]	
Medicare, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cause of CKD, n (%)						
Diabetic kidney disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypertensive disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Glomerular disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Renal tubolo-interstitial disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other/unknown	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Comorbidities						
Angina	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Atrial fibrillation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bradycardia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Heart failure	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Myocardial infarction	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stroke	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other cardiovascular disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hyperkalaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
T2D	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Medications, n (%)						
RASi	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ARNI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Beta-blocker	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Calcium channel blocker	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Diuretics	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Antithrombotic agent	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Statins	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anti-hyperkaliaemic treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anti-diabetic treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[a] Patients in the 'complete case' had an eGFR and uACR measurement within 122 days prior to or at the index date.
Abbreviations: ARNI: angiotensin receptor/neprilysin inhibitor; BMI: body mass index; CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; RASi: renin-angiotensin system inhibitor; SD: standard deviation; SMD: standardised mean difference; T2D: type 2 diabetes; uACR: urinary albumin-creatinine ratio.

Table 42: Baseline characteristics – overall population, Medicare plus missing uACR, 'pooled period'

	Before weighting			After weighting		
Characteristic	**Dapagliflozin (n=[redacted])**	**Empagliflozin (n=[redacted])**	**SMD**	**Dapagliflozin (n=[redacted])**	**Empagliflozin (n=[redacted])**	**SMD**
Age, years, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BMI, kg/m^2						
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Categorical						
<25	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥30	[redacted]	[redacted]		[redacted]	[redacted]	
25.0-29.9	[redacted]	[redacted]		[redacted]	[redacted]	
Missing	[redacted]	[redacted]		[redacted]	[redacted]	
Baseline eGFR, mL/min/1.73m^2 [a]						
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Categorical						
60-89 (G2), n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
45-59 (G3a), n (%)	[redacted]	[redacted]		[redacted]	[redacted]	
30-44 (G3b), n (%)	[redacted]	[redacted]		[redacted]	[redacted]	
15-29 (G4), n (%)	[redacted]	[redacted]		[redacted]	[redacted]	
Baseline uACR, mg/g[a]						
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Categorical						
0-29, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
30-199, n (%)	[redacted]	[redacted]		[redacted]	[redacted]	
≥200, n (%)	[redacted]	[redacted]		[redacted]	[redacted]	
ln_uacr, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Female, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age, n (%)						
<40	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
40-49	[redacted]	[redacted]		[redacted]	[redacted]	
50-59	[redacted]	[redacted]		[redacted]	[redacted]	
60-69	[redacted]	[redacted]		[redacted]	[redacted]	
70-79	[redacted]	[redacted]		[redacted]	[redacted]	
≥80	[redacted]	[redacted]		[redacted]	[redacted]	
Race, n (%)						
Asian	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Black	[redacted]	[redacted]		[redacted]	[redacted]	
Unknown/Other	[redacted]	[redacted]		[redacted]	[redacted]	
White	[redacted]	[redacted]		[redacted]	[redacted]	
Medicare, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cause of CKD, n (%)						
Diabetic kidney disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypertensive disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Glomerular disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Renal tubolo-interstitial disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other/unknown	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Comorbidities						
Angina	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Atrial fibrillation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bradycardia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Heart failure	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Myocardial infarction	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stroke	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other cardiovascular disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hyperkalaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
T2D	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Medications, n (%)						
RASi	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ARNI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Beta-blocker	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Calcium channel blocker	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Diuretics	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Antithrombotic agent	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Statins	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anti-hyperkaliaemic treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anti-diabetic treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[a] Patients in the 'complete case' had an eGFR and uACR measurement within 122 days prior to or at the index date.
Abbreviations: ARNI: angiotensin receptor/neprilysin inhibitor; BMI: body mass index; CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; RASi: renin-angiotensin system inhibitor; SD: standard deviation; SMD: standardised mean difference; T2D: type 2 diabetes; uACR: urinary albumin-creatinine ratio.

Table 43: Baseline characteristics – overall population, Medicare plus missing uACR, 'main period'

	Before weighting			After weighting		
Characteristic	[redacted])	[redacted])	**SMD**	**Dapagliflozin (n=[redacted])**	**Empagliflozin (n=[redacted])**	**SMD**
Age, years, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BMI, kg/m^2						

Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Categorical						
<25	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥30	[redacted]	[redacted]		[redacted]	[redacted]	
25.0-29.9	[redacted]	[redacted]		[redacted]	[redacted]	
Missing	[redacted]	[redacted]		[redacted]	[redacted]	
Baseline eGFR, mL/min/1.73m^2 [a]						
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Categorical						
60-89 (G2), n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
45-59 (G3a), n (%)	[redacted]	[redacted]		[redacted]	[redacted]	
30-44 (G3b), n (%)	[redacted]	[redacted]		[redacted]	[redacted]	
15-29 (G4), n (%)	[redacted]	[redacted]		[redacted]	[redacted]	
Baseline uACR, mg/g[a]						
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Categorical						
0-29, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
30-199, n (%)	[redacted]	[redacted]		[redacted]	[redacted]	
≥200, n (%)	[redacted]	[redacted]		[redacted]	[redacted]	
ln_uacr, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Female, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age, n (%)						
<40	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
40-49	[redacted]	[redacted]		[redacted]	[redacted]	
50-59	[redacted]	[redacted]		[redacted]	[redacted]	
60-69	[redacted]	[redacted]		[redacted]	[redacted]	
70-79	[redacted]	[redacted]		[redacted]	[redacted]	
≥80	[redacted]	[redacted]		[redacted]	[redacted]	
Race, n (%)						
Asian	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Black	[redacted]	[redacted]		[redacted]	[redacted]	
Unknown/Other	[redacted]	[redacted]		[redacted]	[redacted]	
White	[redacted]	[redacted]		[redacted]	[redacted]	
Medicare, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cause of CKD, n (%)						
Diabetic kidney disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypertensive disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Glomerular disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Renal tubulo-interstitial disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other/unknown	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Comorbidities						
Angina	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Atrial fibrillation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bradycardia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Heart failure	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Myocardial infarction	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stroke	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other cardiovascular disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hyperkalaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
T2D	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Medications, n (%)						
RASi	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ARNI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Beta-blocker	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Calcium channel blocker	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Diuretics	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Antithrombotic agent	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Statins	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anti-hyperkaliaemic treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anti-diabetic treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[a] Patients in the 'complete case' had an eGFR and uACR measurement within 122 days prior to or at the index date.
Abbreviations: ARNI: angiotensin receptor/neprilysin inhibitor; BMI: body mass index; CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; RASi: renin-angiotensin system inhibitor; SD: standard deviation; SMD: standardised mean difference; T2D: type 2 diabetes; uACR: urinary albumin-creatinine ratio.

C.2 With T2D

Table 44: Baseline characteristics – with T2D, Medicare plus commercial, 'main period'

	Before weighting			After weighting		
Characteristic	**Dapagliflozin (n=[redacted])**	**Empagliflozin (n=[redacted])**	**SMD**	**Dapagliflozin (n=[redacted])**	**Empagliflozin (n=[redacted])**	**SMD**
Age, years, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BMI, kg/m^2						
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Categorical						
<25	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥30	[redacted]	[redacted]		[redacted]	[redacted]	
25.0-29.9	[redacted]	[redacted]		[redacted]	[redacted]	
Missing	[redacted]	[redacted]		[redacted]	[redacted]	
Baseline eGFR, mL/min/1.73m^2 [a]						
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Categorical						
60-89 (G2), n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
45-59 (G3a), n (%)	[redacted]	[redacted]		[redacted]	[redacted]	
30-44 (G3b), n (%)	[redacted]	[redacted]		[redacted]	[redacted]	
15-29 (G4), n (%)	[redacted]	[redacted]		[redacted]	[redacted]	

Baseline uACR, mg/g[a]						
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Categorical						
0-29, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
30-199, n (%)	[redacted]	[redacted]		[redacted]	[redacted]	
≥200, n (%)	[redacted]	[redacted]		[redacted]	[redacted]	
ln_uacr, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Female, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age, n (%)						
<40	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
40-49	[redacted]	[redacted]		[redacted]	[redacted]	
50-59	[redacted]	[redacted]		[redacted]	[redacted]	
60-69	[redacted]	[redacted]		[redacted]	[redacted]	
70-79	[redacted]	[redacted]		[redacted]	[redacted]	
≥80	[redacted]	[redacted]		[redacted]	[redacted]	
Race, n (%)						
Asian	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Black	[redacted]	[redacted]		[redacted]	[redacted]	
Unknown/Other	[redacted]	[redacted]		[redacted]	[redacted]	
White	[redacted]	[redacted]		[redacted]	[redacted]	
Medicare, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cause of CKD, n (%)						
Diabetic kidney disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypertensive disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Glomerular disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Renal tubulo-interstitial disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other/unknown	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Comorbidities						
Angina	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Atrial fibrillation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bradycardia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Heart failure	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Myocardial infarction	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stroke	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other cardiovascular disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hyperkalaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
T2D	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Medications, n (%)						
RASi	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ARNI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Beta-blocker	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Calcium channel blocker	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Diuretics	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Antithrombotic agent	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Statins	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anti-hyperkaliaemic treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anti-diabetic treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[a] Patients in the 'complete case' had an eGFR and uACR measurement within 122 days prior to or at the index date.
Abbreviations: ARNI: angiotensin receptor/neprilysin inhibitor; BMI: body mass index; CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; RASi: renin-angiotensin system inhibitor; SD: standard deviation; SMD: standardised mean difference; T2D: type 2 diabetes; uACR: urinary albumin-creatinine ratio.

Table 45: Baseline characteristics – with T2D, Medicare plus commercial, 'pooled period'

	Before weighting			After weighting		
Characteristic	**Dapagliflozin (n=[redacted])**	**Empagliflozin (n=[redacted])**	**SMD**	**Dapagliflozin (n=[redacted])**	**Empagliflozin (n=[redacted])**	**SMD**

Age, years, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BMI, kg/m^2						
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Categorical						
<25	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥30	[redacted]	[redacted]		[redacted]	[redacted]	
25.0-29.9	[redacted]	[redacted]		[redacted]	[redacted]	
Missing	[redacted]	[redacted]		[redacted]	[redacted]	
Baseline eGFR, mL/min/1.73m^2 [a]						
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Categorical						
60-89 (G2), n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
45-59 (G3a), n (%)	[redacted]	[redacted]		[redacted]	[redacted]	
30-44 (G3b), n (%)	[redacted]	[redacted]		[redacted]	[redacted]	
15-29 (G4), n (%)	[redacted]	[redacted]		[redacted]	[redacted]	
Baseline uACR, mg/g[a]						
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Categorical						
0-29, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
30-199, n (%)	[redacted]	[redacted]		[redacted]	[redacted]	
≥200, n (%)	[redacted]	[redacted]		[redacted]	[redacted]	
ln_uacr, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Female, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age, n (%)						
<40	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
40-49	[redacted]	[redacted]		[redacted]	[redacted]	
50-59	[redacted]	[redacted]		[redacted]	[redacted]	
60-69	[redacted]	[redacted]		[redacted]	[redacted]	
70-79	[redacted]	[redacted]		[redacted]	[redacted]	

≥80	[redacted]	[redacted]		[redacted]	[redacted]	
Race, n (%)						
Asian	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Black	[redacted]	[redacted]		[redacted]	[redacted]	
Unknown/Other	[redacted]	[redacted]		[redacted]	[redacted]	
White	[redacted]	[redacted]		[redacted]	[redacted]	
Medicare, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cause of CKD, n (%)						
Diabetic kidney disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypertensive disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Glomerular disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Renal tubolo-interstitial disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other/unknown	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Comorbidities						
Angina	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Atrial fibrillation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bradycardia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Heart failure	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Myocardial infarction	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stroke	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other cardiovascular disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hyperkalaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
T2D	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Medications, n (%)						
RASi	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ARNI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Beta-blocker	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Calcium channel blocker	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Diuretics	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Antithrombotic agent	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Statins	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anti-hyperkaliaemic treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anti-diabetic treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[a] Patients in the 'complete case' had an eGFR and uACR measurement within 122 days prior to or at the index date.
Abbreviations: ARNI: angiotensin receptor/neprilysin inhibitor; BMI: body mass index; CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; RASi: renin-angiotensin system inhibitor; SD: standard deviation; SMD: standardised mean difference; T2D: type 2 diabetes; uACR: urinary albumin-creatinine ratio.

Table 46: Baseline characteristics – with T2D, Medicare plus missing uACR, 'main period'

	Before weighting			After weighting		
Characteristic	**Dapagliflozin (n=[redacted])**	**Empagliflozin (n=[redacted])**	**SMD**	**Dapagliflozin (n=[redacted])**	**Empagliflozin (n=[redacted])**	**SMD**
Age, years, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BMI, kg/m^2						
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Categorical						
<25	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥30	[redacted]	[redacted]		[redacted]	[redacted]	
25.0-29.9	[redacted]	[redacted]		[redacted]	[redacted]	
Missing	[redacted]	[redacted]		[redacted]	[redacted]	
Baseline eGFR, mL/min/1.73m^2 [a]						
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Categorical						
60-89 (G2), n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
45-59 (G3a), n (%)	[redacted]	[redacted]		[redacted]	[redacted]	

30-44 (G3b), n (%)	[redacted]	[redacted]		[redacted]	[redacted]	
15-29 (G4), n (%)	[redacted]	[redacted]		[redacted]	[redacted]	
Baseline uACR, mg/g[a]						
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Categorical						
0-29, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
30-199, n (%)	[redacted]	[redacted]		[redacted]	[redacted]	
≥200, n (%)	[redacted]	[redacted]		[redacted]	[redacted]	
ln_uacr, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Female, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age, n (%)						
<40	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
40-49	[redacted]	[redacted]		[redacted]	[redacted]	
50-59	[redacted]	[redacted]		[redacted]	[redacted]	
60-69	[redacted]	[redacted]		[redacted]	[redacted]	
70-79	[redacted]	[redacted]		[redacted]	[redacted]	
≥80	[redacted]	[redacted]		[redacted]	[redacted]	
Race, n (%)						
Asian	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Black	[redacted]	[redacted]		[redacted]	[redacted]	
Unknown/Other	[redacted]	[redacted]		[redacted]	[redacted]	
White	[redacted]	[redacted]		[redacted]	[redacted]	
Medicare, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cause of CKD, n (%)						
Diabetic kidney disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypertensive disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Glomerular disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Renal tubolo-interstitial disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other/unknown	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Comorbidities						
Angina	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Atrial fibrillation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bradycardia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Heart failure	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Myocardial infarction	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stroke	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other cardiovascular disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hyperkalaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
T2D	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Medications, n (%)						
RASi	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ARNI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Beta-blocker	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Calcium channel blocker	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Diuretics	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Antithrombotic agent	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Statins	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anti-hyperkaliaemic treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anti-diabetic treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[a] Patients in the 'complete case' had an eGFR and uACR measurement within 122 days prior to or at the index date.
Abbreviations: ARNI: angiotensin receptor/neprilysin inhibitor; BMI: body mass index; CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; RASi: renin-angiotensin system inhibitor; SD: standard deviation; SMD: standardised mean difference; T2D: type 2 diabetes; uACR: urinary albumin-creatinine ratio.

Table 47: Baseline characteristics – with T2D, Medicare plus missing uACR, 'pooled period'

	Before weighting	After weighting

Characteristic	Dapagliflozin (n=[redacted])	Empagliflozin (n=[redacted])	SMD	Dapagliflozin (n=[redacted])	Empagliflozin (n=[redacted])	SMD
Age, years, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BMI, kg/m^2						
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Categorical						
<25	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥30	[redacted]	[redacted]		[redacted]	[redacted]	
25.0-29.9	[redacted]	[redacted]		[redacted]	[redacted]	
Missing	[redacted]	[redacted]		[redacted]	[redacted]	
Baseline eGFR, mL/min/1.73m^2 [a]						
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Categorical						
60-89 (G2), n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
45-59 (G3a), n (%)	[redacted]	[redacted]		[redacted]	[redacted]	
30-44 (G3b), n (%)	[redacted]	[redacted]		[redacted]	[redacted]	
15-29 (G4), n (%)	[redacted]	[redacted]		[redacted]	[redacted]	
Baseline uACR, mg/g[a]						
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Categorical						
0-29, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
30-199, n (%)	[redacted]	[redacted]		[redacted]	[redacted]	
≥200, n (%)	[redacted]	[redacted]		[redacted]	[redacted]	
ln_uacr, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Female, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age, n (%)						
<40	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
40-49	[redacted]	[redacted]		[redacted]	[redacted]	
50-59	[redacted]	[redacted]		[redacted]	[redacted]	

60-69	[redacted]	[redacted]		[redacted]	[redacted]	
70-79	[redacted]	[redacted]		[redacted]	[redacted]	
≥80	[redacted]	[redacted]		[redacted]	[redacted]	
Race, n (%)						
Asian	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Black	[redacted]	[redacted]		[redacted]	[redacted]	
Unknown/Other	[redacted]	[redacted]		[redacted]	[redacted]	
White	[redacted]	[redacted]		[redacted]	[redacted]	
Medicare, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cause of CKD, n (%)						
Diabetic kidney disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypertensive disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Glomerular disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Renal tubolo-interstitial disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other/unknown	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Comorbidities						
Angina	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Atrial fibrillation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bradycardia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Heart failure	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Myocardial infarction	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stroke	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other cardiovascular disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hyperkalaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
T2D	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Medications, n (%)						

RASi	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ARNI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Beta-blocker	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Calcium channel blocker	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Diuretics	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Antithrombotic agent	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Statins	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anti-hyperkaliaemic treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anti-diabetic treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[a] Patients in the 'complete case' had an eGFR and uACR measurement within 122 days prior to or at the index date.
Abbreviations: ARNI: angiotensin receptor/neprilysin inhibitor; BMI: body mass index; CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; RASi: renin-angiotensin system inhibitor; SD: standard deviation; SMD: standardised mean difference; T2D: type 2 diabetes; uACR: urinary albumin-creatinine ratio.

C.3 Without T2D

Table 48: Baseline characteristics – without T2D, Medicare plus commercial, 'main period'

	Before weighting			After weighting		
Characteristic	**Dapagliflozin (n=[redacted])**	**Empagliflozin (n=[redacted])**	**SMD**	**Dapagliflozin (n=[redacted])**	**Empagliflozin (n=[redacted])**	**SMD**
Age, years, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BMI, kg/m^2						
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Categorical						
<25	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥30	[redacted]	[redacted]		[redacted]	[redacted]	
25.0-29.9	[redacted]	[redacted]		[redacted]	[redacted]	
Missing	[redacted]	[redacted]		[redacted]	[redacted]	
Baseline eGFR, mL/min/1.73m^2 [a]						
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Categorical						
60-89 (G2), n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
45-59 (G3a), n (%)	[redacted]	[redacted]		[redacted]	[redacted]	
30-44 (G3b), n (%)	[redacted]	[redacted]		[redacted]	[redacted]	
15-29 (G4), n (%)	[redacted]	[redacted]		[redacted]	[redacted]	
Baseline uACR, mg/g[a]						
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Categorical						
0-29, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
30-199, n (%)	[redacted]	[redacted]		[redacted]	[redacted]	
≥200, n (%)	[redacted]	[redacted]		[redacted]	[redacted]	
ln_uacr, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Female, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age, n (%)						
<40	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
40-49	[redacted]	[redacted]		[redacted]	[redacted]	
50-59	[redacted]	[redacted]		[redacted]	[redacted]	
60-69	[redacted]	[redacted]		[redacted]	[redacted]	
70-79	[redacted]	[redacted]		[redacted]	[redacted]	
≥80	[redacted]	[redacted]		[redacted]	[redacted]	
Race, n (%)						
Asian	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Black	[redacted]	[redacted]		[redacted]	[redacted]	
Unknown/Other	[redacted]	[redacted]		[redacted]	[redacted]	
White	[redacted]	[redacted]		[redacted]	[redacted]	
Medicare, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cause of CKD, n (%)						
Diabetic kidney disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypertensive disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Glomerular disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Renal tubolo-interstitial disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other/unknown	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Comorbidities						
Angina	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Atrial fibrillation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bradycardia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Heart failure	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Myocardial infarction	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stroke	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other cardiovascular disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hyperkalaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
T2D	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Medications, n (%)						
RASi	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ARNI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Beta-blocker	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Calcium channel blocker	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Diuretics	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Antithrombotic agent	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Statins	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anti-hyperkaliaemic treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anti-diabetic treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[a] Patients in the 'complete case' had an eGFR and uACR measurement within 122 days prior to or at the index date.

