National Institute for Health and Care Excellence

Health Technology Evaluation

Empagliflozin for treating chronic kidney disease ID6131
Response to stakeholder organisation comments on the draft remit and draft scope

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Comment 1: the draft remit and proposed process

Section	Stakeholder	Comments [sic]	Action
Appropriateness of an evaluation and proposed evaluation route	Boehringer Ingelheim	This topic is appropriate to be appraised by NICE via the Single Technology Appraisal (STA) evaluation route.	Comment noted. No action required.
	AstraZeneca	This technology should be appraised through the single technology appraisal process to ensure that the evidence is evaluated in full.	Comment noted. No action required.
	Kidney Care UK	No comment	No action required.
	Kidney Research UK	We welcome the evaluation of empagliflozin given the practice changing findings from the chronic kidney disease (CKD) trials of SGLT2 inhibitors. The EMPA-KIDNEY trial results indicate that the drug would make a significant impact on the risk of progression to kidney failure and might also have a beneficial effect on the risk of cardiovascular events. There are significant levels of unmet need associated with kidney disease on many levels. There are currently 2.3 million people registered with CKD across the UK, and the numbers are rising. When kidneys fail, patients need either dialysis or a transplant to survive. Both options, if available, are	Comment noted. No action required.

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		gruelling, requiring regular, extensive medical treatment. A transplant is not a cure, lasting on average twenty years, and the fear of infection or rejection of the transplant has a significant impact upon patients' mental health.	
	UK Kidney Association	This is a highly appropriate consultation with the high quality of the evidence base. The evaluation proposed is appropriate.	Comment noted. No action required.
Wording	Boehringer Ingelheim	Yes, the wording of the remit, specifically "To appraise the clinical and cost effectiveness of empagliflozin within its marketing authorisation for treating chronic kidney disease" is appropriate.	Comment noted. No action required.
	AstraZeneca	None	No action required.
	Kidney Care UK	The remit states the clinical and cost effectiveness of empagliflozin will be appraised within its marketing authorisation for treating chronic kidney disease. The population to be considered is adults with CKD. However, the drug does not yet have a marketing authorisation for treating CKD. We suggest the remit needs to be reworded to address this.	Comment noted. NICE aims to provide draft guidance to the NHS as close as possible to the date when the marketing authorisation for a technology is granted. No action required.
	Kidney Research UK	We are happy with the proposed wording of the remit.	Comment noted. No action required.
	UK Kidney Association	None	No action required.
Timing issues	Boehringer Ingelheim	CKD is associated with significant excess renal and cardiovascular morbidity and mortality, harmful reductions in patients' health related quality of life (HRQoL), and high-cost renal replacement therapy [1]. Timely NICE evaluation and recommendation of empagliflozin will address an unmet need	Comment noted. NICE aims to provide draft guidance to the NHS as

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		by providing a new nephroprotective treatment option for a broad group of patients with CKD, including those for whom limited treatment options are currently available. EMPA-KIDNEY was a phase III, randomized, double-blind, placebo-controlled clinical trial designed to assess the effect of 10mg of empagliflozin (on top of standard of care), in reducing the risk of kidney disease progression or CV death in adult patients with CKD, with or without diabetes [2]. EMPA-KIDNEY was stopped early due to overwhelming evidence of patient benefit [3]. Results show a 28% reduction in the primary composite outcome of first occurrence of kidney disease progression (defined as end stage kidney disease [ESKD; initiation of maintenance dialysis, or receipt of a kidney transplant], a sustained decline in eGFR to less than 10ml per minute per 1.73m^2, renal death or a sustained decrease from baseline eGFR of ≥40% from randomization) or cardiovascular death [4]. In addition to being the largest trial of sodium-glucose cotransporter-2 inhibitors (SGLT2i) in CKD to date, EMPA-KIDNEY had broad eligibility criteria that included adult CKD patients who are typically seen in clinical practice but have been under-represented in previous SGTL2i trials, including patients with and without T2D, and with wide ranges of both eGFR and levels of albuminuria [2,3]. These patients remain at risk of disease progression and its associated morbidity due to limited treatment options currently available to them. BI understand that the proposed submission date is [redacted] and request that timelines for the evaluation of empagliflozin be upheld to ensure a timely recommendation as close as possible to MHRA approval ([redacted]).	close as possible to the date when the marketing authorisation for a technology is granted. NICE has scheduled this topic into its work programme. No action required.