Abbreviations: ARNI: angiotensin receptor/neprilysin inhibitor; BMI: body mass index; CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; RASi: renin-angiotensin system inhibitor; SD: standard deviation; SMD: standardised mean difference; T2D: type 2 diabetes; uACR: urinary albumin-creatinine ratio.

Table 49: Baseline characteristics – without T2D, Medicare plus commercial, 'pooled period'

	Before weighting			After weighting		
Characteristic	**Dapagliflozin (n=[redacted])**	**Empagliflozin (n=[redacted])**	**SMD**	**Dapagliflozin (n=[redacted])**	**Empagliflozin (n=[redacted])**	**SMD**
Age, years, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BMI, kg/m^2						
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Categorical						
<25	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥30	[redacted]	[redacted]		[redacted]	[redacted]	
25.0-29.9	[redacted]	[redacted]		[redacted]	[redacted]	
Missing	[redacted]	[redacted]		[redacted]	[redacted]	
Baseline eGFR, mL/min/1.73m^2 [a]						
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Categorical						
60-89 (G2), n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
45-59 (G3a), n (%)	[redacted]	[redacted]		[redacted]	[redacted]	
30-44 (G3b), n (%)	[redacted]	[redacted]		[redacted]	[redacted]	
15-29 (G4), n (%)	[redacted]	[redacted]		[redacted]	[redacted]	
Baseline uACR, mg/g[a]						
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Categorical						
0-29, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
30-199, n (%)	[redacted]	[redacted]		[redacted]	[redacted]	
≥200, n (%)	[redacted]	[redacted]		[redacted]	[redacted]	
ln_uacr, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Female, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age, n (%)						
<40	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

40-49	[redacted]	[redacted]		[redacted]	[redacted]	
50-59	[redacted]	[redacted]		[redacted]	[redacted]	
60-69	[redacted]	[redacted]		[redacted]	[redacted]	
70-79	[redacted]	[redacted]		[redacted]	[redacted]	
≥80	[redacted]	[redacted]		[redacted]	[redacted]	
Race, n (%)						
Asian	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Black	[redacted]	[redacted]		[redacted]	[redacted]	
Unknown/Other	[redacted]	[redacted]		[redacted]	[redacted]	
White	[redacted]	[redacted]		[redacted]	[redacted]	
Medicare, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cause of CKD, n (%)						
Diabetic kidney disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypertensive disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Glomerular disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Renal tubolo-interstitial disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other/unknown	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Comorbidities						
Angina	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Atrial fibrillation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bradycardia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Heart failure	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Myocardial infarction	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stroke	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other cardiovascular disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hyperkalaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

T2D	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Medications, n (%)						
RASi	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ARNI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Beta-blocker	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Calcium channel blocker	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Diuretics	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Antithrombotic agent	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Statins	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anti-hyperkaliaemic treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anti-diabetic treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[a] Patients in the 'complete case' had an eGFR and uACR measurement within 122 days prior to or at the index date.
Abbreviations: ARNI: angiotensin receptor/neprilysin inhibitor; BMI: body mass index; CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; RASi: renin-angiotensin system inhibitor; SD: standard deviation; SMD: standardised mean difference; T2D: type 2 diabetes; uACR: urinary albumin-creatinine ratio.

Table 50: Baseline characteristics – without T2D, Medicare plus missing uACR, 'main period'

	Before weighting			After weighting		
Characteristic	**Dapagliflozin (n=[redacted])**	**Empagliflozin (n=[redacted])**	**SMD**	**Dapagliflozin (n=[redacted])**	**Empagliflozin (n=[redacted])**	**SMD**
Age, years, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BMI, kg/m^2						
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Categorical						
<25	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥30	[redacted]	[redacted]		[redacted]	[redacted]	
25.0-29.9	[redacted]	[redacted]		[redacted]	[redacted]	
Missing	[redacted]	[redacted]		[redacted]	[redacted]	
Baseline eGFR, mL/min/1.73m^2 [a]						

Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Categorical						
60-89 (G2), n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
45-59 (G3a), n (%)	[redacted]	[redacted]		[redacted]	[redacted]	
30-44 (G3b), n (%)	[redacted]	[redacted]		[redacted]	[redacted]	
15-29 (G4), n (%)	[redacted]	[redacted]		[redacted]	[redacted]	
Baseline uACR, mg/g[a]						
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Categorical						
0-29, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
30-199, n (%)	[redacted]	[redacted]		[redacted]	[redacted]	
≥200, n (%)	[redacted]	[redacted]		[redacted]	[redacted]	
ln_uacr, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Female, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age, n (%)						
<40	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
40-49	[redacted]	[redacted]		[redacted]	[redacted]	
50-59	[redacted]	[redacted]		[redacted]	[redacted]	
60-69	[redacted]	[redacted]		[redacted]	[redacted]	
70-79	[redacted]	[redacted]		[redacted]	[redacted]	
≥80	[redacted]	[redacted]		[redacted]	[redacted]	
Race, n (%)						
Asian	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Black	[redacted]	[redacted]		[redacted]	[redacted]	
Unknown/Other	[redacted]	[redacted]		[redacted]	[redacted]	
White	[redacted]	[redacted]		[redacted]	[redacted]	
Medicare, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cause of CKD, n (%)						
Diabetic kidney disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Hypertensive disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Glomerular disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Renal tubolo-interstitial disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other/unknown	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Comorbidities						
Angina	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Atrial fibrillation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bradycardia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Heart failure	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Myocardial infarction	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stroke	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other cardiovascular disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hyperkalaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
T2D	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Medications, n (%)						
RASi	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ARNI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Beta-blocker	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Calcium channel blocker	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Diuretics	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Antithrombotic agent	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Statins	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anti-hyperkaliaemic treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anti-diabetic treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[a] Patients in the 'complete case' had an eGFR and uACR measurement within 122 days prior to or at the index date.

Abbreviations: ARNI: angiotensin receptor/neprilysin inhibitor; BMI: body mass index; CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; RASi: renin-angiotensin system inhibitor; SD: standard deviation; SMD: standardised mean difference; T2D: type 2 diabetes; uACR: urinary albumin-creatinine ratio.

Table 51: Baseline characteristics – without T2D, Medicare plus missing uACR, 'pooled period'

	Before weighting			After weighting		
Characteristic	**Dapagliflozin (n=[redacted])**	**Empagliflozin (n=[redacted])**	**SMD**	**Dapagliflozin (n=[redacted])**	**Empagliflozin (n=[redacted])**	**SMD**
Age, years, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BMI, kg/m^2						
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Categorical						
<25	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥30	[redacted]	[redacted]		[redacted]	[redacted]	
25.0-29.9	[redacted]	[redacted]		[redacted]	[redacted]	
Missing	[redacted]	[redacted]		[redacted]	[redacted]	
Baseline eGFR, mL/min/1.73m^2 [a]						
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Categorical						
60-89 (G2), n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
45-59 (G3a), n (%)	[redacted]	[redacted]		[redacted]	[redacted]	
30-44 (G3b), n (%)	[redacted]	[redacted]		[redacted]	[redacted]	
15-29 (G4), n (%)	[redacted]	[redacted]		[redacted]	[redacted]	
Baseline uACR, mg/g[a]						
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Categorical						
0-29, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
30-199, n (%)	[redacted]	[redacted]		[redacted]	[redacted]	
≥200, n (%)	[redacted]	[redacted]		[redacted]	[redacted]	
ln_uacr, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Female, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Age, n (%)						
<40	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
40-49	[redacted]	[redacted]		[redacted]	[redacted]	
50-59	[redacted]	[redacted]		[redacted]	[redacted]	
60-69	[redacted]	[redacted]		[redacted]	[redacted]	
70-79	[redacted]	[redacted]		[redacted]	[redacted]	
≥80	[redacted]	[redacted]		[redacted]	[redacted]	
Race, n (%)						
Asian	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Black	[redacted]	[redacted]		[redacted]	[redacted]	
Unknown/Other	[redacted]	[redacted]		[redacted]	[redacted]	
White	[redacted]	[redacted]		[redacted]	[redacted]	
Medicare, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cause of CKD, n (%)						
Diabetic kidney disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypertensive disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Glomerular disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Renal tubolo-interstitial disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other/unknown	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Comorbidities						
Angina	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Atrial fibrillation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bradycardia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Heart failure	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Myocardial infarction	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stroke	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other cardiovascular disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Anaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hyperkalaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
T2D	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Medications, n (%)						
RASi	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ARNI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Beta-blocker	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Calcium channel blocker	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Diuretics	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Antithrombotic agent	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Statins	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anti-hyperkaliaemic treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anti-diabetic treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[a] Patients in the 'complete case' had an eGFR and uACR measurement within 122 days prior to or at the index date.
Abbreviations: ARNI: angiotensin receptor/neprilysin inhibitor; BMI: body mass index; CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; RASi: renin-angiotensin system inhibitor; SD: standard deviation; SMD: standardised mean difference; T2D: type 2 diabetes; uACR: urinary albumin-creatinine ratio.

C.4 Low uACR (<200 mg/g)

Table 52: Baseline characteristics – low uACR (<200 mg/g), Medicare plus commercial, 'main period'

	Before weighting			After weighting		
Characteristic	**Dapagliflozin (n=[redacted])**	**Empagliflozin (n=[redacted])**	**SMD**	**Dapagliflozin (n=[redacted])**	**Empagliflozin (n=[redacted])**	**SMD**
Age, years, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BMI, kg/m²						
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Categorical						
<25	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥30	[redacted]	[redacted]		[redacted]	[redacted]	

25.0-29.9	[redacted]	[redacted]		[redacted]	[redacted]	
Missing	[redacted]	[redacted]		[redacted]	[redacted]	
Baseline eGFR, mL/min/1.73m^2 [a]						
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Categorical[b]						
15-29 (G4), n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline uACR, mg/g[a]						
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Categorical[b]						
30-199, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ln_uacr, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Female, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age, n (%)						
40-49	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
50-59	[redacted]	[redacted]		[redacted]	[redacted]	
60-69	[redacted]	[redacted]		[redacted]	[redacted]	
70-79	[redacted]	[redacted]		[redacted]	[redacted]	
≥80	[redacted]	[redacted]		[redacted]	[redacted]	
Race, n (%)						
Asian	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Black	[redacted]	[redacted]		[redacted]	[redacted]	
Unknown/Other	[redacted]	[redacted]		[redacted]	[redacted]	
White	[redacted]	[redacted]		[redacted]	[redacted]	
Medicare, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cause of CKD, n (%)						
Diabetic kidney disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypertensive disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Glomerular disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Renal tubolo-interstitial disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Other/unknown	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Comorbidities						
Angina	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Atrial fibrillation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bradycardia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Heart failure	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Myocardial infarction	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stroke	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other cardiovascular disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hyperkalaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
T2D	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Medications, n (%)						
RASi	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ARNI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Beta-blocker	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Calcium channel blocker	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Diuretics	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Antithrombotic agent	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Statins	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anti-hyperkaliaemic treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anti-diabetic treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[a] Patients in the 'complete case' had an eGFR and uACR measurement within 122 days prior to or at the index date. [b] Reported as binary categories. All remaining patients were in the 30-45 mL/min/1.73 m^2 eGFR category or the 0-29 mg/g uACR category.

Abbreviations: ARNI: angiotensin receptor/neprilysin inhibitor; BMI: body mass index; CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; RASi: renin-angiotensin system inhibitor; SD: standard deviation; SMD: standardised mean difference; T2D: type 2 diabetes; uACR: urinary albumin-creatinine ratio.

Table 53: Baseline characteristics – low uACR (<200 mg/g), Medicare plus commercial, 'pooled period'

	Before weighting			After weighting		
Characteristic	**Dapagliflozin (n=[redacted])**	**Empagliflozin (n=[redacted])**	**SMD**	**Dapagliflozin (n=[redacted])**	**Empagliflozin (n=[redacted])**	**SMD**
Age, years, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BMI, kg/m^2						
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Categorical						
<25	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥30	[redacted]	[redacted]		[redacted]	[redacted]	
25.0-29.9	[redacted]	[redacted]		[redacted]	[redacted]	
Missing	[redacted]	[redacted]		[redacted]	[redacted]	
Baseline eGFR, mL/min/1.73m^2 [a]						
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Categorical[b]						
15-29 (G4), n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline uACR, mg/g[a]						
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Categorical[b]						
30-199, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ln_uacr, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Female, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age, n (%)						
<40	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
40-49	[redacted]	[redacted]		[redacted]	[redacted]	
50-59	[redacted]	[redacted]		[redacted]	[redacted]	
60-69	[redacted]	[redacted]		[redacted]	[redacted]	
70-79	[redacted]	[redacted]		[redacted]	[redacted]	
≥80	[redacted]	[redacted]		[redacted]	[redacted]	

Race, n (%)						
Asian	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Black	[redacted]	[redacted]		[redacted]	[redacted]	
Unknown/Other	[redacted]	[redacted]		[redacted]	[redacted]	
White	[redacted]	[redacted]		[redacted]	[redacted]	
Medicare, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cause of CKD, n (%)						
Diabetic kidney disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypertensive disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Glomerular disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Renal tubolo-interstitial disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other/unknown	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Comorbidities						
Angina	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Atrial fibrillation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bradycardia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Heart failure	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Myocardial infarction	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stroke	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other cardiovascular disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hyperkalaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
T2D	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Medications, n (%)						
RASi	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ARNI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Beta-blocker	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Calcium channel blocker	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Diuretics	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Antithrombotic agent	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Statins	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anti-hyperkaliaemic treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anti-diabetic treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[a] Patients in the 'complete case' had an eGFR and uACR measurement within 122 days prior to or at the index date. [b] Reported as binary categories. All remaining patients were in the 30-45 mL/min/1.73 m^2 eGFR category or the 0-29 mg/g uACR category.
Abbreviations: ARNI: angiotensin receptor/neprilysin inhibitor; BMI: body mass index; CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; RASi: renin-angiotensin system inhibitor; SD: standard deviation; SMD: standardised mean difference; T2D: type 2 diabetes; uACR: urinary albumin-creatinine ratio.

C.5 High uACR (≥200 mg/g)

Table 54: Baseline characteristics – high uACR (≥200 mg/g), Medicare plus commercial, 'main period'

	Before weighting			After weighting		
Characteristic	**Dapagliflozin (n=[redacted])**	**Empagliflozin (n=[redacted])**	**SMD**	**Dapagliflozin (n=[redacted])**	**Empagliflozin (n=[redacted])**	**SMD**
Age, years, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BMI, kg/m^2						
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Categorical						
<25	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥30	[redacted]	[redacted]		[redacted]	[redacted]	
25.0-29.9	[redacted]	[redacted]		[redacted]	[redacted]	
Missing	[redacted]	[redacted]		[redacted]	[redacted]	
Baseline eGFR, mL/min/1.73m^2 [a]						
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Categorical						
60-89 (G2), n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

45-59 (G3a), n (%)	[redacted]	[redacted]		[redacted]	[redacted]	
30-44 (G3b), n (%)	[redacted]	[redacted]		[redacted]	[redacted]	
15-29 (G4), n (%)	[redacted]	[redacted]		[redacted]	[redacted]	
Baseline uACR, mg/g[a]						
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Categorical						
≥200, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ln_uacr, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Female, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age, n (%)						
<40	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
40-49	[redacted]	[redacted]		[redacted]	[redacted]	
50-59	[redacted]	[redacted]		[redacted]	[redacted]	
60-69	[redacted]	[redacted]		[redacted]	[redacted]	
70-79	[redacted]	[redacted]		[redacted]	[redacted]	
≥80	[redacted]	[redacted]		[redacted]	[redacted]	
Race, n (%)						
Asian	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Black	[redacted]	[redacted]		[redacted]	[redacted]	
Unknown/Other	[redacted]	[redacted]		[redacted]	[redacted]	
White	[redacted]	[redacted]		[redacted]	[redacted]	
Medicare, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cause of CKD, n (%)						
Diabetic kidney disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypertensive disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Glomerular disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Renal tubolo-interstitial disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other/unknown	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Comorbidities						

Angina	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Atrial fibrillation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bradycardia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Heart failure	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Myocardial infarction	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stroke	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other cardiovascular disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hyperkalaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
T2D	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Medications, n (%)						
RASi	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ARNI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Beta-blocker	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Calcium channel blocker	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Diuretics	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Antithrombotic agent	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Statins	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anti-hyperkaliaemic treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anti-diabetic treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[a] Patients in the 'complete case' had an eGFR and uACR measurement within 122 days prior to or at the index date.
Abbreviations: ARNI: angiotensin receptor/neprilysin inhibitor; BMI: body mass index; CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; RASi: renin-angiotensin system inhibitor; SD: standard deviation; SMD: standardised mean difference; T2D: type 2 diabetes; uACR: urinary albumin-creatinine ratio.

Table 55: Baseline characteristics – high uACR (≥200 mg/g), Medicare plus commercial, 'pooled period'

	Before weighting	After weighting

Characteristic	Dapagliflozin (n=[redacted])	Empagliflozin (n=[redacted])	SMD	Dapagliflozin (n=[redacted])	Empagliflozin (n=[redacted])	SMD
Age, years, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BMI, kg/m^2						
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Categorical						
<25	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥30	[redacted]	[redacted]		[redacted]	[redacted]	
25.0-29.9	[redacted]	[redacted]		[redacted]	[redacted]	
Missing	[redacted]	[redacted]		[redacted]	[redacted]	
Baseline eGFR, mL/min/1.73m^2 [a]						
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Categorical						
60-89 (G2), n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
45-59 (G3a), n (%)	[redacted]	[redacted]		[redacted]	[redacted]	
30-44 (G3b), n (%)	[redacted]	[redacted]		[redacted]	[redacted]	
15-29 (G4), n (%)	[redacted]	[redacted]		[redacted]	[redacted]	
Baseline uACR, mg/g[a]						
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Categorical						
≥200, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ln_uacr, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Female, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age, n (%)						
<40	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
40-49	[redacted]	[redacted]		[redacted]	[redacted]	
50-59	[redacted]	[redacted]		[redacted]	[redacted]	
60-69	[redacted]	[redacted]		[redacted]	[redacted]	
70-79	[redacted]	[redacted]		[redacted]	[redacted]	

≥80	[redacted]	[redacted]		[redacted]	[redacted]	
Race, n (%)						
Asian	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Black	[redacted]	[redacted]		[redacted]	[redacted]	
Unknown/Other	[redacted]	[redacted]		[redacted]	[redacted]	
White	[redacted]	[redacted]		[redacted]	[redacted]	
Medicare, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cause of CKD, n (%)						
Diabetic kidney disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypertensive disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Glomerular disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Renal tubolo-interstitial disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other/unknown	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Comorbidities						
Angina	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Atrial fibrillation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bradycardia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Heart failure	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Myocardial infarction	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stroke	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other cardiovascular disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hyperkalaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
T2D	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Medications, n (%)						
RASi	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ARNI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Beta-blocker	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Calcium channel blocker	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Diuretics	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Antithrombotic agent	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Statins	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anti-hyperkaliaemic treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anti-diabetic treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[a] Patients in the 'complete case' had an eGFR and uACR measurement within 122 days prior to or at the index date.
Abbreviations: ARNI: angiotensin receptor/neprilysin inhibitor; BMI: body mass index; CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; RASi: renin-angiotensin system inhibitor; SD: standard deviation; SMD: standardised mean difference; T2D: type 2 diabetes; uACR: urinary albumin-creatinine ratio.

C.6 With T2D and low uACR (<200 mg/g)

Table 56: Baseline characteristics – with T2D and low uACR (<200 mg/g), Medicare plus commercial, 'main period'

	Before weighting			After weighting		
Characteristic	**Dapagliflozin (n=[redacted])**	**Empagliflozin (n=[redacted])**	**SMD**	**Dapagliflozin (n=[redacted])**	**Empagliflozin (n=[redacted])**	**SMD**
Age, years, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BMI, kg/m^2						
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Categorical						
<25	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥30	[redacted]	[redacted]		[redacted]	[redacted]	
25.0-29.9	[redacted]	[redacted]		[redacted]	[redacted]	
Missing	[redacted]	[redacted]		[redacted]	[redacted]	
Baseline eGFR, mL/min/1.73m^2 [a]						
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Categorical[b]						
15-29 (G4), n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Baseline uACR, mg/g[a]						
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Categorical[b]						
30-199, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ln_uacr, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Female, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age, n (%)						
40-49	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
50-59	[redacted]	[redacted]		[redacted]	[redacted]	
60-69	[redacted]	[redacted]		[redacted]	[redacted]	
70-79	[redacted]	[redacted]		[redacted]	[redacted]	
≥80	[redacted]	[redacted]		[redacted]	[redacted]	
Race, n (%)						
Asian	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Black	[redacted]	[redacted]		[redacted]	[redacted]	
Unknown/Other	[redacted]	[redacted]		[redacted]	[redacted]	
White	[redacted]	[redacted]		[redacted]	[redacted]	
Medicare, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cause of CKD, n (%)						
Diabetic kidney disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypertensive disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Glomerular disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Renal tubolo-interstitial disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other/unknown	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Comorbidities						
Angina	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Atrial fibrillation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bradycardia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Heart failure	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Hypertension	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Myocardial infarction	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stroke	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other cardiovascular disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hyperkalaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
T2D	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Medications, n (%)						
RASi	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ARNI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Beta-blocker	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Calcium channel blocker	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Diuretics	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Antithrombotic agent	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Statins	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anti-hyperkaliaemic treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anti-diabetic treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[a] Patients in the 'complete case' had an eGFR and uACR measurement within 122 days prior to or at the index date. [b] Reported as binary categories. All remaining patients were in the 30-45 mL/min/1.73 m^2 eGFR category or the 0-29 mg/g uACR category.
Abbreviations: ARNI: angiotensin receptor/neprilysin inhibitor; BMI: body mass index; CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; RASi: renin-angiotensin system inhibitor; SD: standard deviation; SMD: standardised mean difference; T2D: type 2 diabetes; uACR: urinary albumin-creatinine ratio.

Table 57: Baseline characteristics – with T2D and low uACR (<200 mg/g), Medicare plus commercial, 'pooled period'

	Before weighting			After weighting		
Characteristic	**Dapagliflozin (n=[redacted])**	**Empagliflozin (n=[redacted])**	**SMD**	**Dapagliflozin (n=[redacted])**	**Empagliflozin (n=[redacted])**	**SMD**
Age, years, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BMI, kg/m^2						

Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Categorical						
<25	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥30	[redacted]	[redacted]		[redacted]	[redacted]	
25.0-29.9	[redacted]	[redacted]		[redacted]	[redacted]	
Missing	[redacted]	[redacted]		[redacted]	[redacted]	
Baseline eGFR, mL/min/1.73m^2 [a]						
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Categorical[b]						
15-29 (G4), n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline uACR, mg/g[a]						
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Categorical[b]						
30-199, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ln_uacr, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Female, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age, n (%)						
40-49	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
50-59	[redacted]	[redacted]		[redacted]	[redacted]	
60-69	[redacted]	[redacted]		[redacted]	[redacted]	
70-79	[redacted]	[redacted]		[redacted]	[redacted]	
≥80	[redacted]	[redacted]		[redacted]	[redacted]	
Race, n (%)						
Asian	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Black	[redacted]	[redacted]		[redacted]	[redacted]	
Unknown/Other	[redacted]	[redacted]		[redacted]	[redacted]	
White	[redacted]	[redacted]		[redacted]	[redacted]	
Medicare, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cause of CKD, n (%)						

Diabetic kidney disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypertensive disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Glomerular disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Renal tubolo-interstitial disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other/unknown	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Comorbidities						
Angina	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Atrial fibrillation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bradycardia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Heart failure	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Myocardial infarction	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stroke	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other cardiovascular disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hyperkalaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
T2D	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Medications, n (%)						
RASi	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ARNI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Beta-blocker	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Calcium channel blocker	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Diuretics	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Antithrombotic agent	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Statins	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anti-hyperkaliaemic treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Anti-diabetic treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[a] Patients in the 'complete case' had an eGFR and uACR measurement within 122 days prior to or at the index date. [b] Reported as binary categories. All remaining patients were in the 30-45 mL/min/1.73 m^2 eGFR category or the 0-29 mg/g uACR category.
Abbreviations: ARNI: angiotensin receptor/neprilysin inhibitor; BMI: body mass index; CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; RASi: renin-angiotensin system inhibitor; SD: standard deviation; SMD: standardised mean difference; T2D: type 2 diabetes; uACR: urinary albumin-creatinine ratio.

C.7 With T2D and high uACR (≥200 mg/g)

Table 58: Baseline characteristics – with T2D and high uACR (≥200 mg/g), Medicare plus commercial, 'main period'

	Before weighting			After weighting		
Characteristic	**Dapagliflozin (n=[redacted])**	**Empagliflozin (n=[redacted])**	**SMD**	**Dapagliflozin (n=[redacted])**	**Empagliflozin (n=[redacted])**	**SMD**
Age, years, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BMI, kg/m²						
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Categorical						
<25	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥30	[redacted]	[redacted]		[redacted]	[redacted]	
25.0-29.9	[redacted]	[redacted]		[redacted]	[redacted]	
Missing	[redacted]	[redacted]		[redacted]	[redacted]	
Baseline eGFR, mL/min/1.73m² [a]						
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Categorical						
60-89 (G2), n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
45-59 (G3a), n (%)	[redacted]	[redacted]		[redacted]	[redacted]	
30-44 (G3b), n (%)	[redacted]	[redacted]		[redacted]	[redacted]	
15-29 (G4), n (%)	[redacted]	[redacted]		[redacted]	[redacted]	
Baseline uACR, mg/g[a]						
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Categorical						
≥200, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ln_uacr, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Female, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age, n (%)						
<40	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
40-49	[redacted]	[redacted]		[redacted]	[redacted]	
50-59	[redacted]	[redacted]		[redacted]	[redacted]	
60-69	[redacted]	[redacted]		[redacted]	[redacted]	
70-79	[redacted]	[redacted]		[redacted]	[redacted]	
≥80	[redacted]	[redacted]		[redacted]	[redacted]	
Race, n (%)						
Asian	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Black	[redacted]	[redacted]		[redacted]	[redacted]	
Unknown/Other	[redacted]	[redacted]		[redacted]	[redacted]	
White	[redacted]	[redacted]		[redacted]	[redacted]	
Medicare, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cause of CKD, n (%)						
Diabetic kidney disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypertensive disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Glomerular disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Renal tubolo-interstitial disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other/unknown	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Comorbidities						
Angina	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Atrial fibrillation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bradycardia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Heart failure	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Myocardial infarction	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stroke	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Other cardiovascular disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hyperkalaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
T2D	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Medications, n (%)						
RASi	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ARNI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Beta-blocker	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Calcium channel blocker	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Diuretics	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Antithrombotic agent	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Statins	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anti-hyperkaliaemic treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anti-diabetic treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[a] Patients in the 'complete case' had an eGFR and uACR measurement within 122 days prior to or at the index date.
Abbreviations: ARNI: angiotensin receptor/neprilysin inhibitor; BMI: body mass index; CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; RASi: renin-angiotensin system inhibitor; SD: standard deviation; SMD: standardised mean difference; T2D: type 2 diabetes; uACR: urinary albumin-creatinine ratio.

Table 59: Baseline characteristics – with T2D and high uACR (≥200 mg/g), Medicare plus commercial, 'pooled period'

	Before weighting			After weighting		
Characteristic	**Dapagliflozin (n=[redacted])**	**Empagliflozin (n=[redacted])**	**SMD**	**Dapagliflozin (n=[redacted])**	**Empagliflozin (n=[redacted])**	**SMD**
Age, years, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BMI, kg/m^2						
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Categorical						
<25	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥30	[redacted]	[redacted]		[redacted]	[redacted]	

25.0-29.9	[redacted]	[redacted]		[redacted]	[redacted]	
Missing	[redacted]	[redacted]		[redacted]	[redacted]	
Baseline eGFR, mL/min/1.73m^2 [a]						
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Categorical						
60-89 (G2), n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
45-59 (G3a), n (%)	[redacted]	[redacted]		[redacted]	[redacted]	
30-44 (G3b), n (%)	[redacted]	[redacted]		[redacted]	[redacted]	
15-29 (G4), n (%)	[redacted]	[redacted]		[redacted]	[redacted]	
Baseline uACR, mg/g[a]						
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Categorical						
≥200, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ln_uacr, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Female, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age, n (%)						
<40	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
40-49	[redacted]	[redacted]		[redacted]	[redacted]	
50-59	[redacted]	[redacted]		[redacted]	[redacted]	
60-69	[redacted]	[redacted]		[redacted]	[redacted]	
70-79	[redacted]	[redacted]		[redacted]	[redacted]	
≥80	[redacted]	[redacted]		[redacted]	[redacted]	
Race, n (%)						
Asian	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Black	[redacted]	[redacted]		[redacted]	[redacted]	
Unknown/Other	[redacted]	[redacted]		[redacted]	[redacted]	
White	[redacted]	[redacted]		[redacted]	[redacted]	
Medicare, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cause of CKD, n (%)						

Diabetic kidney disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypertensive disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Glomerular disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Renal tubolo-interstitial disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other/unknown	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Comorbidities						
Angina	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Atrial fibrillation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bradycardia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Heart failure	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Myocardial infarction	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stroke	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other cardiovascular disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hyperkalaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
T2D	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Medications, n (%)						
RASi	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ARNI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Beta-blocker	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Calcium channel blocker	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Diuretics	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Antithrombotic agent	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Statins	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anti-hyperkaliaemic treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Anti-diabetic treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[a] Patients in the 'complete case' had an eGFR and uACR measurement within 122 days prior to or at the index date.
Abbreviations: ARNI: angiotensin receptor/neprilysin inhibitor; BMI: body mass index; CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; RASi: renin-angiotensin system inhibitor; SD: standard deviation; SMD: standardised mean difference; T2D: type 2 diabetes; uACR: urinary albumin-creatinine ratio.

C.8 Without T2D and low uACR (<200 mg/g)

Table 60: Baseline characteristics – without T2D and low uACR (<200 mg/g), Medicare plus commercial, 'main period'

	Before weighting			After weighting		
Characteristic	**Dapagliflozin (n=[redacted])**	**Empagliflozin (n=[redacted])**	**SMD**	**Dapagliflozin (n=[redacted])**	**Empagliflozin (n=[redacted])**	**SMD**
Age, years, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BMI, kg/m^2						
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Categorical						
<25	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥30	[redacted]	[redacted]		[redacted]	[redacted]	
25.0-29.9	[redacted]	[redacted]		[redacted]	[redacted]	
Missing	[redacted]	[redacted]		[redacted]	[redacted]	
Baseline eGFR, mL/min/1.73m^2 [a]						
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Categorical[b]						
15-29 (G4), n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline uACR, mg/g[a]						
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Categorical[b]						
30-199, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ln_uacr, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Female, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age, n (%)						

40-49	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
50-59	[redacted]	[redacted]		[redacted]	[redacted]	
60-69	[redacted]	[redacted]		[redacted]	[redacted]	
70-79	[redacted]	[redacted]		[redacted]	[redacted]	
≥80	[redacted]	[redacted]		[redacted]	[redacted]	
Race, n (%)						
Asian	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Black	[redacted]	[redacted]		[redacted]	[redacted]	
Unknown/Other	[redacted]	[redacted]		[redacted]	[redacted]	
White	[redacted]	[redacted]		[redacted]	[redacted]	
Medicare, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cause of CKD, n (%)						
Diabetic kidney disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypertensive disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Glomerular disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Renal tubolo-interstitial disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other/unknown	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Comorbidities						
Angina	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Atrial fibrillation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bradycardia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Heart failure	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Myocardial infarction	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stroke	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other cardiovascular disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hyperkalaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

T2D	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Medications, n (%)						
RASi	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ARNI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Beta-blocker	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Calcium channel blocker	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Diuretics	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Antithrombotic agent	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Statins	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anti-hyperkaliaemic treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anti-diabetic treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[a] Patients in the 'complete case' had an eGFR and uACR measurement within 122 days prior to or at the index date. [b] Reported as binary categories. All remaining patients were in the 30-45 mL/min/1.73 m^2 eGFR category or the 0-29 mg/g uACR category.
Abbreviations: ARNI: angiotensin receptor/neprilysin inhibitor; BMI: body mass index; CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; RASi: renin-angiotensin system inhibitor; SD: standard deviation; SMD: standardised mean difference; T2D: type 2 diabetes; uACR: urinary albumin-creatinine ratio.

Table 61: Baseline characteristics – without T2D and low uACR (<200 mg/g), Medicare plus commercial, 'pooled period'

	Before weighting			After weighting		
Characteristic	**Dapagliflozin (n=[redacted])**	**Empagliflozin (n=[redacted])**	**SMD**	**Dapagliflozin (n=[redacted])**	**Empagliflozin (n=[redacted])**	**SMD**
Age, years, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BMI, kg/m^2						
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Categorical						
<25	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥30	[redacted]	[redacted]		[redacted]	[redacted]	
25.0-29.9	[redacted]	[redacted]		[redacted]	[redacted]	
Missing	[redacted]	[redacted]		[redacted]	[redacted]	
Baseline eGFR, mL/min/1.73m^2 [a]						

Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Categorical[b]						
15-29 (G4), n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline uACR, mg/g[a]						
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Categorical[b]						
30-199, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ln_uacr, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Female, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age, n (%)						
<40	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
40-49	[redacted]	[redacted]		[redacted]	[redacted]	
50-59	[redacted]	[redacted]		[redacted]	[redacted]	
60-69	[redacted]	[redacted]		[redacted]	[redacted]	
70-79	[redacted]	[redacted]		[redacted]	[redacted]	
≥80	[redacted]	[redacted]		[redacted]	[redacted]	
Race, n (%)						
Asian	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Black	[redacted]	[redacted]		[redacted]	[redacted]	
Unknown/Other	[redacted]	[redacted]		[redacted]	[redacted]	
White	[redacted]	[redacted]		[redacted]	[redacted]	
Medicare, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cause of CKD, n (%)						
Diabetic kidney disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypertensive disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Glomerular disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Renal tubolo-interstitial disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other/unknown	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Comorbidities						

Angina	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Atrial fibrillation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bradycardia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Heart failure	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Myocardial infarction	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stroke	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other cardiovascular disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hyperkalaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
T2D	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Medications, n (%)						
RASi	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ARNI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Beta-blocker	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Calcium channel blocker	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Diuretics	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Antithrombotic agent	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Statins	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anti-hyperkaliaemic treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anti-diabetic treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[a] Patients in the 'complete case' had an eGFR and uACR measurement within 122 days prior to or at the index date. [b] Reported as binary categories. All remaining patients were in the 30-45 mL/min/1.73 m^2 eGFR category or the 0-29 mg/g uACR category.
Abbreviations: ARNI: angiotensin receptor/neprilysin inhibitor; BMI: body mass index; CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; RASi: renin-angiotensin system inhibitor; SD: standard deviation; SMD: standardised mean difference; T2D: type 2 diabetes; uACR: urinary albumin-creatinine ratio.

C.9 Without T2D and high uACR (≥200 mg/g)

Table 62: Baseline characteristics – without T2D and high uACR (≥200 mg/g), Medicare plus commercial, 'main period'

	Before weighting			After weighting		
Characteristic	**Dapagliflozin (n=[redacted])**	**Empagliflozin (n=[redacted])**	**SMD**	**Dapagliflozin (n=[redacted])**	**Empagliflozin (n=[redacted])**	**SMD**
Age, years, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BMI, kg/m^2						
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Categorical						
<25	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥30	[redacted]	[redacted]		[redacted]	[redacted]	
25.0-29.9	[redacted]	[redacted]		[redacted]	[redacted]	
Missing	[redacted]	[redacted]		[redacted]	[redacted]	
Baseline eGFR, mL/min/1.73m^2 [a]						
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Categorical						
60-89 (G2), n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
45-59 (G3a), n (%)	[redacted]	[redacted]		[redacted]	[redacted]	
30-44 (G3b), n (%)	[redacted]	[redacted]		[redacted]	[redacted]	
15-29 (G4), n (%)	[redacted]	[redacted]		[redacted]	[redacted]	
Baseline uACR, mg/g[a]						
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Categorical						
≥200, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ln_uacr, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Female, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age, n (%)						
<40	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
40-49	[redacted]	[redacted]		[redacted]	[redacted]	

50-59	[redacted]	[redacted]		[redacted]	[redacted]	
60-69	[redacted]	[redacted]		[redacted]	[redacted]	
70-79	[redacted]	[redacted]		[redacted]	[redacted]	
≥80	[redacted]	[redacted]		[redacted]	[redacted]	
Race, n (%)						
Asian	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Black	[redacted]	[redacted]		[redacted]	[redacted]	
Unknown/Other	[redacted]	[redacted]		[redacted]	[redacted]	
White	[redacted]	[redacted]		[redacted]	[redacted]	
Medicare, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cause of CKD, n (%)						
Diabetic kidney disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypertensive disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Glomerular disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Renal tubolo-interstitial disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other/unknown	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Comorbidities						
Angina	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Atrial fibrillation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bradycardia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Heart failure	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Myocardial infarction	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stroke	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other cardiovascular disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hyperkalaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
T2D	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Medications, n (%)						
RASi	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ARNI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Beta-blocker	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Calcium channel blocker	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Diuretics	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Antithrombotic agent	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Statins	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anti-hyperkaliaemic treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anti-diabetic treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[a] Patients in the 'complete case' had an eGFR and uACR measurement within 122 days prior to or at the index date.
Abbreviations: ARNI: angiotensin receptor/neprilysin inhibitor; BMI: body mass index; CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; RASi: renin-angiotensin system inhibitor; SD: standard deviation; SMD: standardised mean difference; T2D: type 2 diabetes; uACR: urinary albumin-creatinine ratio.

Table 63: Baseline characteristics – without T2D and high uACR (≥200 mg/g), Medicare plus commercial, 'pooled period'

	Before weighting			After weighting		
Characteristic	Dapagliflozin (n=[redacted])	Empagliflozin (n=[redacted])	SMD	Dapagliflozin (n=[redacted])	Empagliflozin (n=[redacted])	SMD
Age, years, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BMI, kg/m^2						
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Categorical						
<25	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥30	[redacted]	[redacted]		[redacted]	[redacted]	
25.0-29.9	[redacted]	[redacted]		[redacted]	[redacted]	
Missing	[redacted]	[redacted]		[redacted]	[redacted]	
Baseline eGFR, mL/min/1.73m^2 [a]						
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Categorical						
60-89 (G2), n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
45-59 (G3a), n (%)	[redacted]	[redacted]		[redacted]	[redacted]	
30-44 (G3b), n (%)	[redacted]	[redacted]		[redacted]	[redacted]	
15-29 (G4), n (%)	[redacted]	[redacted]		[redacted]	[redacted]	
Baseline uACR, mg/g[a]						
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Categorical						
≥200, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ln_uacr, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Female, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age, n (%)						
<40	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
40-49	[redacted]	[redacted]		[redacted]	[redacted]	
50-59	[redacted]	[redacted]		[redacted]	[redacted]	
60-69	[redacted]	[redacted]		[redacted]	[redacted]	
70-79	[redacted]	[redacted]		[redacted]	[redacted]	
≥80	[redacted]	[redacted]		[redacted]	[redacted]	
Race, n (%)						
Asian	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Black	[redacted]	[redacted]		[redacted]	[redacted]	
Unknown/Other	[redacted]	[redacted]		[redacted]	[redacted]	
White	[redacted]	[redacted]		[redacted]	[redacted]	
Medicare, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cause of CKD, n (%)						
Diabetic kidney disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypertensive disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Glomerular disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Renal tubolo-interstitial disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Other/unknown	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Comorbidities						
Angina	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Atrial fibrillation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bradycardia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Heart failure	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Myocardial infarction	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stroke	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other cardiovascular disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hyperkalaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
T2D	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Medications, n (%)						
RASi	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ARNI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Beta-blocker	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Calcium channel blocker	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Diuretics	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Antithrombotic agent	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Statins	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anti-hyperkaliaemic treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anti-diabetic treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[a] Patients in the 'complete case' had an eGFR and uACR measurement within 122 days prior to or at the index date.