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		[1] Evans et. al (2022) A Narrative Review of Chronic Kidney Disease in Clinical Practice: Current Challenges and Future Perspectives. *Advances in Therapy*, 39(1):pp 33-43. [Online] Accessed 20 November 2022. Available at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8569052/ [2] The EMPA-KIDNEY Collaborative Group (2022) Design, recruitment, and baseline characteristics of the EMPA-KIDNEY trial. *Nephrology Dialysis Transplantation*, 37(7):pp 1317-1329. [Online] Accessed 18 November 2022. Available at https://academic.oup.com/ndt/article/37/7/1317/6541871 [3] Boehringer Ingelheim (2022). *Jardiance® (empagliflozin) Phase III EMPA-KIDNEY trial will stop early due to clear positive efficacy in people with chronic kidney disease.* [Online] Accessed 18 November 2022. Available at https://www.boehringer-ingelheim.com/human-health/metabolic-diseases/early-stop-chronic-kidney-disease-trial-efficacy [4] The EMPA-KIDNEY Collaborative Group (2022) Empagliflozin in Patients with Chronic Kidney Disease. *NEJM*. [Online] Accessed 18 November 2022. Available at https://www.nejm.org/doi/10.1056/NEJMoa2204233	

	AstraZeneca	Dapagliflozin is already recommended as an option for treating chronic kidney disease (CKD) in adults if:
		• it is an add-on to optimised standard care including the highest tolerated licensed dose of angiotensin-converting enzyme (ACE) inhibitors or angiotensin-receptor blockers (ARBs), unless these are contraindicated, and
		• people 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:
		  ○ have type 2 diabetes or
		  ○ have a urine albumin-to-creatinine ratio (uACR) of 22.6 mg/mmol or more
		It is established clinical care and the unmet need in the above populations is low therefore the relative urgency to the NHS is low.
			Comment noted. NICE aims to provide draft guidance to the NHS as close as possible to the date when the marketing authorisation for a technology is granted. The committee will consider all available information at the time of the committee meeting. NICE has scheduled this topic into its work programme. No action required.

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	Kidney Care UK	No comment	No action required.
	Kidney Research UK	It is important that this evaluation is looked at with urgency. Kidney disease affects around 3.5 million people in the UK, with over 1 million people unaware they have the disease. The number of people affected by chronic kidney disease is growing due to the increasing prevalence of the risk factors associated with CKD, mainly diabetes, hypertension and obesity. Recently the NHS CVDPREVENT primary care audit identified CKD as a high-risk condition for cardiovascular disease.	Comment noted. NICE aims to provide draft guidance to the NHS as close as possible to the date when the marketing authorisation for a technology is granted. NICE has scheduled this topic into its work programme. No action required.
	UK Kidney Association	Based on the recent New England of Journal of Medicine publication of a very large randomised controlled trial showing an impact on hard end-points with patients recruited down to an eGFR of 20 ml/min and on patients without significant proteinuria, based on the patient numbers and effect of the intervention then this should be a prioritised evaluation.	Comment noted. NICE aims to provide draft guidance to the NHS as close as possible to the date when the marketing authorisation for a technology is granted. NICE has scheduled this topic into its work programme. No action required.
Additional comments on the draft remit	Boehringer Ingelheim	None	No action required.
	AstraZeneca	None	No action required.

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	Kidney Care UK	None	No action required.
	Kidney Research UK	None	No action required.
	UK Kidney Association	None	No action required.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action

Background information	Boehringer Ingelheim	**There is an error in the marketing authorisations presented in the background section.**
		Empagliflozin is indicated for symptomatic heart failure across the full ejection fraction spectrum in adults; however, the draft scope authorisation refers to reduced ejection fraction only. Please cite the correct indications, as follows:
		"*Empagliflozin does have a marketing authorisation for:*
		• *the treatment of adults with insufficiently controlled type 2 diabetes mellitus as an adjunct to diet and exercise*
		  ○ *as monotherapy when metformin is considered inappropriate due to intolerance*
		  ○ *in addition to other medicinal products for the treatment of diabetes*
		• *the treatment of symptomatic chronic heart failure in adults.*"
		
		The background information generally provides accurate context on the morbidity and mortality burden of CKD relating to its association with hypertension, T2D and CVD. An omission is the inclusion of broader
			Comments noted. The background section of the draft scope is intended to give a broad introduction to the condition and is therefore not exhaustive. However, the following update has been made to the scope:
			• removed 'with ejection fraction' wording from the technology marketing

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		aetiologies and adverse outcomes of CKD. BI therefore requests the below text be added to the background information to acknowledge the total burden of CKD and the broad population included in the EMPA-KIDNEY trial: "*In addition to T2D and hypertension, there are other important aetiologies for CKD, such as glomerulonephritis [1]. Additionally, whilst CVD is a prominent CKD-associated adverse outcome, patients' morbidity burden extends further with increased risk of other adverse outcomes including infections, mineral bone disorders, and anaemia [2–4].*" [1] NHS (2019) *Overview chronic kidney disease*. [Online] Accessed 18 November 2022 Available at https://www.nhs.uk/conditions/kidney-disease/ [2] Ishigami & Matsushita (2019) Clinical epidemiology of infectious disease among patients with chronic kidney disease. *Clinical and Experimental Nephrology*, 23(4): pp. 437-447. [Online]. Accessed 24 November 2022. Available athttps://www.ncbi.nlm.nih.gov/pmc/articles/PMC6435626/ [3] Hou, Lu & Lu (2018) Mineral bone disorders in chronic kidney disease. *Nephrology*, 23 (4): pp. 88-94. Accessed 24 November 2022. Available at https://onlinelibrary.wiley.com/doi/full/10.1111/nep.13457 [4] Portoles, Martin, Broseta & Cases (2021) Anemia in Chronic Kidney Disease: From Pathophysiology and Current Treatments, to Future Agents. *Frontiers in Medicine*, 8. [Online] Accessed 24 November 2022. Available at https://www.frontiersin.org/articles/10.3389/fmed.2021.642296/full	authorisation description
	AstraZeneca	No comments	No action required.
	Kidney Care UK	Kidney Care UK recommend that the numbers of people receiving renal replacement therapy (dialysis and transplant) are included. The latest data (2020) from the UK Renal Registry shows 68,249 are currently on renal replacement therapy in the UK.	Comment noted. The scope has been updated to include the renal replacement therapy estimates.