Abbreviations: ARNI: angiotensin receptor/neprilysin inhibitor; BMI: body mass index; CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; RASi: renin-angiotensin system inhibitor; SD: standard deviation; SMD: standardised mean difference; T2D: type 2 diabetes; uACR: urinary albumin-creatinine ratio.

Appendix D Sensitivity analyses: Propensity score matching

D.1 Overall population

D.1.1 Medicare plus commercial

A density plot of the PS and weight distribution after matching are presented in Figure 74 for the 'main period' and Figure 75 for the 'pooled period'.

Figure 74: Density plot of PS and weight distribution following PS weighting for dapagliflozin and empagliflozin – overall population, Medicare plus commercial, 'main period'

[redacted]

Abbreviations: PS: propensity score.

Figure 75: Density plot of PS and weight distribution following PS weighting for dapagliflozin and empagliflozin – overall population, Medicare plus commercial, 'pooled period'

[redacted]

Abbreviations: PS: propensity score.

D.1.2 Medicare plus missing uACR

A density plot of the PS and weight distribution after matching are presented in Figure 76 for the 'main period' and Figure 77 for the 'pooled period'.

Figure 76: Density plot of PS and weight distribution following PS weighting for dapagliflozin and empagliflozin – overall population, Medicare plus missing uACR, 'main period'

[redacted]

Abbreviations: PS: propensity score.

Figure 77: Density plot of PS and weight distribution following PS weighting for dapagliflozin and empagliflozin – overall population, Medicare plus missing uACR, 'pooled period'

[redacted]

Abbreviations: PS: propensity score.

D.2 With T2D

D.2.1 Medicare plus commercial

A density plot of the PS and weight distribution after matching are presented in Figure 78 for the 'main period' and Figure 79 for the 'pooled period'.

Figure 78: Density plot of PS and weight distribution following PS weighting for dapagliflozin and empagliflozin – with T2D, Medicare plus commercial, 'main period'

[redacted]

Abbreviations: PS: propensity score.

Figure 79: Density plot of PS and weight distribution following PS weighting for dapagliflozin and empagliflozin – with T2D, Medicare plus commercial, 'pooled period'

[redacted]

Abbreviations: PS: propensity score.

D.2.2 Medicare plus missing uACR

A density plot of the PS and weight distribution after matching are presented in Figure 80 for the 'main period' and Figure 81 for the 'pooled period'.

Figure 80: Density plot of PS and weight distribution following PS weighting for dapagliflozin and empagliflozin – with T2D, Medicare plus missing uACR, 'main period'

[redacted]

Abbreviations: PS: propensity score.

Figure 81: Density plot of PS and weight distribution following PS weighting for dapagliflozin and empagliflozin – with T2D, Medicare plus missing uACR, 'pooled period'

[redacted]

Abbreviations: PS: propensity score.

D.3 Without T2D

D.3.1 Medicare plus commercial

A density plot of the PS and weight distribution after matching are presented in Figure 82 for the 'main period' and Figure 83 for the 'pooled period'.

Figure 82: Density plot of PS and weight distribution following PS weighting for dapagliflozin and empagliflozin – without T2D, Medicare plus commercial, 'main period'

[redacted]

Abbreviations: PS: propensity score.

Figure 83: Density plot of PS and weight distribution following PS weighting for dapagliflozin and empagliflozin – without T2D, Medicare plus commercial, 'pooled period'

[redacted]

Abbreviations: PS: propensity score.

D.3.2 Medicare plus missing uACR

A density plot of the PS and weight distribution after matching are presented in Figure 84 for the 'main period' and Figure 85 for the 'pooled period'.

Figure 84: Density plot of PS and weight distribution following PS weighting for dapagliflozin and empagliflozin – without T2D, Medicare plus missing uACR, 'main period'

[redacted]

Abbreviations: PS: propensity score.

Figure 85: Density plot of PS and weight distribution following PS weighting for dapagliflozin and empagliflozin – without T2D, Medicare plus missing uACR, 'pooled period'

[redacted]

Abbreviations: PS: propensity score.

D.4 Low uACR (<200 mg/g)

D.4.1 Medicare plus commercial

A density plot of the PS and weight distribution after matching are presented in Figure 86 for the 'main period' and Figure 87 for the 'pooled period'.

Figure 86: Density plot of PS and weight distribution following PS weighting for dapagliflozin and empagliflozin – low uACR, Medicare plus commercial, 'main period'

[redacted]

Abbreviations: PS: propensity score.

Figure 87: Density plot of PS and weight distribution following PS weighting for dapagliflozin and empagliflozin – low uACR, Medicare plus commercial, 'pooled period'

[redacted]

Abbreviations: PS: propensity score.

D.5 High uACR (≥200 mg/g)

D.5.1 Medicare plus commercial

A density plot of the PS and weight distribution after matching are presented in Figure 88 for the 'main period' and Figure 89 for the 'pooled period'.

Figure 88: Density plot of PS and weight distribution following PS weighting for dapagliflozin and empagliflozin – high uACR, Medicare plus commercial, 'main period'

[redacted]

Abbreviations: PS: propensity score.

Figure 89: Density plot of PS and weight distribution following PS weighting for dapagliflozin and empagliflozin – high uACR, Medicare plus commercial, 'pooled period'

[redacted]

Abbreviations: PS: propensity score.

D.6 With T2D and low uACR (<200 mg/g)

D.6.1 Medicare plus commercial

A density plot of the PS and weight distribution after matching are presented in Figure 90 for the 'main period' and Figure 91 for the 'pooled period'.

Figure 90: Density plot of PS and weight distribution following PS weighting for dapagliflozin and empagliflozin – with T2D and low uACR, Medicare plus commercial, 'main period'

[redacted]

Abbreviations: PS: propensity score.

Figure 91: Density plot of PS and weight distribution following PS weighting for dapagliflozin and empagliflozin – with T2D and low uACR, Medicare plus commercial, 'pooled period'

[redacted]

Abbreviations: PS: propensity score.

D.7 With T2D and high uACR (≥200 mg/g)

D.7.1 Medicare plus commercial

A density plot of the PS and weight distribution after matching are presented in Figure 92 for the 'main period' and Figure 93 for the 'pooled period'.

Figure 92: Density plot of PS and weight distribution following PS weighting for dapagliflozin and empagliflozin – with T2D and high uACR, Medicare plus commercial, 'main period'

[redacted]

Abbreviations: PS: propensity score.

Figure 93: Density plot of PS and weight distribution following PS weighting for dapagliflozin and empagliflozin – with T2D and high uACR, Medicare plus commercial, 'pooled period'

[redacted]

Abbreviations: PS: propensity score.

D.8 Without T2D and low uACR (<200 mg/g)

D.8.1 Medicare plus commercial

A density plot of the PS and weight distribution after matching are presented in Figure 94 for the 'main period' and Figure 95 for the 'pooled period'.

Figure 94: Density plot of PS and weight distribution following PS weighting for dapagliflozin and empagliflozin – without T2D and low uACR, Medicare plus commercial, 'main period'

[redacted]

Abbreviations: PS: propensity score.

Figure 95: Density plot of PS and weight distribution following PS weighting for dapagliflozin and empagliflozin – without T2D and low uACR, Medicare plus commercial, 'pooled period'

[redacted]

Abbreviations: PS: propensity score.

D.9 Without T2D and high uACR (≥200 mg/g)

D.9.1 Medicare plus commercial

A density plot of the PS and weight distribution after matching are presented in Figure 96 for the 'main period' and Figure 97 for the 'pooled period'.

Figure 96: Density plot of PS and weight distribution following PS weighting for dapagliflozin and empagliflozin – without T2D and high uACR, Medicare plus commercial, 'main period'

[redacted]

Abbreviations: PS: propensity score.

Figure 97: Density plot of PS and weight distribution following PS weighting for dapagliflozin and empagliflozin – without T2D and high uACR, Medicare plus commercial, 'pooled period'

[redacted]

Abbreviations: PS: propensity score.

8 References

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Cost Comparison Appraisal

Dapagliflozin for treating chronic kidney disease [ID6411]

Clarification questions

February 2025

File name	Version	Contains confidential information	Date
ID6411 dapagliflozin clarification questions 24-02-2025 [CON]	**1.0**	**Yes**	**24-02-2025**

Notes for company

Highlighting in the template

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Section A: Clarification on effectiveness data

Key issues

A1. Priority question: Please discuss whether and to what extent the evidence presented in ID6411 Dapagliflozin Additional data 11112024KM [CON] addresses each of the five key issues raised in ID6411 Dapagliflozin EAR 050924 [CON], Section 1, pp.8-12.

For each issue identified by the External Assessment Group (EAG), a discussion of how the Optum Clinformatics Data Mart (CDM) analyses address the issue is provided below. Across Issues 2–5, the EAG express concerns regarding the data sources previously presented in the Company Submission and Company Addendum to support clinical equivalence of dapagliflozin and empagliflozin. In response to these, AstraZeneca conducted adjusted comparative efficacy analyses of dapagliflozin versus empagliflozin using Optum CDM across the EMPA-KIDNEY population. As such, further discussion of the strengths of the Optum CDM analyses is presented at the bottom of this response.

Issue 1: The company decision problem only includes a small subset of the NICE scope population.

The EAG expressed concerns that the Company decision problem focused on five CKD subgroups for which empagliflozin is recommended but dapagliflozin is not. Therefore, the subpopulations from the National Institute for Health and Care Excellence (NICE) final scope in which dapagliflozin is already recommended have been omitted. To resolve this issue, the EAG stated that robust evidence is required

to show equivalence between dapagliflozin and empagliflozin across the NICE scope population.

As highlighted in response to Clarification Question A1 (received in August 2024), the aim of this submission is to review the current NICE recommendation for dapagliflozin in chronic kidney disease (CKD; TA775) and align it with the NICE recommendation for empagliflozin as a treatment for CKD (TA942).[1,2] This submission is not intended to re-evaluate the subgroups in which dapagliflozin and empagliflozin are currently recommended and have already been evaluated by NICE. As such, this submission originally focused on a subset of the overall NICE scope population, which is the subgroups in which empagliflozin is currently recommended but dapagliflozin is not. Importantly, these subgroups are based on the subgroups of patients that are recommended for empagliflozin but not recommended for dapagliflozin, rather than being clinically significant or different CKD subgroups.

Regardless, in response to the EAG's concerns, AstraZeneca have conducted comparative effectiveness analyses of dapagliflozin versus empagliflozin across the entire EMPA-KIDNEY population using Optum CDM, rather than focusing on the specific subgroups in which empagliflozin is recommended but dapagliflozin is not. Clinically relevant subgroup analyses were conducted to explore any differences in relative treatment effect. These analyses were presented and discussed in ID6411 Dapagliflozin Additional data.

The Optum CDM analyses provide robust evidence of the relative efficacy of dapagliflozin versus empagliflozin across the total EMPA-KIDNEY population, aligned with the population informing TA942 and the NICE final scope for this appraisal. These data provide robust evidence of the relative efficacy of dapagliflozin versus empagliflozin across the entire CKD population, including the subgroups in which both empagliflozin and dapagliflozin are already recommended, and demonstrate that dapagliflozin is at least clinically equivalent to empagliflozin. These robust comparative effectiveness data provide compelling evidence to support a cost-comparison for dapagliflozin versus empagliflozin across the entire empagliflozin recommended population.

Issue 2: Lack of direct evidence for dapagliflozin for the CKD subpopulations included in the company decision problem.

The EAG stated that there was a lack of direct evidence for dapagliflozin in the CKD subpopulations included in the Company decision problem. To resolve this issue, the EAG stated that robust evidence is required to show equivalence between dapagliflozin and empagliflozin, noting that individual patient data (IPD) from dapagliflozin randomised controlled trials (RCTs) may be used to show effectiveness in the five CKD subgroups.

AstraZeneca acknowledge that there is a lack of data for dapagliflozin in the specific subgroups that empagliflozin is recommended in but dapagliflozin is not, due to the subgroup evidence available from the dapagliflozin RCTs and the published real-world evidence (RWE) studies. To mitigate this limitation, AstraZeneca provided an abundance of evidence and clinical rationale underlying the consistent and equivalent treatment effect expected for dapagliflozin and empagliflozin across CKD subgroups.

However, in response to the EAG's concerns raised under Issue 1 (as outlined above), AstraZeneca have provided additional evidence of the efficacy of dapagliflozin across the

entire CKD population, aligned with the population included in EMPA-KIDNEY and the NICE final scope, instead of the specific subgroups in which empagliflozin is recommended but dapagliflozin is not. These analyses provide evidence of the clinical equivalence of dapagliflozin versus empagliflozin across the empagliflozin recommended population. The subgroups in which empagliflozin is recommended but dapagliflozin is not, are not clinically relevant subgroups and, therefore, were not explored in the Optum CDM analyses; instead, clinically important subgroup analyses were conducted which demonstrate a consistent relative treatment effect of dapagliflozin and empagliflozin across the CKD population.

Issue 3: Limited applicability of RCT evidence for dapagliflozin to the company decision problem.

The EAG noted concerns regarding the applicability of the dapagliflozin RCTs to the subgroups included within the Company decision problem, in particular highlighting that DAPA-CKD excludes four of the five subgroups. The EAG suggests that individual patient-level data (IDP) from dapagliflozin RCTs could be used to conduct subgroup analyses for the specific subgroups in the Company decision problem, but highlight that these will be limited and likely insufficient to resolve this issue.

In line with the response above to Issues 1 and 2, AstraZeneca have provided adjusted comparative effectiveness for dapagliflozin versus empagliflozin across the entire empagliflozin recommended population, in line with the NICE final scope population, rather than focusing on the specific subgroups in which empagliflozin is recommended but dapagliflozin is not. As the EAG highlight that IPD from dapagliflozin RCTs in these specific subgroups would likely be insufficient to resolve this issue, instead, the comparative data across the entire CKD population provide robust evidence of the effectiveness of dapagliflozin, and that dapagliflozin is at least clinically equivalent to empagliflozin across the EMPA-KIDNEY population. This can be used as the basis of a cost-comparison appraisal, as stated in the EAG report for this appraisal.

Issue 4: Limited internal validity and applicability of non-randomised evidence.

The EAG express concerns regarding the retrospective, observational studies that were presented as supportive evidence, noting limitations regarding the study design and generalisability to the UK. The EAG propose that adjusted comparisons and matched comparisons using the observational studies could be conducted, but this would likely be insufficient to resolve it fully.

AstraZeneca acknowledge limitations associated with the retrospective, observational data presented to support this review and provided a response to some of these limitations in the factual accuracy check of the EAG report.

In further response to these concerns from the EAG, AstraZeneca have provided additional comparative effectiveness evidence for dapagliflozin versus empagliflozin across the EMPA-KIDNEY population, using real-world data (RWD) from Optum CDM. These analyses provide robust evidence that dapagliflozin is at least clinically equivalent to empagliflozin across the EMPA-KIDNEY population, therefore, addressing the EAG's concerns regarding the supportive evidence provided previously. Further details on the strengths of these analyses are discussed below. In addition, EMPA-KIDNEY was deemed generalisable to the UK

population in TA942 and, therefore, as the inclusion criteria for the comparative analyses from OPTUM align to that of EMPA-KIDNEY, it can be deemed generalisable to the UK.

Issue 5: Lack of robust evidence to show the equivalence in effectiveness and safety between dapagliflozin and empagliflozin.

The EAG express concerns that only a naïve comparison of DAPA-CKD and EMPA-KIDNEY was presented, noting the inherent limitations of naïve comparisons. The EAG state that "ideally, a well-conducted RCT comparing dapagliflozin and empagliflozin in the population under the NICE scope would help to resolve this issue". However, acknowledge the infeasibility of this request, the EAG note that an adjusted indirect treatment comparison (ITC) would help to resolve the issue.

AstraZeneca acknowledge the limitations associated with naïve comparisons. In response to this, AstraZeneca have conducted additional adjusted comparative analyses to evaluate the relative effectiveness of dapagliflozin versus empagliflozin across the total CKD population using RWD from Optum CDM. These analyses address the limitations associated with naïve comparisons and the EAG's request for an adjusted ITC to provide robust evidence of the relative efficacy of dapagliflozin versus empagliflozin across the population included within the NICE final scope. This comparative data further supports the ITC that was presented and deemed appropriate for decision making in TA942 which showed comparability of empagliflozin versus dapagliflozin across the DAPA-CKD population.[3]

Discussion of the robustness of Optum CDM

Underpinning issues 2–5 in the EAG report are concerns regarding the data that were provided as part of the original Company Submission and the Company Addendum. An abundance of evidence was provided including data from RCTs for dapagliflozin in CKD and other indications of relevance (DAPA-CKD, DAPA-HF and DECLARE-TIMI 58), data from RWE studies (OPTIMISE–CKD [Svensson et al. 2024; Tangri et al. 2024] and Nakhleh et al. 2024), discussion of the mechanism of action and biological similarity of dapagliflozin and empagliflozin, and clinical expert support for the clinical equivalence of the two sodium-glucose cotransporter-2 (SGLT2) inhibitors.[4-9]

In response to these concerns, AstraZeneca have conducted additional comparative analyses to evaluate the relative effectiveness of dapagliflozin versus empagliflozin across the total CKD population using RWD from Optum CDM. The robust methodology employed for these analyses address many of the concerns of the EAG regarding limitations of the evidence base previously presented. To further highlight how the Optum CDM analyses have addressed these issues, a discussion of the strengths of these analyses is presented below.

Strengths of the analyses conducted using Optum CDM

Optum CDM is a US-based database which includes RWD on more than 78 million people across 50 states, including data on dispensation of dapagliflozin and empagliflozin. Optum CDM represents a robust data source with a very large sample size, similar to that observed in CKD RCTs, including patients across the entire CKD population.[10] Further details on the appropriateness of Optum CDM, including its generalisability to UK clinical practice, and the selection of this data source are presented in response to Clarification Question A2. The use

of RWD to provide comparative efficacy data for dapagliflozin versus empagliflozin aligns with NICE's RWE framework [ECD9][11] and commitments to using RWE to address uncertainty.

Robust methodologies were employed when conducting the analyses to minimise bias in the comparison conducted, broadly aligned with NICE guidance and previous analyses accepted by NICE. This included the use of propensity score (PS) weighting which accounts for observed prognostic factors and treatment effect modifiers, in line with the list used in Tangri et al. (2024);[5] further details on the selection of variables to include in the PS weighting are provided in response to Clarification Question A9. Despite this, as is the case for any non-randomised comparison, some residual confounding and unobserved confounding may be present, which introduces some uncertainty. However, as data in this comparison are all sourced from patients in the same geographic region, from Medicare only patients (in the primary analysis) in the same calendar period, and empagliflozin and dapagliflozin are seen as equivalent by clinicians, homogeneity of the source population is expected to minimise any bias in the treatment effect introduced by residual or unobserved confounding. Furthermore, the use of the 'main period' minimises the possibility of either population being influenced by underlying factors for prescribing empagliflozin or dapagliflozin and therefore being enriched with patients with other conditions (i.e., heart failure [HF] or type 2 diabetes [T2D]).

Data from Optum CDM are deemed generalisable to patients with CKD in the UK; subgroup analyses of CKD RCT's (e.g., DAPA-CKD), show that there is no significant variation in treatment effect between geographical regions, including Europe and North America.[1] As such, the analyses provided based on Optum CDM can be considered to provide robust evidence on the relative effectiveness of dapagliflozin versus empagliflozin that is generalisable to UK clinical practice. In addition, the population included in the comparative analysis from Optum CDM aligns with the EMPA-KIDNEY trial inclusion criteria which was deemed generalisable to the UK and founded the basis of the empagliflozin recommendation in TA942.

Conclusions

Based on the comparative RWE analyses from Optum CDM of dapagliflozin versus empagliflozin in patients with CKD, there is no evidence to suggest that dapagliflozin is not at least clinically equivalent to empagliflozin in patients across the CKD population. Many analyses show a numerical benefit in favour of dapagliflozin, with some differences having a p-value < 0.05, and results were consistent across the population subgroup analyses and sensitivity analyses. As such, dapagliflozin and empagliflozin can be considered at least clinically equivalent across the empagliflozin recommended CKD population. This supports the case for the cost-comparison analysis presented previously to support this appraisal.

This conclusion aligns with all prior evidence presented as part of this review which demonstrated a consistent treatment effect of dapagliflozin across CKD subgroups and at least clinical equivalence with empagliflozin in patients with CKD, where it was feasible to assess. Conclusions are aligned with the ITC considered as part of empagliflozin TA942 in CKD demonstrating no difference in clinical effectiveness between dapagliflozin and empagliflozin. The ITC is further supported by a published meta-analysis showing consistent benefits and safety between SGLT2i's irrespective of diabetes status, baseline eGFR, and baseline urine albumin-creatinine ratio (uACR) levels (see Question 5, Review Addendum

31072024 [CON]).[12] This is further supported and endorsed by UK clinicians and societies,[2] and also aligns with the similar mechanism of action of dapagliflozin and empagliflozin and the consideration of SGLT2 inhibitors as demonstrating a class effect.

Study selection

A2. Priority question: Please justify the inclusion of Optum Clinformatics Data Mart (CDM) as a relevant source of evidence. Please clarify what methods, if any, were used to select this data source, and whether other sources (e.g. Clinical Practice Research Datalink [CPRD]), or references were searched for or considered in addition to those already discussed and presented in the June 2024 company submission to NICE and August 2024 addendum.

Dapagliflozin was recommended by NICE in March 2022[1] and empagliflozin was recommended by NICE in December 2023[3] for treating CKD. Therefore, to study outcomes of dapagliflozin compared to empagliflozin in clinical practice for this patient population, data were required after both SGLT2 inhibitors had been recommended by NICE.

Other UK specific data sources, including hospital episode statistics (HES) and CPRD were considered. However, for UK data to be useful for this analysis, the HES and CPRD data would need to be linked in order to collect relevant patient outcomes. At the time of submission of the ID6411 Additional Data appendix (8th November 2024), the most recent linked dataset of HES and CPRD available only provided data up to March 2021 and, therefore did not include the period during which dapagliflozin and empagliflozin were licensed and reimbursed for CKD. As such, CPRD-HES linked data were not available to address the decision problem. The linked dataset has since been updated on 21st November 2024, however, this was after the ID6411 Additional Data appendix submission of 8th November 2024 and would still be an insufficient time period to collect the relevant comparative data for the broad CKD population. Therefore, at the time of submission, Optum CDM was the only relevant dataset that would enable a comprehensive RWE comparison of dapagliflozin versus empagliflozin in the EMPA-KIDNEY population.

Moreover, in addition to being the most appropriate RWE dataset available, despite being US-based, data from Optum CDM are deemed generalisable to patients with CKD in the UK (see answer to Clarification Question A1).

Optum CDM study population

A3. Priority question: ID6411 Dapagliflozin Additional data 11112024KM [CON] Table 1, p.7 indicates that patients with an estimated glomerular filtration rate (eGFR) ≥45 mL/min/1.73m^2 and known urine albumin-creatinine ratio (uACR) <200 mg/g at index were excluded from the Optum CDM analysis. This means that patients with diabetes type 2 (T2D), eGFR between 45 mL/min/1.73m^2 and <90 mL/min/1.73m^2 and (known) uACR<200 mg/g, who fall within the NICE final

scope population and NICE recommendations for empagliflozin (TA942), were excluded.

a. **Please justify the exclusion of this population from the Optum CDM analysis.**

As EMPA-KIDNEY informed the NICE recommendation for empagliflozin in CKD, aligning the Optum CDM population with the EMPA-KIDNEY population was deemed the most appropriate approach to demonstrating the relative efficacy of empagliflozin versus dapagliflozin across the empagliflozin NICE recommended population to meet the criteria for a cost-comparison case. EMPA-KIDNEY was deemed suitable to inform the NICE recommendation for empagliflozin, which includes patients with eGFR ≥45 to <90 mL/min/1.73m^2 and T2D. As such, the Optum CDM analyses presented (which align with the EMPA-KIDNEY population) should be deemed equally suitable and sufficient to expand the dapagliflozin recommendation to align with that of empagliflozin, including patients with eGFR ≥45 to <90 mL/min/1.73m^2 and T2D.

As per the EMPA-KIDNEY protocol, the following inclusion criteria were applied:

- Evidence of progressive CKD at risk of kidney disease progression is defined on the basis of local laboratory results recorded at least 3 months before and at the time of the Screening visit, and requires that:

  a) CKD-EPI eGFR ≥20 to <45 mL/min/1.73m²; or

  b) CKD-EPI eGFR ≥45 to <90 mL/min/1.73m^2 with uACR ≥200 mg/g (or protein: creatinine ratio ≥300 mg/g)

Consequently, EMPA-KIDNEY and the Optum CDM analyses excluded patients with eGFR ≥45 mL/min/1.73m^2 and known uACR <200 mg/g **regardless of T2D status**. Therefore, both EMPA-KIDNEY and the Optum CDM analyses excluded patients with eGFR ≥45 mL/min/1.73m^2, known uACR <200 mg/g and T2D, who fall within the NICE final scope population and NICE recommendations for empagliflozin (TA942). However, this was not deemed an issue when empagliflozin was recommended in patients with eGFR ≥45 mL/min/1.73m^2 and T2D by NICE based on EMPA-KIDNEY. Moreover, the population of patients with CKD and T2D has already been assessed in dapagliflozin TA775 based on data from DECLARE-TIMI-58 (see ID6411 Company submission and ID6411 addendum).

Conclusions drawn from the Optum CDM analyses align with the prior evidence presented as part of this appraisal, demonstrating a consistent treatment effect of dapagliflozin across CKD subgroups and at least clinical equivalence with empagliflozin in patients with CKD across the EMPA-KIDNEY population and empagliflozin NICE recommended population. This includes data from RCTs for dapagliflozin in CKD and other indications of relevance (DAPA-CKD, DAPA-HF and DECLARE-TIMI 58), data from RWE studies (OPTIMISE–CKD [Svensson *et al.* 2024; Tangri *et al.* 2024] and Nakhleh *et al.* 2024), and discussion of the mechanism of action and biological similarity of dapagliflozin and empagliflozin.[4-9]

b. Please provide an estimate of the approximate size of this population relative to the whole NICE scope population.

Subgroup of patients with eGFR ≥45 to <90 mL/min/1.73m2, (known) uACR <200 mg/g and T2D

The population size of the subgroup of patients in Optum CDM with eGFR ≥45 to <90 mL/min/1.73m^2, (known) uACR <200 mg/g and T2D is provided in Table 1. In order to provide an approximate size of the requested population relative to the entire CKD population, the population size of the 'overall population' included within the Optum CDM analyses is presented as a reference. This 'overall population' was defined by the inclusion and exclusion criteria presented in Table 1 of ID6411 Dapagliflozin Additional data, which are aligned to the EMPA-KIDNEY inclusion and exclusion criteria.

Table 1: Eligible patients with T2D, eGFR ≥45 to <90 mL/min/1.73m^2 and UACR <200 mg/g in the Optum CDM analysis dataset

	Patients with T2D, eGFR ≥45 to <90 mL/min/1.73m2 and UACR <200 mg/g			Overall population[a]
	Dapagliflozin	Empagliflozin	Total	Total
Main period	[redacted]	[redacted]	[redacted]	[redacted]
Pooled period	[redacted]	[redacted]	[redacted]	[redacted]

[a] The 'overall population' is defined by the inclusion and exclusion criteria applied to Optum CDM, presented in Table 4 of ID6411 Dapagliflozin Additional data. This size of this overall population is smaller than the population of patients with T2D, eGFR ≥45 to <90 mL/min/1.73m^2 and uACR ≥200 mg/g as the population is aligned to that of EMPA-KIDNEY; EMPA-KIDNEY excluded patients with CKD who have an eGFR ≥45 to <90 mL/min/1.73m^2 with uACR ≥200 mg/g (or protein: creatinine ratio ≥300 mg/g).
Abbreviations: eGFR: estimated glomerular filtration rate; T2D: type 2 diabetes; uACR: urine albumin-creatinine ratio.

Subgroup of patients with eGFR ≥45 to <90 mL/min/1.73m^2 and T2D

However, the specific population above is not highlighted in the NICE scope or empagliflozin recommendation. The relevant populations within the NICE scope (and the empagliflozin NICE recommendation) is patients with eGFR ≥45 to <90 mL/min/1.73m^2 and T2D, or eGFR ≥45 to <90 mL/min/1.73m^2 and uACR ≥200 mg/g.

The population with eGFR ≥45 to <90 mL/min/1.73m^2 and T2D has not fully been covered in the Optum CDM analysis nor the EMPA-KIDNEY trial as both EMPA-KIDNEY and the Optum CDM analyses excluded patients with eGFR ≥45 mL/min/1.73m^2 and known uACR <200 mg/g (regardless of T2D). Therefore, patients with eGFR ≥45 mL/min/1.73m^2 **and** T2D **and** known uACR <200 mg/g were not included.

For completeness, the population size of the subgroup of patients in Optum CDM with eGFR ≥45 to <90 mL/min/1.73m^2 and T2D is provided in Table 2. In order to provide an approximate size of the requested population relative to the entire CKD population, the population size of the 'overall population' included within the Optum CDM analyses is presented as a reference. This 'overall population' was defined by the inclusion and exclusion criteria applied to Optum CDM, presented in Table 1 of ID6411 Dapagliflozin Additional data. However, there would be substantial overlap between the subgroup of patients with T2D and eGFR ≥45 to <90 mL/min/1.73m^2 and the 'overall population' included

within the Optum CDM analyses originally presented (specifically, patients with uACR >200 mg/g).

Table 2: Eligible patients with T2D and eGFR ≥45 to <90 mL/min/1.73m² in the Optum CDM analysis dataset

	Patients with T2D and eGFR ≥45 to <90 mL/min/1.73m²			Overall population[a]
	Dapagliflozin	Empagliflozin	Total	Total
Main period	[redacted]	[redacted]	[redacted]	[redacted]
Pooled period	[redacted]	[redacted]	[redacted]	[redacted]

[a] The 'overall population' is defined by the inclusion and exclusion criteria applied to Optum CDM, presented in Table 4 of ID6411 Dapagliflozin Additional data. This size of this overall population is smaller than the population of patients with T2D, eGFR ≥45 to <90 mL/min/1.73m² and uACR ≥200 mg/g as the population is aligned to that of EMPA-KIDNEY; EMPA-KIDNEY excluded patients with CKD who have an eGFR ≥45 to <90 mL/min/1.73m² with uACR ≥200 mg/g (or protein: creatinine ratio ≥300 mg/g).
Abbreviations: eGFR: estimated glomerular filtration rate; T2D: type 2 diabetes; uACR: urine albumin-creatinine ratio.

For completeness, additional analyses of the Optum CDM have been conducted using the subgroup of patients with eGFR ≥45 to <90 mL/min/1.73m² and T2D across three key outcomes: time to hospitalisation for CKD, time to hospitalisation for HF, and time to in-hospital mortality. Comparable outcomes for the main period in time-to-event analysis are observed between dapagliflozin and empagliflozin, although numerical reductions favour dapagliflozin (Table 3). These outcomes are consistent with those already presented Optum CDM results in ID6411 Dapagliflozin Additional data.

Table 3: Time-to-event in first CKD hospitalisation, first hospitalisation for HF, and in-hospital mortality in patients with T2D and eGFR ≥45 to <90 mL/min/1.73m² in the Optum CDM analysis dataset – main period

	Main HR (adjusted)	Pooled HR (adjusted)
Time to first CKD hospitalisation	[redacted]	[redacted]
Time to first hospitalisation for HF	[redacted]	[redacted]
Time to in-hospital mortality	[redacted]	[redacted]

Abbreviations: CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; HF: heart failure; HR: hazard ratio; T2D: type 2 diabetes.

c. Please discuss implications for the company submission's ability to inform the decision problem.

As outlined in response to part a of this question, EMPA-KIDNEY informed the NICE recommendation for empagliflozin in CKD. Therefore, the most appropriate approach to demonstrating the relative efficacy of empagliflozin versus dapagliflozin across the empagliflozin NICE recommended population was to align the Optum CDM population with the EMPA-KIDNEY population. Based on the Optum CDM analyses, there is no evidence to suggest that dapagliflozin is not at least clinically equivalent to empagliflozin in patients across the CKD population. Many analyses show a numerical benefit in favour of dapagliflozin, with a few differences having [redacted], and results were consistent across the extensive population subgroup analyses and sensitivity analyses (see ID6411 Dapagliflozin

Additional data 11112024KM [CON]). As such, dapagliflozin and empagliflozin can be considered at least clinically equivalent across the empagliflozin recommended CKD population.

EMPA-KIDNEY was deemed suitable to inform the NICE recommendation for empagliflozin, which includes patients with eGFR ≥45 to <90 mL/min/1.73m^2 and T2D. As such, the Optum CDM analyses presented (which align with the EMPA-KIDNEY population) should be deemed equally suitable to expand the dapagliflozin recommendation to align with that of empagliflozin, including patients with eGFR ≥45 to <90 mL/min/1.73m^2 and T2D. In addition, [redacted]

Furthermore, an abundance of additional evidence was presented in the Company Submission Addendum, including data from RCTs for dapagliflozin in CKD and other indications of relevance (DAPA-CKD, DAPA-HF and DECLARE-TIMI 58), data from RWE studies (OPTIMISE–CKD [Svensson *et al.* 2024; Tangri *et al.* 2024] and Nakhleh *et al.* 2024), and discussion of the mechanism of action and biological similarity of dapagliflozin and empagliflozin.[4-9] The totality of evidence provided can be used to conclude that dapagliflozin is at least clinically equivalent to empagliflozin across the population included in the decision problem.

A4. Priority question: Please provide baseline median (IQR) eGFR before and after weighting for the 'main period' and 'pooled period' (as per baseline mean [standard deviation] eGFR in Additional data 11112024KM [CON], Tables 4 and 24).

The baseline median (interquartile range [IQR]) eGFR before and after weighting for both the main period and the pooled period are presented in Table 4.

Table 4: Median baseline eGFR (mL/min/1.73m^2) before and after weighting for the 'main period' and 'pooled period' of the Optum CDM analysis dataset

	Dapagliflozin	Empagliflozin
Main period		
Crude - Median baseline eGFR (IQR)	[redacted]	[redacted]
Weighted - Median baseline eGFR (IQR)	[redacted]	[redacted]
Pooled period		
Crude - Median baseline eGFR (IQR)	[redacted]	[redacted]
Weighted - Median baseline eGFR (IQR)	[redacted]	[redacted]

Abbreviations: eGFR: estimated glomerular filtration rate; IQR: interquartile range.

A5. Additional data 11112024KM [CON], Tables 4 and 24 to 63 include an eGFR 15-29mL/min/1.73m^2 category. Eligibility criteria in Table 1 indicate that people with eGFR<20 mL/min/1.73m^2 were excluded. Please confirm whether this is the case, and that the eGFR 15-29 mL/min/1.73m^2 category in Table 4 only

effectively includes people with baseline eGFR between 20 and 29 mL/min/1.73m^2.

Yes, patients with eGFR<20 mL/min/1.73m^2 were excluded from the Optum CDM analyses. As such, the minimum eGFR value in the eGFR 15–29 mL/min/1.73m^2 category is 20 mL/min/1.73m^2.

Optum CDM analysis

A6. Priority question: Please justify why kidney replacement, kidney failure, albuminuria, hospitalisation (all cause), death (including outside of hospital) and adverse effects, which are listed in the NICE final scope, were not included in the Optum CDM analysis.

Outcomes of dapagliflozin in terms of kidney replacement, kidney failure, albuminuria, hospitalisation (all cause), death (including outside of hospital) and adverse effects have already been provided and assessed in the appraisal of dapagliflozin in CKD (TA775), empagliflozin in CKD (TA942), ID6411 Company Submission, and ID6411 Company Addendum. Therefore, the Optum CDM analysis presented in ID6411 Dapagliflozin Additional data aimed to explore the comparative effects between dapagliflozin and empagliflozin by focusing on the following endpoints:

- eGFR slope
- Time to first hospitalisation for CKD
- Time to first hospitalisation for HF
- Time to death within hospital

These endpoints were selected as Optum CDM provided robust data for these outcomes and they were deemed clinically important outcomes in CKD.

Other endpoints available in Optum CDM were explored but were deemed not suitable for inclusion in this analysis, or were associated with data limitations and would, therefore, not provide robust relative efficacy estimates. Further details on why certain outcomes listed in the NICE final scope were not included in the analysis are provided below.

Kidney Replacement Therapy (KRT)

KRT, which includes dialysis and kidney transplantation, typically occurs in patients with eGFR <15 mL/min/1.73m². The population included in this analysis was patients with baseline eGFR ≥20 mL/min/1.73m², meaning that very few, if any, patients were expected to have reached the threshold for KRT initiation during the follow-up period.

Kidney Failure

Kidney failure, often defined as an eGFR <15 mL/min/1.73m², or in the included population a baseline eGFR ≥20 mL/min/1.73m² with a substantial decline in kidney function (>5 mL/min/1.73m²) would be required within the study follow-up period to observe meaningful kidney failure events. The number of events was expected to be low based on the inclusion

criterion of having eGFR >20 leading to results associated with substantial uncertainty. This is further supported by having only [redacted] and [redacted] of dapagliflozin and empagliflozin patients in the main period that had a baseline eGFR of <30 mL/min/1.73m², (See Tsai *et al*. 2017[13] for expected annual decline).

Albuminuria (UACR, UPCR)

uACR and urine protein-creatinine ratio (uPCR) are biomarkers of kidney damage. However, these are not consistently recorded in Optum CDM. Baseline data from Optum CDM show that uACR is infrequently measured in routine clinical practice, leading to significant missing data concerns. Given that post-index uACR would be treated as an outcome variable, missing data could introduce bias, making results unreliable. As such, albuminuria was not explored as an endpoint in the analysis.

All-Cause Hospitalisation

All-cause hospitalisation was not deemed a relevant endpoint to include in the analysis, as hospitalisations unrelated to CKD (e.g., due to chronic obstructive pulmonary disease [COPD], pneumonia or fractures) would dilute the treatment effect and reduce interpretability and clinical significance of the results. The goal of the analysis was to address treatment-related effects and including all-cause hospitalisation could lead to misleading equivalence assumptions.

Death (including outside of hospital)

Data on time to all-cause death within hospital are presented in the absence of data on all-cause mortality in all settings, as these data were not available within the Optum CDM database in totality.

The analysis presented included deaths recording within Optum CDM, which are formally referred to as deaths within hospital. However, Optum CDM defines death using multiple validated data sources, ranked by reliability:

- Center for Medicare & Medicaid Services (CMS)
- Social Security Administration Death Master File (DMF)
- Facility claims where discharge status is ‘expired’
- Member coverage termination due to death
- Optum EHR clinical records
- Externally sourced obituary data

As such, the time to death within hospital endpoint presented in ID6411 Dapagliflozin Additional data is comprehensive and utilises multiple validated data sources to approximate all-cause mortality even if this cannot be analysed directly due to the lack of data availability.

Adverse effects

Identifying adverse effects requires defining and validating specific adverse event codes, which is a complex process. Additionally, differentiating treatment-related adverse effects from background rates in the general population requires careful consideration. A minimum follow-up period of four weeks is needed to assess treatment-emergent adverse events.

Moreover, as discussed previously in the Company Submission Addendum, published data indicate consistency of safety outcomes across sodium-glucose co-transporter-2 (SGLT2) inhibitors.[12]

A7. Priority question: Additional data 11112024KM [CON], p.5 states that all analyses were repeated over two time periods (the 'main period' and the 'pooled period'). Please provide the median, range and inter-quartile range of the follow-up duration for both periods.

The median, range and IQR for the follow-up duration (time to death or disenrollment of the Optum CDM dataset) for the main period and the pooled period are presented in Table 5 and Table 6.

Table 5: Time in days to death or disenrollment of the Optum CDM analysis dataset– Main period

	Min	Q1	Median	Q3	Max
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dapagliflozin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Empagliflozin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: min: minimum; max: maximum; Q: quartile.

Table 6: Time in days to death or disenrollment of the Optum CDM analysis dataset– Pooled period

	Min	Q1	Median	Q3	Max
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dapagliflozin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Empagliflozin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: min: minimum; max: maximum; Q: quartile.

A8. Please justify the use of median values for eGFR slope analyses as opposed to means, as used elsewhere.[14]

Both mean and median values for change in eGFR were calculated for the slope analysis. Examination of baseline eGFR values showed these had skewed distribution (see response to Clarification Question A12, part C) meaning that median values were preferred over means and were used as the primary estimand. For the primary analysis, the same trends are observed when using median or mean values for eGFR slope analyses so the use of median values should not be considered a source of uncertainty.

A9. Please provide an explanation for the inclusion of variables in the Propensity Score (PS) model.

a. **Please clarify whether any other potentially relevant covariates were considered but excluded from the PS model with reasons (e.g. lack of data availability).**

The covariates selected for inclusion in the PS model were based on Tangri *et al*., 2024[5] a peer-reviewed publication assessing dapagliflozin real-world effectiveness among patients with lower levels of albuminuria, which was also conducted in the Optum CDM dataset. As such, there were no issues of lack of data availability as these covariates had already been established as available in a previous study.

b. **We understand that further adjustments were conducted for piecewise log_{10}uACR, piecewise eGFR, T2D (as well as BMI) in addition to PS matching. Please discuss whether there is a risk that additional adjustment for uACR, eGFR and T2D might lead to over-adjusting (by effectively adjusting for these variables twice).**

While all analyses were conducted in the weighted population, weighted but unadjusted results and then results further adjusted for body mass index [BMI], piecewise log_{10}uACR and piecewise eGFR were provided, as described above.

BMI was not included in the propensity score model as it had high levels of missing data. Conditioning on BMI would mean conditioning on measurement error, which was unnecessary given the relatively good balance in BMI after propensity scoring (SMD < 0.20). Subsequently, to control for the potential confounding effects of BMI, further adjustment post weighting was conducted.

The results prior to and after further adjustment are presented with no difference in the results or change to the overall conclusions. Therefore, these data are provided for completeness, and it is not likely that conclusions are biased due to over adjustment.

A10. Please provide full definitions of time to event outcomes (hospitalisation for HF, hospitalisation for CKD, and time to death) including censoring rules. Please confirm whether the index date for these outcomes was defined as the day of prescription as per Additional data 11112024KM [CON], Table 1, p11.

Index date for all outcomes was the date of prescription of dapagliflozin/empagliflozin. Individuals were followed up from index date until the first censoring event, which include death, disenrollment, event of interest, or end of data availability (1/4/2024). For those with events, survival time was taken as the date of the event minus index date plus one.

In the analysis of in-hospital mortality, individuals are censored at the earliest of the date of death, disenrollment, or end of data availability. Cause of death was not assessed (i.e., all-cause in-hospital mortality was assessed). Within Optum CDM, only month and year of

death are provided in lieu of a full date of death. Death was, therefore, imputed to be the first day of each month. Any downstream events (HF/CKD hospitalisation) after imputed date of death were discarded. This is not expected to introduce bias in the analysis as it is assumed that date of events does not differ between treatment arms and, therefore, the treatment effect on CKD/HF is not impacted by a small number of discarded events. In any case, given that there are more deaths in empagliflozin arm, AstraZeneca feel that this is a conservative approach.

In the analysis of CKD, individuals are followed up until first CKD hospitalisation, death, disenrollment, or end of data availability.

In the analysis of HF, individuals with HF are followed up until first HF hospitalisation, death, disenrollment, or end of data availability. However, HF hospitalisations within the first 7 days were discarded due to the presence of several day zero events that suggested that these were existing and emerging HF events that were in progress prior to treatment inception. They were deemed not causally related to treatment and, therefore, not relevant to the study objectives. Patients with HF hospitalisations within 7 days of treatment inception were not censored and all follow-up time and events post 7-days were included.

The code lists for CKD/HF hospitalisations were those ICD9/10 codes used in Tangri *et al*., 2024. The full code lists of these outcomes are presented in Table 7.

Table 7: List of ICD9/10 codes used to identify hospitalisations for heart failure / chronic kidney disease

Codes for heart failure hospitalisation		Codes for CKD hospitalisation	
Classification system	Code	Classification system	Code
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
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[redacted]	[redacted]	[redacted]	[redacted]
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[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

Codes for heart failure hospitalisation		Codes for CKD hospitalisation	
Classification system	**Code**	**Classification system**	**Code**
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
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[redacted]	[redacted]	[redacted]	[redacted]
		[redacted]	[redacted]

Codes for heart failure hospitalisation		Codes for CKD hospitalisation	
Classification system	Code	Classification system	Code
		[redacted]	[redacted]
		[redacted]	[redacted]
		[redacted]	[redacted]
		[redacted]	[redacted]
		[redacted]	[redacted]
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		[redacted]	[redacted]

Risk of bias

A11. Please present a risk of bias assessment for the Optum CDM analysis using a suitable quality assessment tool such as ROBINS-I or ROBINS-I V2.[15 16]

The ROBINS-I assessment for the Optum CDM analyses is provided in Table 8.

Table 8: ROBINS-I assessment of the Optum CDM analyses

Category	Description	Justification
Bias due to confounding	Low.	Propensity scoring is applied and subgroup analyses show equivalent result to overall analyses.
Bias in selection of participants into the study	Low.	Results for medicare only, for medicare + commercial, and for including patients with missing uACR are aligned. Subgroup analyses show equivalent results.
Bias in classification of interventions	Low	This is just coding intended intervention is dapagliflozin and empagliflozin in whatever way it is used, but prescribed on label.
Bias due to deviations from the intended intervention	Low.	Intended intervention is dapagliflozin and empagliflozin in whatever way it is used, but prescribed on label.
Bias due to missing data	Low.	Missingness is likely independent of treatment as treatments are clinically seen as equivalent.
Bias in measurement of outcomes	Not realistic	
Bias in selection of the reported result	Not selected	
Overall risk of bias	Low	

Abbreviations: eGFR: estimated glomerular filtration rate; uACR: urine albumin-creatinine ratio.

Results

A12. Priority question: Figures reporting eGFR slopes (Figures 3, 7, 13, 16, 19, 22, 25, 28, 31, 34, 37, 40, 43, 46, 49 and 52) lack details and are therefore difficult to interpret. Please provide additional information:

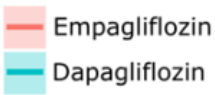
a. **Please clarify what units the change in eGFR is expressed as (e.g. units per year) for all time points (90 days, 180 days and total slope).**

The units for change in eGFR are the median annualised change in eGFR slope measured in mL/min/1.73m^2.

b. **Please clarify which colour in the figures refer to which treatment.**

In ID6411 Dapagliflozin Additional data, red is used to refer to empagliflozin and blue is used to refer to dapagliflozin (Figure 1).

Figure 1: Colour coding for dapagliflozin and empagliflozin in ID6411 Dapagliflozin Additional data



c. **Please clarify why 95% confidence intervals for eGFR slope results reported in Figures 3, 7, 13, 16, 19, 22, 25, 28, 31, 34, 37, 40, 43, 46, 49**

and 52 are asymmetrical. Was skewness in baseline eGFR distributions assessed? If so, please provide relevant test results and figures.

The asymmetrical confidence intervals are downstream of both skewed data and the use of bootstrapping to generate 95% confidence intervals, where symmetrical distributions around the median sample is not expected. Note that quantile regression is used, adequate for skewed distributions in eGFR slope.

Skewness was assessed visually by assessing histograms of baseline eGFR values (Figure 2). These showed evidence of significant skew, likely driven by inclusion/exclusion criteria.

Figure 2: Histogram of baseline eGFR values of the Optum CDM analysis dataset - Overall population, pooled period

Abbreviations: eGFR: estimated glomerular filtration rate.

A13. Priority question: Based on the information presented, most of the eGFR slope results appear implausibly large for both groups. Clinical advisers to the EAG are concerned they may lack face validity. Please comment on the clinical plausibility of the eGFR slope results.

As the eGFR rates are annualised, it is anticipated that data sparse areas may produce exaggerated trends where acute trends are magnified. Given the observational nature of the Optum CDM dataset, data collection is predicated on physician request rather than regular and routine collection. As the population for the eGFR slope analysis requires both a baseline eGFR and two follow-up data points to be at least 30 days apart for calculation of a slope, only a small percentage of patients had sufficient values to calculate a slope, particularly when the observation period was restricted to 90 days. It is expected that those who have repeated physician ordered datapoints within a small period to be clinically distinct to those with less measurements, and that individuals with more measurements may have clinical profiles consistent with larger and more regular drops in eGFR than the full analysis population. However, it is not expected that this data collection differs by treatment arm, as

exemplified by the high level of consistency between baseline eGFR measures after weighting (SMD=0.004 in both pooled and main periods).

Therefore, even if the magnitude of effect may be exaggerated, the purpose of the Optum CDM analyses was to compare dapagliflozin and empagliflozin treatment effects, and despite limitations listed above, the results support the conclusion that dapagliflozin is at least clinically equivalent to empagliflozin in patients with CKD.

A14. Priority question: Please discuss the following potential limitations of the data informing the eGFR slope analyses:

a. **Patient numbers included in eGFR slope analyses are substantially different to those reported in for time-to-event analyses (see for instance, Additional data 11112024KM [CON], Figure 3 vs. Figure 4, despite being both conducted for the overall population, 'main period'). Please clarify why.**

As outlined in response to Clarification Question A13, given the observational nature of the Optum CDM dataset, data collection is predicated on physician request rather than regular and routine collection. As the analytic population for the eGFR slope analysis requires both a baseline eGFR and two follow-up data points to be at least 30 days apart for calculation of a slope, only a small percentage of patients had sufficient values to calculate a slope, particularly when the observation period was restricted to 90 days. The same conditions are not imposed on the time-to-event analyses as the full population are at risk of hospitalisation at any given time, and, therefore, it is expected that this analysis population is larger than that of the eGFR analysis population, which is implicitly a subset of the time-to-event analysis population.

b. **OPTUM CDM has been criticised elsewhere for the incompleteness of its laboratory data.[17] Please discuss whether and to what extent missing data may affect the internal validity of the eGFR slope analysis results.**

Optum CDM along with other secondary data sources have specific limitations in completeness of laboratory data. The eGFR data are not collected routinely but at physician discretion, and it is not expected that data captured at physician discretion are differential between treatment arms, as evidenced by the high comparability of markers of severity between treatment groups at baseline.

Within the 'main period', a total of [redacted] dapagliflozin patients and [redacted] empagliflozin patients were included in the eGFR slope analysis. The low participation in this analysis is a function of the limited follow-up during the 'main period' (median follow-up of [redacted]) which naturally curtails the ability to have a sufficient number of eGFR values recorded with 30 days in between. During the 'pooled period', completion rates were higher for both dapagliflozin patients ([redacted] and empagliflozin patients ([redacted] where the longer median follow up time ([redacted]) facilitated greater numbers of in-scope eGFR values.

Given the comparable level of participation in the eGFR analysis in both groups and consistency in both the pooled and main period results, there is limited evidence to suggest that missing eGFR data may affect the internal validity of the data for the treatment comparison.

c. **Unlike in a trial setting, the OPTUM CMD did not have a prespecified schedule of assessments for eGFR. Between-group differences in eGFR slopes could be biased if there are systematic differences in the timing of assessment between treatment groups. Please discuss whether such bias could have occurred for eGFR slope analyses at each of the reported time point (90 days, 180 days, total slope) in the 'main period' and 'pooled period'.**

The eGFR data are not collected routinely, but rather at physician discretion. Data captured at physician discretion do not differ between treatment arms, as evidenced by the high comparability of markers of severity between treatment groups at baseline post-weighting. As eGFR was collected at physician discretion, it aligns to what is performed in clinical practice and, therefore, is a real-world reflection of the timing between assessments for eGFR.

d. **Please discuss any other limitations as appropriate (e.g. number of time points, follow-up duration, imprecision, etc.).**

In addition to the discussion provided above, the following response focuses on the number of time points, follow-up duration and imprecision and the relevance of these factors as limitations of the Optum CDM analyses.

Number of time points

Regarding the number of time points, the eGFR analytic cohort requires two post-baseline eGFR values that are greater than 30 days apart from each other and over 30 days from baseline. While these criteria restrict the size of the eGFR analysis cohort, they allow a greater ability to estimate longitudinal trends in eGFR. Furthermore, as this is a retrospective study based on RWD, the eGFR measurement time points are reflective of standard clinical practice and therefore provide a robust overview of the treatment effect of dapagliflozin and empagliflozin in terms of eGFR slope.

Follow-up duration

As discussed in ID6411 Dapagliflozin Additional data, analyses were presented over two time periods: the 'main period' and the 'pooled period'. The 'main period' is the time during which both empagliflozin and dapagliflozin were both approved for use in patients with CKD in the US, as well as T2D and HF. The primary analyses use the 'main period' as it represents the time period during which dapagliflozin and empagliflozin have equivalent marketing authorisations.

However, given the limited period of data available in the 'main period' (22nd September 2023 to 31st March 2024), the duration of follow-up is shortened, and this restriction impacts

the ability to find multiple eGFR records with the required intra-record period of 30 days. However, to explore any uncertainty introduced by the shortened duration of follow-up, sensitivity analyses were conducted using the 'pooled period' for all subgroups. The consistent finding of results between the main and pooled periods demonstrates that the limited follow-up does not bias the conclusions of the eGFR slope analysis and this should not be considered a substantial source of uncertainty that impacts decision-making.

Imprecision

For the analyses of the 'main period' and the 90-day slope analysis of the 'pooled period'. eGFR data are sparse. As a result, 95% CIs are wide and eGFR slope estimates may be imprecise.

However, as highlighted above, due to the smaller sample size and follow-up duration of the 'main period', all analyses were also run using the 'pooled period' which includes a greater number of eGFR observations. Considering the 'pooled period' analyses, 95% CIs are substantially narrower, especially for the total slope analysis where the 95% CIs for annualised difference in median eGFR slope is <2 mL/min/1.73m^2. Conclusions drawn from the 'main period' analyses are consistent with the 'pooled period' analyses, which both show that there is no significant reduction in eGFR decline in patients receiving dapagliflozin. The consistency of the conclusions demonstrates that concerns regarding lower precision do not impact the conclusions and should not be a substantial source of uncertainty that impacts decision-making.

Conclusion

Although there are potential limitations associated with the eGFR slope analyses using Optum CDM, as discussed above, numerous sensitivity analyses were conducted to explore the impact of potential limitations on the results and conclusions that can be drawn. Across all sensitivity analyses conducted, the same conclusion can be drawn: dapagliflozin is at least clinically equivalent to empagliflozin across the total CKD population. As such, it is apparent that the potential limitations of the eGFR slope analyses do not bias the results and change the conclusions that are drawn. These limitations should not be viewed as a substantial source of uncertainty and should not impact decision-making.

A15. Subgroup analyses were presented by T2DM status and baseline uACR level, but not according to baseline eGFR. Please justify:

a. the exclusion of eGFR from the subgroup analyses;

There were a planned series of *a priori* eGFR subgroup analyses, namely to investigate those with and without T2D plus a baseline eGFR of >75 mL/min/1.73m^2. This subgroup was prioritised as individuals with an eGFR of >75 to <90 mL/min/1.73m^2 were included in the EMPA-KIDNEY trial but excluded from the DAPA-CKD trial.

However, there were insufficient numbers of individuals in either subgroup (i.e., with and without T2D) to conduct analyses for any endpoints. No further eGFR subgroups were considered *a priori* and were, therefore, not explored for the analyses.

b. the conclusion in Additional data 11112024KM [CON], p.5. that, based on the Optum CDM analyses, "dapagliflozin and empagliflozin can be considered at least clinically equivalent, regardless of baseline eGFR", in the absence of eGFR specific data;

Prior to the development of ID6411 Dapagliflozin Additional data based on the Optum analyses, an abundance of evidence was presented that demonstrates the consistent treatment effect of dapagliflozin across the total CKD population, including across baseline eGFR subgroups. This included the ITC presented as part of empagliflozin TA942 in CKD demonstrating no difference in clinical effectiveness between dapagliflozin and empagliflozin. The ITC is further supported by a published meta-analysis showing consistent benefits and safety between SGLT2i's irrespective of diabetes status, baseline eGFR, and baseline uACR levels (see Question 5, Review Addendum 31072024 [CON]).[12]

The analyses of dapagliflozin versus empagliflozin based on Optum CDM demonstrate that dapagliflozin is at least clinically equivalent to empagliflozin across the entire CKD population, aligned with the population included within EMPA-KIDNEY. This population includes patients across the range of baseline eGFR and uACR values, and patients with and without T2D. Across all subgroups explored, the results show that dapagliflozin is at least clinically equivalent to empagliflozin. Although variation in baseline eGFR was not explored explicitly as a defined subgroup analysis, baseline eGFR will have varied across the subgroups explored (as demonstrated in the baseline characteristics tables presented in Appendix A of ID6411 Dapagliflozin Additional data). As such, the consistent treatment effect of dapagliflozin versus empagliflozin observed across all subgroup analyses conducted demonstrates that dapagliflozin and empagliflozin are at least clinically equivalent, regardless of baseline eGFR.

c. why people with cardiovascular disease, and people with other causes of CKD, which are subgroups specified in the NICE final scope, were not analysed in the Optum CDM analysis.

The population included within the Optum CDM analyses includes all patients prescribed dapagliflozin or empagliflozin with CKD as defined in EMPA-KIDNEY (i.e., eGFR ≥20 to <45 mL/min/1.73m², or eGFR ≥45 to <90 mL/min/1.73m2 with uACR ≥200 mg/g), **regardless of the cause of CKD**, as presented in Table 1 of ID6411 Dapagliflozin Additional data. While patients with a CKD diagnosis as defined above were included in the Optum CDM analysis, patients with CKD often have comorbidities, including cardiovascular disease (CVD). In the Optum CDM analyses, [redacted] of dapagliflozin and empagliflozin treated patients in the main and pooled periods had HF at baseline, and [redacted] had hypertension at baseline.

As highlighted in Section 2.4 of ID6411 Dapagliflozin Additional data, analyses were conducted over two time periods. The 'main period' represents the time during which both empagliflozin and dapagliflozin were both approved for use in patients with CKD in the US, as well as T2D and HF. The 'pooled period' represents time periods during which dapagliflozin and empagliflozin were licensed for T2D and/or HF, but not both for CKD. As patients with T2D and HF may have comorbid CKD, data are available within Optum CDM that show outcomes relevant to CKD from these patients. The presence of the pooled period (during which empagliflozin was only licensed for T2D and HF, not CKD) demonstrates that

patients with CKD were included within the analysis, regardless of the cause of their CKD. As such, patients with cardiovascular disease and other causes of CKD, as specified in the NICE final scope, are included within the presented Optum CDM analyses.

Section B: Clarification on cost-comparison data

Not applicable. No additional data specific to the cost-comparison was submitted.

Section C: Textual clarification and additional points

C1. Please provide diagrams, similarly to OPTIMISE-CKD (Svensson 2024, Figure 1)[18] summarising the selection of participants into the OPTUM CKD analysis 'main period' and 'pooled period' including numbers included/excluded and main reasons for exclusion.

Inclusion/exclusion diagrams for the ‘pooled period’ and the ‘main period’ are provided in Figure 3 and Figure 4, respectively.

Figure 3: Inclusion/Exclusion diagram for pooled period of the Optum CDM analysis dataset

Abbreviations: CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; T1DM: type 1 diabetes mellitus; T2D: type 2 diabetes; SGLT2: sodium-glucose co-transporter 2; uACR: urine albumin-creatinine ratio.

Figure 4: Inclusion/Exclusion diagram for main period of the Optum CDM analysis dataset

Abbreviations: CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; T1DM: type 1 diabetes mellitus; T2D: type 2 diabetes; SGLT2: sodium-glucose co-transporter 2; uACR: urine albumin-creatinine ratio.

C2. Additional data 11112024KM [CON], Table 4, p.14 presents baseline characteristics for both dapagliflozin and empagliflozin groups and SMDs before and after PS matching. Please clarify how SMDs were calculated for count variables (e.g. cause of CKD). The numbers provided in Table 4 are counts and percentages. Please also provide the means and standard deviations used for the SMD calculations.

The standardised differences of binary variables can be calculated using the proportion in treatment and control groups as outlined by Austin, 2011, where $\widehat{P}treatment$ and $\widehat{P}control$ denote the prevalence of the dichotomous variable in treated and untreated subjects, respectively (Figure 5).[19] Categorical covariates are dealt with by treating these as a series of binary covariates. As proportions are used to calculate the standardised differences for count variables, there are no means or standard deviations used to calculate the SMD for this table.

Figure 5: Calculation of standardised differences for binary variables

$$d = \frac{(\hat{P}treatment - \hat{P}control)}{\sqrt{\frac{\hat{P}treatment(1-\hat{P}treatment) + \hat{P}control(1-\widehat{Pcontrol})}{2}}}$$

Source: Austin, 2011.[19]

C3. Additional data 11112024KM [CON], p.29 states "It was not possible to produce visual representations of difference in median eGFR slope due to the measurement scale." Similarly, p.72 states "it was not possible to produce

visual representations of eGFR slope due to the measurement scale." Please clarify.

Due to variation in difference in median eGFR and the associated 95% CIs across the subgroups, a plot summarising all the results would require a very wide scale or transformation of scale or any other alternative method. It was therefore not possible to produce meaningful forest plots at the time the analysis was performed. The plots produced for time-to-event endpoints are summary figures only and no data are omitted due to the lack of a summary forest plot of eGFR slope changes. The full eGFR slope change data for each scenario is provided in the relevant sections of ID6411 Dapagliflozin Additional data.

For time-to-event endpoints, the relative treatment effect is expressed as a HR which is in general between 0 and 2. It was therefore possible to generate forest plots for these outcomes as the scale was narrow.

C4. Please specify the Y axis (including metric and unit) and X axes (including title, metric and unit) for all plots of weight distribution in Figure 2 and Figures 57 to 73.

For all weight distribution plots (Figure 2, Figure 57–73 in the ID6411 Dapagliflozin Additional Data submission) the X axis refers to the raw value corresponding to the size of the weights and the Y axis refers to the numeric counts of each weight value.

The units for weight for Figure 6 are included below.

Figure 6: Weight distribution for dapagliflozin patients in the main period following PS weighting of the Optum CDM analysis dataset

Note: Y axis: numeric counts; X axis: Weight
Abbreviations: dapa: dapagliflozin.

C5. Please specify the Y axis (including metric and unit) for all figures reporting eGFR slopes (Figures 3, 7, 13, 16, 19, 22, 25, 28, 31, 34, 37, 40, 43, 46, 49 and 52).

The Y axis in figures reporting eGFR slopes (Figures 3, 7, 13, 16, 19, 22, 25, 28, 31, 34, 37, 40, 43, 46, 49 and 52 in the ID6411 Dapagliflozin Additional Data submission) is the annualised median change in eGFR slope (mL/min/1.73m^2).

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Addendum to the External Assessment Group Report

Cost comparison evaluation process

Dapagliflozin for the treatment of adults with chronic kidney disease (Review of TA775) [ID6411]

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Date completed	17/03/2025

Source of funding

This report was commissioned by the NIHR Evidence Synthesis Programme as project number NIHR168093.

Declared competing interests of the authors: None.

Acknowledgements

Prof. James Fotheringham (Sheffield Teaching Hospitals NHS Trust) and Prof. Hugh Gallagher (Epsom and St. Helier NHS Trust) provided expert clinical advice and commented on the draft report.

Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.

Note on the text

All commercial-in-confidence (CIC) data have been highlighted in blue and underlined.

Contents

1 INTRODUCTION

In November 2024, Astra Zeneca (the company) submitted additional evidence based on a retrospective analysis of individual participant data extracted from Optum Clinformatics Data Mart (CDM).[1] The Optum CDM analysis was submitted in response to issues raised by the EAG in its EAR submitted in September 2024[2] which considered the company submissions from June 2024[3] and August 2024.[4]

The EAR raised five issues regarding the relative efficacy of dapagliflozin and empagliflozin across the whole chronic kidney disease (CKD) population to support a cost-comparison.[2] Key Issue 1 highlighted that the company decision problem did not include the whole NICE scope population, but only the five CKD subpopulations for which empagliflozin is recommended by NICE and dapagliflozin is not; Key Issue 2 discussed the lack of direct evidence for dapagliflozin for the CKD subpopulations included in the company decision problem; Key Issue 3 highlighted the limited applicability of the RCT evidence supporting the company submission; Key Issue 4 discussed the limited internal validity and applicability of the non-randomised evidence submitted; and Key Issue 5 highlighted the lack of robust evidence to show equivalence in effectiveness and safety between dapagliflozin and empagliflozin.

In February 2025, the EAG requested and received further clarifications from the company regarding the Optum CDM analysis. This document provides a critique of the Optum CDM analysis, building on the EAR and Addendum to the EAR submitted in August 2024[2, 5] and discusses the extent to which this new analysis addresses the Key Issues raised in the EAR.

2 SUMMARY AND CRITIQUE OF ADDITIONAL EVIDENCE

The aims of the Optum CDM analysis were to estimate the relative treatment effect of dapagliflozin versus empagliflozin in patients with CKD and demonstrate the consistency of treatment effect between these treatments.

The company extracted IPD from Optum CDM, a US insurance claims database, for patients diagnosed with CKD who were prescribed either dapagliflozin or empagliflozin. Patients with the following baseline characteristics were included:

- Estimated glomerular filtration rate (eGFR) ≥ 20 and < 45 mL/min/m^2, and any urine albumin-creatinine ratio (uACR), or
- baseline eGFR ≥ 45 and < 90 mL/min/m^2 and uACR ≥ 200 mg/g.

Baseline imbalances between dapagliflozin and empagliflozin treatment groups were adjusted using propensity score weighting. Outcomes including eGFR slope, time to hospitalisation for CKD and for heart failure (HF), and death within hospital, were compared between treatment groups.

Up to [redacted] patients were included in the primary analyses (median follow-up [redacted] days). These showed [redacted].

The EAG finds the Optum CDM analysis relevant to inform the decision problem and it addresses some of the key issues raised in the EAR, by providing evidence comparing dapagliflozin and empagliflozin across most of the NICE scope population. However, the Optum CDM data has several limitations. Optum CDM is a US-based insurance claims database which may not reflect NHS practice (Sections 2.1.2 and 2.1.6). Primary analysis results are limited by insufficient follow-up (Section 2.1.7) and eGFR slope results lack face validity and are at critical risk of bias due to substantial levels of missing data at follow-up (Sections 2.1.4, 2.1.5 and 2.1.7). In addition, most outcomes listed in the NICE scope were not measured, including all-cause mortality, all-cause hospitalisation, kidney failure, kidney replacement, albuminuria, health related quality of life or adverse events (Section 2.1.3). The following subsections provide a summary and critique of the Optum CDM evidence.

2.1.1 Study selection

No systematic review was performed to identify the evidence presented in the November Addendum. In response to a clarification request from the EAG, the company stated that other UK specific data sources, including hospital episode statistics (HES) and Clinical Practice Research Datalink (CPRD) were considered (Clarification response 25052025, A2).[6] However, at the time of submission of the November Addendum, the most recent linked dataset of HES and CPRD available only provided data up to March 2021, which preceded the period during which both dapagliflozin and empagliflozin were recommended by NICE for CKD. The company stated that, therefore, Optum CDM was the only dataset that would enable a comprehensive comparison of dapagliflozin versus empagliflozin in the EMPA-KIDNEY population at the time of the submission.

EAG comments

Although the November Addendum still does not include a systematic review, the justification for excluding CPRD and HES appears reasonable, and the EAG is not aware of other relevant evidence sources beyond those submitted by the company between June and November 2024.

2.1.2 Optum CDM population selection

The Optum CDM database is a nationwide US insurance database that contains patient-level data (IPD) from claims submitted for medical and pharmacy health care services in the US, including privately insured patients with commercial or Medicare Advantage coverage.

Inclusion and exclusion criteria for patients included in the CDM analyses are reported in Additional Data 11112024, Table 1.[1] Included patients were prescribed dapagliflozin 10mg or empagliflozin 10mg. Patients with the following baseline characteristics were included:

- eGFR ≥ 20 and < 45 mL/min/m^2 and any uACR, or
- eGFR ≥ 45 and < 90 mL/min/m^2 and uACR ≥ 200 mg/g were included.

Baseline, or 'index date', was the date of prescription of dapagliflozin or empagliflozin.

Analyses were conducted over two time periods, which are described in Additional Data 11112024, Section 2.4, p.8.[1] The 'main period' includes the time during which both empagliflozin and dapagliflozin were approved for use in patients with CKD in the US, as well as type 2 diabetes (T2D) and HF: from 22nd September 2023 to 31st March 2024 (latest available date). The 'pooled period' covers time periods during which dapagliflozin and empagliflozin were licensed for T2D and/or HF, but were not both licensed for CKD. This period covers 24th February 2022 to 31st March 2024, and informed additional sensitivity analyses.

The main period of the Optum CDM analysis dataset included [redacted] patients ([redacted] with dapagliflozin, and [redacted] with empagliflozin). The 'pooled period' included [redacted] patients ([redacted] with dapagliflozin, and [redacted] with empagliflozin).

The primary analysis was conducted in the overall population (Medicare only), which comprised patients with eGFR measurement and uACR measurements in the 122 days up to the index date during the 'main period'. The company's clarification response presents diagrams summarising the selection of the main period and pooled period populations (Clarification response, 25022025, C1, Figures 3 and 4).

EAG comments

The Optum CDM analysis includes a population that is more reflective of the NICE scope than the company submissions from June and August 2024, as the scope of this additional evidence submission is not limited to the five CKD subpopulations for which empagliflozin is recommended and dapagliflozin is not. However, the Optum CDM excludes a potentially large subpopulation of patients with T2D: eGFR between 45 mL/min/1.73m^2 and 90 mL/min/1.73m^2 and (known) uACR < 200 mg/g, which is included in the NICE scope and empagliflozin NICE guidance.[7]

In response to a clarification question from the EAG, the company explained that the population selected for the Optum CDM analyses was meant to align with the population of EMPA-KIDNEY, the pivotal trial in the company submission for TA942 (empagliflozin), which also excluded people with baseline eGFR ≥ 45 mL/min/1.73m^2 and uACR < 200 mg/g (Clarification response 25052025, A3a).

The company showed that the excluded population of patients with T2D, eGFR ≥ 45 to < 90 mL/min/1.73m^2 and uACR < 200 mg/g who were otherwise eligible for the main period analyses was [redacted] than the population included in the main period ([redacted]) (Clarification response 25052025, A3b). Additional time-to-event analyses for the subpopulation with T2D, eGFR ≥ 45 to < 90 mL/min/1.73m^2 were [redacted]. These are presented and discussed in Section 2.1.7.5.

2.1.3 Outcomes

Treatment effect of dapagliflozin compared to empagliflozin was assessed in the company additional analysis according to the following outcomes:

- eGFR slope
- Time to first hospitalisation for CKD
- Time to first hospitalisation for HF
- Time to death within hospital

In response to a clarification request from the EAG, the company acknowledged that other endpoints available in Optum CDM were explored but were deemed not suitable for inclusion in the analyses, or were associated with data limitations and would, therefore, not provide robust relative efficacy estimates (Clarification response 25052025, A6). These included: kidney replacement therapy, kidney failure, albuminuria (uACR, urinary protein-to-creatinine ratio), all-cause hospitalisation, death (including outside of hospital), and adverse effects.

Definitions of time to event outcomes (including index time, events and censoring) were provided in response to a clarification request from the EAG (Clarification response 25052025, A10). Index time was time of dapagliflozin/empagliflozin prescription for all outcomes. Mortality in all settings (i.e. including outside of hospital) was not available in the Optum Database so time to death within hospital is presented as a proxy. Within Optum CDM, only month and year of death are provided in lieu of a full date of death, therefore death was imputed to be the first day of each month. The company argued that this is not expected to introduce bias in the analysis as it is assumed that date of events does not differ between treatment arms and that their approach is [redacted]

Follow-up durations for the 'main' and 'pooled' periods were provided in response to a clarification request from the EAG (A7, Tables 5 and 6 respectively). The median duration was [redacted] days (interquartile range [IQR] [redacted] to [redacted]) for the 'main period' and [redacted] days (IQR [redacted] to [redacted]) for the 'pooled period'. In both periods, the

[redacted] (Clarification response 25052025, A7, Tables 5 and 6).

EAG comments

The additional analyses include a limited range of outcomes. Kidney replacement, kidney failure, albuminuria, hospitalisation (all cause), death (including outside of hospital), adverse effects and health-related quality of life (HRQOL), which are listed in the NICE final scope, were not reported in the Optum CDM analysis.

The company justified the exclusion of kidney replacement therapy and kidney failure by stating that few events were expected in view of the baseline eGFR levels and follow-up duration of the analyses. The actual number of events during both study periods is unknown. Although the EAG acknowledges that few events may be expected given the baseline characteristics of the treatment cohorts and the limited follow-up duration of the main period, the 'pooled period' may have captured more events to inform relevant analyses. The company's approach appears somewhat inconsistent, as death within hospital (also a relatively rare event) was reported for both study periods.

Although the EAG acknowledges the company's argument that all-cause hospitalisation may include events unrelated to CKD, this outcome was specified in the NICE final scope (and measured in EMPA-KIDNEY) and should have been included in the additional analyses. Adverse events are coded in the Optum CDM database but were not analysed. This said, EAG clinical advisers noted there is no known reason to expect that outcomes including hospitalisation for causes other than CKD or HF, mortality outside of hospital, or adverse events should differ between dapagliflozin and empagliflozin groups.

Albuminuria data is inconsistently and infrequently reported in Optum CDM, (Clarification response 25052025, A7) and HRQOL is not reported, therefore their exclusion from the additional analyses was justified. EAG clinical advisers did not expect these outcomes to differ between treatment groups.

Overall, the median follow-up duration for the 'main period' is very short, which limits the clinical relevance of the analysis results.

2.1.4 Statistical methods

The company conducted a propensity score analysis assuming that eligible patients who were prescribed empagliflozin were the 'target population' and those who were prescribed dapagliflozin were weighted to the empagliflozin group. The propensity score model included covariates listed in Additional Data 11112024, Section 2.6.2, p.13-14.[1] These included uACR, eGFR, T2D, along with nearly all other variables adjusted for in OPTIMIZE-CKD.[8] Further adjustments were conducted for piecewise $\log_{10}$uACR, piecewise eGFR, T2D status, as they were deemed important. BMI was also

adjusted for after propensity score (PS) weighting, as it was excluded from the PS model due to high levels of missing data. PS model adjusted results were presented prior to and after these further adjustments.

Median eGFR slopes estimates were presented at three time points: 90 days, 180 days and total slope. It appears that the earlier two timepoints were defined as *up to* 90 days and *up to* 180 days respectively (Clarification response 25052025, A13). No definition was provided for 'total slope'. In response to a clarification request from the EAG (Clarification response 25052025, A8c), the company indicated that the distribution of baseline eGFR in the 'main' and 'pooled' periods was positively skewed (tail extended towards higher values). Therefore, the EAG believes the use of median eGFR slope (rather than means) was justified. For time-to-event analyses, Kaplan-Meier curves and the number of events and HR with 95% CIs presented from cumulative incidence analyses were presented.

In addition to the main analysis (people with CKD), the company conducted subgroup analyses within specific subpopulations defined by presence of T2D, uACR thresholds and combination of these factors. Additional supportive analyses by time period are also presented according to the availability of empagliflozin and dapagliflozin for the treatment of CKD, T2D and heart failure and sensitivity analyses according to the type of insurance patients and also including patients with missing baseline uACR values. The EAG requested clarification from the company explaining why subgroup analyses were not conducted according to baseline eGFR (Clarification response 25052025, A15a). The company responded that, as individuals with an eGFR of > 75 to < 90 mL/min/1.73m^2 were included in the EMPA-KIDNEY trial but excluded from the DAPA-CKD trial, they planned to run subgroup analyses for patients with and without T2D plus a baseline eGFR of > 75 mL/min/1.73m^2, but failed to do so due to insufficient patient numbers. The company stated that no further eGFR subgroups were considered a priori and were, therefore, not explored for the analyses. The EAG had no access to an analysis plan.

EAG comments

In the absence of randomised evidence, the choice of a PS weighting approach is appropriate to attempt to correct for imbalances in known baseline characteristics across the dapagliflozin and empagliflozin groups.

The covariates used for PS weighting seem generally appropriate, although some potentially relevant variables were not included. Although the company stated these covariates were those included in the OPTIMISE-CKD adjusted analyses by Tangri (2024)[8] it appears that, unlike Tangri (2024), the Additional Data analyses excluded time since CKD diagnosis and previous hospitalization from PS weighting, and did not include an interaction between angiotensin receptor/neprilysin inhibitor (ARNI) and heart failure for weighting patients. Systolic blood pressure had a statistically significant

interaction with the primary outcome of the DAPA-CKD trial (sustained decline in eGFR of at least 50%, progression to end-stage kidney disease, or death from a renal or cardiovascular cause)[9] but was not included in the PS model. Overall, although it is uncertain whether all relevant covariates were accounted for, the EAG believe it is unlikely that the exclusion of covariates from the PS model introduced significant bias.

uACR, eGFR and T2D status were included in the PS model. Therefore, the EAG believes that the decision to further adjust for these variables following PS weighting could lead to overadjustment. This is further discussed in Section 2.1.7.

The PS model for the main analysis of time-to-event outcomes appeared to be well implemented. However, in response to a clarification request from the EAG (Clarification response 25052025, A14b), the company acknowledged that

[redacted]. This is further discussed in Sections 2.1.5 and 2.1.7.

The lack of subgroup analysis by eGFR is a limitation. The EAG was unable to assess the risk of selective outcomes reporting as it did not have access to an analysis plan.

2.1.5 Risk of bias

In response to a clarification request from the EAG (Clarification response 25052025, A11), the company provided a risk of bias assessment for the Optum CDM analyses using the ROBINS-I tool.[10] The company concluded that the study was at low risk of bias overall.

The EAG conducted a separate assessment using the ROBINS-I v2 tool,[11] assessing risk of bias separately for eGFR slope results ('main period', PS weighted, Additional Data 11112024, Section 3.3.1),[1] and time-to-event outcomes ('main period', PS weighted, time to hospitalisation for HF, time to hospitalisation for CKD, and time to death within hospital, Additional Data 11112024, Sections 3.3.2-4).[1] A single risk of bias assessment was conducted across all three specified time-to-event outcomes as there were no differences in judgments between these.

Risk of bias assessments for the company and EAG are summarised in Table 1. The main difference in assessment relates to missing data for eGFR slope results. As discussed in Section 2.1.4,

[redacted] Therefore, the risk of bias for eGFR slope outcomes in the 'main period' was critical. The EAG found that the risk of bias for time-to-event outcomes was low overall.

Table 1 ROBINS-I assessment of the Optum CDM analyses by the company and EAG

Domain	Company judgment	EAG judgment	
		eGFR slope[1]	Time-to-event outcomes[2]
Bias due to confounding	Low	Low	Low
Bias in selection of participants into the study	Low	Low	Low
Bias in classification of interventions	Low	Low	Low
Bias due to deviations from the intended intervention	Low	Low	Low
Bias due to missing data	Low	*Critical*[3]	Low
Bias in measurement of outcomes	Not realistic	Low	Low
Bias in selection of the reported result	Not selected	*Uncertain*[4]	*Uncertain*[4]
Overall risk of bias	Low	*Critical*[3]	Low

Italics indicate a difference in judgment between the company and the EAG.
[1] 'Main period', PS weighted, Additional Data 11112024, Section 3.3.1
[2] 'Main period', PS weighted, time to hospitalisation for HF, time to hospitalisation for CKD, and time to death within hospital, Additional Data 11112024, Sections 3.3.2-4
[3] [redacted]
[4] Uncertain due to lack of reported analysis plan, but considered unlikely to introduce significant bias

2.1.6 Population characteristics

Baseline characteristics of patients included in the primary analysis are reported in Additional Data 11112024, Table 4, by treatment group, before and after weighting.[1]

Although inclusion criteria broadly reflected those of the EMPA-KIDNEY trial, the Optum CDM population was substantially older overall (mean age [redacted] years in the dapagliflozin and empagliflozin groups, versus 64 years in the trial). The prevalence of T2D was also substantially higher ([redacted] and [redacted] in the dapagliflozin and empagliflozin groups, versus 45% in the EMPA-KIDNEY empagliflozin arm). Mean eGFR was higher in the Optum CDM population ([redacted] and [redacted] versus 37.4 with the EMPA-KIDNEY empagliflozin arm), and so was uACR ([redacted] mg/g and [redacted] mg/g versus 219 mg/g). Renin-angiotensin system inhibitor (RASi) prescription rates were between Optum CDM ([redacted] versus 85.7% in EMPA-KIDNEY).

Baseline characteristics were largely comparable between the dapagliflozin and empagliflozin groups of Optum CDM before and after weighting (Additional Data 11112024, Table 4).[1]

EAG comments

The Optum CDM population is older, with a higher prevalence of T2D and with generally higher rates of comorbidities compared with EMPA-KIDNEY or DAPA-CKD trials. EAG clinical advisers found that compared with trial populations, the Optum CDM population was likely to be more representative of clinical practice, although it included larger proportion of patients with heart failure than the UK. Compared with the UK CKD population, the Optum CDM analysis population substantially overrepresents patients with albuminuria (uACR > 200). It also substantially underrepresents people with eGFR between 45 and 90 mL/min/m^2 relative to patients with lower eGFR.[12] In response to a clarification request from the EAG (Clarification response 25052025, A12c), the company showed that the Optum CDM population baseline eGFR distribution was substantially skewed. The EAG agrees with the company that this is likely a consequence of the Optum CDM analysis selection criteria, which excluded patients with T2D, eGFR ≥ 45 to < 90 mL/min/1.73m^2 and uACR < 200 mg/g (see Section 2.1.2). The fact that eGFR and uACR was measured at physician discretion, rather than systematically, and the requirement for multiple laboratory measurements for inclusion means that patients who were included in the Optum CDM analysis are a small, likely clinically distinct, subset of US Medicaid patients who were prescribed dapagliflozin or empagliflozin. Overall, the EAG believes that the Optum CDM analysis population is not reflective of UK practice.

Baseline characteristics were balanced between the two Optum CDM treatment arms before and after weighting. Although the non-randomised design of Optum CDM means that some residual confounding due to baseline imbalances may remain after PS weighting, the EAG believes that the risk of confounding due to lack of randomisation is low.

2.1.7 Results

2.1.7.1 Propensity score weighting results

Additional Data 11112024, Section 3.1, Table 4 shows that baseline characteristics were generally well weighted between the dapagliflozin and empagliflozin arms before adjustment, and that PS score weighting had a relatively limited impact on the characteristics of the dapagliflozin group. Additional Data 11112024, Section 3.2, Figure 1 showed good overlap between the dapagliflozin and empagliflozin population in the 'main period'.[1] The company reported that no extreme weights were observed (Clarification response C4, Figure 6).

EAG comments

The EAG has no significant concerns regarding the PS weighting results.

2.1.7.2 Median eGFR slope

For eGFR slope results, the 'main period' included [redacted] dapagliflozin patients and [redacted] empagliflozin patients, with a median follow-up of [redacted]. During the 'pooled

period', completion rates were higher for both dapagliflozin patients [redacted] and empagliflozin patients [redacted], (median [redacted] follow-up).

Additional Data 11112024, Section 3.3.1, Figure 3, presents Median eGFR slopes for patients receiving dapagliflozin and empagliflozin in the 'main period'.[1] Results are PS weighted and expressed as median annualised change in eGFR slope measured in mL/min/1.73m^2 at three time points (90 days, 180 days and total slope). Blue and red lines correspond to dapagliflozin and empagliflozin slopes respectively (Clarification response, A12).

The figure shows a steep decline in eGFR for both dapagliflozin and empagliflozin at all three time points, with the steepest decline observed in the 90 days slope. The difference in median eGFR slopes between the dapagliflozin and empagliflozin groups for the main period are presented in Additional Data 11112024, Section 3.3.1, Table 5.[1]

[redacted]

Additional Data 11112024, Section 4.1, Figure 7, presents median eGFR slopes for patients receiving dapagliflozin and empagliflozin for the 'pooled period'.[1] The results of this sensitivity analysis were broadly consistent with the primary analysis, although results for the total slope were significantly less extreme in both arms. As with the primary analysis,

[redacted] (Additional Data 11112024, Section 4.1, Table 6).[1]

[redacted]

Subgroup analyses by T2D and/or uACR for the main and pooled periods are presented in Additional Data 11112024, Section 5.[1]

[redacted]

EAG comments

The EAG has several concerns regarding the validity of the eGFR slope results. EAG clinical advisers noted that these absolute declines were clinically concerning and lacked face validity. In response to a request for clarification from the EAG (Clarification response 25052025, A13), the company acknowledged that the magnitude of eGFR slope decline observed may be exaggerated. They noted

that only a small percentage of patients had sufficient data to calculate an eGFR slope (i.e. a baseline eGFR and two follow-up data points to be at least 30 days apart), most notably when the observation period was restricted to 90 days. The EAG did not have access to the baseline characteristics of this patient subset. As laboratory measures were not collected systematically, but at physician discretion, the EAG agrees with the company that it is likely that those who have repeated physician ordered datapoints within a small period are likely to be clinically distinct to those with fewer measurements. For instance, these patients might have worse CKD prognosis, may be more likely to have started other medications that can influence kidney function and/or have a different response to treatment compared with patients missing at follow-up.

EAG clinical advisers noted that 90 days results (and to a lesser extent, results up to 180 days) may be confounded by acute trends. As noted in Section 2.1.5, no adjustments were made to account for missing eGFR follow-up data, and it is unclear whether the dapagliflozin and empagliflozin subpopulations with eGFR data at follow-up were well-weighted.

Confidence interval for median eGFR slopes and between-group differences were wide and asymmetrical. The EAG agrees with the company that imprecision in eGFR slope estimates is likely a consequence of sparse eGFR data (Clarification response 25052025, A14d). In response to a clarification request from the EAG, the company explained that asymmetry was a consequence of skewed eGFR distributions and the use of bootstrapping to generate 95% confidence intervals (Clarification response 25052025, A12c).

Results of sensitivity analyses and subgroup analyses indicated that [redacted] The 'pooled period' results included a longer time period than the 'main period' and total slope results were consequently less likely to be affected by acute trends; the pooled period also had less missing data (although still substantial). However, results from the 'pooled period' sensitivity analyses should be interpreted with caution as they cover a period during which empagliflozin was not licensed for CKD, which increases the risk of confounding due to population differences and potentially limits applicability.

2.1.7.3 Time-to-hospitalisation for CKD and HF

Time to hospitalisation for CKD is presented in Additional Data 11112024, Section 3.3.3.[1] The total number of events across both treatment arms was [redacted] (n=[redacted]) in the 'main period'. There was no statistically significant difference in hospitalisation for CKD (PS weighted HR [redacted]; 95% CIs: [redacted] to [redacted]).

Time to hospitalisation for HF is presented in Additional Data 11112024, Section 3.3.2.[1] The total number of events across both treatment arms was [redacted] (n=[redacted]) in the 'main period'. There was no

statistically significant difference in hospitalisation for CKD (PS weighted HR [redacted]; 95% CIs: [redacted] to [redacted]).

Additional Data 11112024, Sections 4.2-3, present corresponding time-to-hospitalisation analysis results for the 'pooled period'.[1] The total number of events was significantly greater ([redacted] hospitalisations for CKD and [redacted] hospitalisations for HF out of n=[redacted]). The direction of results of the sensitivity analysis was broadly consistent with the primary analysis, showing no statistically significant difference between dapagliflozin and empagliflozin (Time to hospitalisation for CKD: PS weighted HR [redacted]; 95% CI [redacted] to [redacted]; time to hospitalisation for HF: PS weighted HR [redacted]; 95% CI [redacted] to [redacted]).

Subgroup analyses by T2D and/or uACR for the main and pooled periods are presented in Additional Data 11112024, Section 5.[1]

[redacted]

EAG comments

The primary analyses show no evidence of a difference in time-to-hospitalisation for CKD and time-to-hospitalisation for HF between dapagliflozin and empagliflozin. However, these analyses are limited by missing data, imprecision (as shown by the wide confidence intervals) and limited follow-up duration. The 'pooled period' analyses also showed no evidence of a difference in time-to-hospitalisation outcomes, yielded more precise estimates of effect, and included a longer-follow-up duration. However, as with eGFR slope results (Section 2.1.7.2), these results are potentially limited as they cover a period during which empagliflozin was not licensed for CKD.

2.1.7.4 Time-to-death in hospital

Time-to-death in hospital is presented in Additional Data 11112024, Section 3.3.4.[1] The total number of events across both treatment arms was [redacted] (n=[redacted]) in the 'main period'. There was no statistically significant difference in time to death in hospital (PS weighted HR [redacted]; 95% CIs: [redacted] to [redacted]).

Additional Data 11112024, Sections 4.2-3, present corresponding time-to-death within analysis results for the 'pooled period'.[1] The total number of events across both treatment arms in the 'pooled period' was [redacted] (n=[redacted]) in the 'main period'. The PS weighted analyses showed a statistically significant benefit of dapagliflozin versus empagliflozin (HR [redacted], 95% CIs: [redacted] to [redacted]), whilst no statistically significant difference was found for the PS weighted adjusted results.

EAG comments

The primary analyses show no evidence of a difference in time-to-death within hospital between dapagliflozin and empagliflozin. However, these analyses are limited by imprecision (as shown by the wide confidence intervals) and limited follow-up duration. The 'pooled period' PS weighted analyses showed a statistically significant effect on time-to-death within hospital favouring dapagliflozin. Although the PS weighted adjusted analysis were not statistically significant at conventional levels, the results between the two analyses were very similar, suggesting that the effect of additional adjustment (and potential 'overadjustment', as discussed in Section 2.1.4) was limited for this outcome. As with eGFR slope results and time-to-hospitalisation (Sections 2.1.7.2 and 2.1.7.3), the 'pooled period' estimates of effect were more precise and included a longer-follow-up duration. However, these results are potentially limited as they cover a period during which empagliflozin was not licensed for CKD.

As discussed in Section 2.1.3, the mortality data does not include death outside of hospital, and the exact timing of death was imputed to be the first day of each month, as only month and year of death are available within Optum CDM (Clarification response 25052025, A10). Although these are limitations to the mortality data, the EAG does not expect them to affect the dapagliflozin and empagliflozin groups differently and introduce bias in relative estimates between the two groups.

2.1.7.5 Additional time-to-event analyses for excluded subpopulation

Patients with T2D, eGFR between 45 mL/min/1.73m2 and 90 mL/min/1.73m^2 and (known) uACR< 200 mg/g, who are within the NICE final scope population and NICE recommendations for empagliflozin (TA942), were excluded. In response to a clarification question (Clarification response 25052025, A3b, Table 3), the company provided results of additional time-to-event analyses for the population of patients with T2D, eGFR ≥ 45 to < 90 mL/min/1.73m^2 who were otherwise eligible for the 'main' period analyses [redacted]. Adjusted HR for time to CKD hospitalisation, time-to-hospitalisation for HF, and time-to- death in hospital

[redacted].

EAG comments

These additional results are

[redacted]

3 OUTSTANDING AREAS OF UNCERTAINTY

In the EAR, five key issues of uncertainty were raised, one relating to the alignment of the company decision problem to the NICE scope population (Key Issue 1), three relating to the limited evidence from RCTs and from non-randomised studies to inform the clinical effectiveness of dapagliflozin (Key Issues 2-4) and one relating to lack of robust evidence to inform clinical equivalence of dapagliflozin and empagliflozin (Key Issue 5).

The EAG considers that the additional analyses partially resolve Key Issues 1 and 5, although comparative analyses have not been performed for most outcomes listed in the NICE scope. The EAG considers that the additional analyses do not currently resolve uncertainties related to Key Issues 2-4.

The EAG finds the Optum CDM analysis relevant to inform the decision problem and addresses some of the key issues raised in the September 2024 EAR. However, the Optum CDM analysis is notably limited by the generalisability, quality and completeness of its underpinning data.

Overall, this additional evidence shows [redacted]

4 CONCLUSIONS

The EAG believes that the additional data presented by the company does not provide robust evidence to conclude that dapagliflozin and empagliflozin have equivalent effectiveness and safety across the NICE scope population. However, there is no evidence to suggest that dapagliflozin is less clinically effective than empagliflozin in people with CKD, and it is clinically plausible that dapagliflozin and empagliflozin have equivalent effectiveness and safety across the NICE scope population.

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Single Technology Appraisal

Dapagliflozin for treating chronic kidney disease [ID6411]

EAG report – factual accuracy check and confidential information check

"Data owners may be asked to check that confidential information is correctly marked in documents created by others in the evaluation before release." (Section 5.4.9, NICE health technology evaluations: the manual).

You are asked to check the EAG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on 27 March 2025** using the below comments table.

All factual errors will be highlighted in a report and presented to the appraisal committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and information that is submitted as 'confidential' should be highlighted in turquoise and all information submitted as 'depersonalised data' in pink.

Issue 1 Misinterpretations of analyses conducted in the Optum CDM analyses

Description of problem	Description of proposed amendment	Justification for amendment	EAG Response
The EAG report 17/03/2025 states that: p.4 “Baseline imbalances between dapagliflozin and empagliflozin treatment groups were adjusted using propensity score matching.” p.8 “were matched to the empagliflozin group.”, “Body Mass Index (BMI) was also adjusted for after PS matching, as it was”, and “the choice of a PS matching approach” p.9 “The covariates used for PS matching seem generally appropriate, although some potentially relevant variables were not included. Although the company stated these covariates matched those included in the OPTIMISE-CKD adjusted analyses by Tangri (2024)[8] it appears that, unlike Tangri (2024), the Additional Data analyses	The Company requests that throughout the EAG reports, the word 'matched'/'matching' is replaced by 'weighted'/'weighting' as the methods used is propensity score weighting as opposed to matching as well as erase the mention that no rationale for choosing such approach was not provided. “Baseline imbalances between dapagliflozin and empagliflozin treatment groups were adjusted using propensity score **weighting** ~~**matching**~~.” “were ~~**matched**~~ **weighted** to the empagliflozin group.” “BMI was also adjusted for after propensity score (PS) **weighting** ~~**matching**~~, as it was” “the choice of a PS **weighting** ~~**matching**~~ approach” “The covariates used for PS **weighting** ~~**matching**~~ seem generally appropriate, although some potentially relevant variables were not included.	As described in ID6411 Dapagliflozin Additional data 11112024KM [CON], p.10: “Inverse probability weights generated by the propensity score (PS) models were used to weight individuals within the overlapping regions by the inverse of the probability of the patients occurring in the population first prescribed empagliflozin in the ‘main period’. This is preferred to a matching analysis, as the number of patients prescribed empagliflozin was larger than the number of patients prescribed dapagliflozin (in the same time period), and so matching would either have to compensate for sampling with replacement of the dapagliflozin subgroup, or would have to thin the empagliflozin subgroup. The weighting process was repeated for each subgroup analyses to ensure balance between subgroups.” Therefore, the methods used is propensity score weighting as opposed to matching and the rationale why such approach is preferred was provided upfront.	Edits made as suggested.

Description of problem	Description of proposed amendment	Justification for amendment	EAG Response
excluded time since CKD diagnosis and previous hospitalization from PS matching, and did not include an interaction between angiotensin receptor/neprilysin inhibitor (ARNI) and heart failure for matching patients.", "Therefore, the EAG believes that the decision to further adjust for these variables following PS matching could lead to overadjustment.", and [redacted] p.11 "2.1.7.1 Propensity score matching results", and "characteristics were generally well matched between" p.12 "The EAG has no significant concerns regarding the PS matching results"	Although the company stated these covariates ~~matched~~ **weighted to** those included in the OPTIMISE-CKD adjusted analyses by Tangri (2024)[8] it appears that, unlike Tangri (2024), the Additional Data analyses excluded time since CKD diagnosis and previous hospitalization from PS **weighting** ~~matching~~, and did not include an interaction between angiotensin receptor/neprilysin inhibitor (ARNI) and heart failure for **weighting** ~~matching~~ patients." "Therefore, the EAG believes that the decision to further adjust for these variables following PS **weighting** ~~matching~~ could lead to overadjustment." [redacted] "2.1.7.1Propensity score **weighting** ~~matching~~ results" "characteristics were generally well ~~matched~~ **weighted** between"		

Description of problem	Description of proposed amendment	Justification for amendment	EAG Response
p.13 “subpopulations with eGFR data at follow-up were well-matched”	“The EAG has no significant concerns regarding the PS **weighting** ~~**matching**~~ results” “subpopulations with eGFR data at follow-up were well-~~**matched**~~ **weighted**”		

Issue 2 Typographical and referencing errors

Description of problem	Description of proposed amendment	Justification for amendment	EAG Response
The EAG report 17/03/2025 states that: P. 10, “Although inclusion criteria broadly reflected those of the EMPA-KIDNEY trial, the Optum CDM population was significantly older overall (mean age 76 years in the dapagliflozin and empagliflozin groups, versus 64 years in the trial). The prevalence of T2D was also significantly higher (75% and 82% in the dapagliflozin and empagliflozin groups, versus 45% in the EMPA-	The Company kindly requests that this text is amended as follows: “Although inclusion criteria broadly reflected those of the EMPA-KIDNEY trial, the Optum CDM population was ~~**significantly**~~ **substantially** older overall (mean age 76 years in the dapagliflozin and empagliflozin groups, versus 64 years in the trial). The prevalence of T2D was also ~~**significantly**~~ **substantially** higher (75% and 82% in the dapagliflozin and empagliflozin groups, versus 45% in the EMPA-KIDNEY empagliflozin arm).”	Typographical error. No statistical analyses have been conducted to compare the Optum CDM analysis baseline characteristics compared to those from the EMPA-KIDNEY trial or the UK CKD population. Therefore, the terminology significant is incorrect.	The terminology is not incorrect as it was not referring to *statistical* significance. However, to avoid any confusion, the term has been replaced as suggested.

Description of problem	Description of proposed amendment	Justification for amendment	EAG Response
KIDNEY empagliflozin arm).” P.11, “Compared with the UK CKD population, the Optum CDM analysis population significantly overrepresents patients with albuminuria (uACR > 200). It also significantly underrepresents people with eGFR between 45 and 90 mL/min/m2 relative to patients with lower eGFR”	“Compared with the UK CKD population, the Optum CDM analysis population ~~**significantly**~~ **substantially** overrepresents patients with albuminuria (uACR > 200). It also ~~**significantly**~~ **substantially** underrepresents people with eGFR between 45 and 90 mL/min/m2 relative to patients with lower eGFR”		
The EAG report 17/03/2025 states that: P.5, “Analyses were conducted over two time periods, which are described in Additional Data 11112024, Section 2.4, p.12.”	The Company kindly requests that this text is amended as follows: “Analyses were conducted over two time periods, which are described in Additional Data 11112024, Section 2.4, p.~~12~~**29**.”	Referencing error.	Amended.