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	Kidney Research UK	In addition to discussion of high blood pressure as a common cause of kidney failure, it should be added that diabetes and obesity are also risk factors associated with chronic kidney diseases, and that NHS CVDPREVENT primary care audit recently identified CKD as a high-risk condition for cardiovascular disease.	Comments noted. The background section of the draft scope is intended to give a broad introduction to the condition and is therefore not exhaustive. No action required.
	UK Kidney Association	Appropriate	Comment noted. No action required.
Population	Boehringer Ingelheim	The population definition of 'adults with chronic kidney disease having individually optimised standard care' is appropriate. This population is reflective of the patient population included in the EMPA-KIDNEY trial and NHS England CKD patients who will be eligible for empagliflozin.	Comment noted. No action required.
	AstraZeneca	No comments	No action required.
	Kidney Care UK	Yes	Comment noted. No action required.
	Kidney Research UK	We believe that the evidence indicates that empagliflozin (or other SGLT2i) should be used in patients with CKD at risk of progression, regardless of any response to treatment with standard care. Its benefits appear to be proportionally larger than those of Angiotensin-converting enzyme inhibitors (ACEIs) or Angiotensin II type 1 receptor blockers (ARB). Among such patients receiving standard care, risks of further progression and premature cardiovascular morbidity and mortality remain, so SGLT2i should be used to	Comment noted. No action required.

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		reduce these risks. They will likely be most effective early in the treatment of CKD, with the potential for delivery in primary care according to certain criteria.	
	UK Kidney Association	Appropriate	Comment noted. No action required.
Subgroups	Boehringer Ingelheim	BI contends that there are no groups within the population that should be considered separately. Further subgroup analyses are likely to offer limited actionable evidence for NICE as the EMPA- KIDNEY trial demonstrated generally comparable benefits across all subgroups, including those with and without T2D and CVD. Clinical effectiveness for the groups with CVD and T2D has already been established in the CKD subgroups of previous relevant trials of empagliflozin, specifically EMPA-REG OUTCOME, EMPEROR-Reduced, and EMPEROR-Preserved [1–4]. [1] Wanner et. al (2018) Empagliflozin and Clinical Outcomes in Patients with Type 2 Diabetes Mellitus, Established Cardiovascular Disease, and Chronic Kidney Disease. *Circulation*, 137 (2): pp. 119-129. [Online] Accessed 19 November 2022. Available at https://www.ahajournals.org/doi/epub/10.1161/CIRCULATIONAHA.117.028268 [2] Zannad et al. (2021) Cardiac and Kidney Benefits of Empagliflozin in Heart Failure Across the Spectrum of Kidney Function. *Circulation*, 143 (4): pp. 310-321. [Online] Accessed 21 November 2022. Available at https://www.ahajournals.org/doi/epub/10.1161/CIRCULATIONAHA.120.051685 [3] Packet et. al (20220) Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure. *NEJM*, 383: pp.1413-1424. [Online] Accessed 29 November 2022. Available at https://www.nejm.org/doi/full/10.1056/NEJMoa2022190 [4] Anker et. al (2021) Empagliflozin in Heart Failure with a Preserved Ejection Fraction. *NEJM*, 385: pp. 1451-1461. [Online] Accessed 29 November 2022. Available at https://www.nejm.org/doi/full/10.1056/NEJMoa2107038	Comment noted. The appraisal committee will consider all relevant evidence and make recommendations for relevant subgroups where appropriate.

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	AstraZeneca	Albuminuric and non-albuminuric CKD phenotypes are different in their pathophysiology, clinical characteristics and the impact on disease progression. In the EMPA-KIDNEY study the benefit effect of empagliflozin was not consistent across the albuminuric and non-albuminuric subgroups; therefore, the following subgroups need to be examined separately to consider the clinical and cost effectiveness of empagliflozin in the broad population included in the study: • People by levels of albuminuria (as defined by Kidney Disease: Improving Global Outcomes (KDIGO- A1, A2 and A3) • People with mild to moderate eGFR decline and microalbuminuria Chronic Kidney Disease Epidemiology Collaboration (CKD – EPI) eGFR 45-90 with a uACR >200 mg/g or protein-to-creatinine ratio (PCR) >300 mg/g 1. OR • People with severe eGFR decline >20-<45 ml/min Diabetic vs non-diabetic phenotypes of CKD are different in terms of pathophysiology, clinical characteristics and impact on disease progression. In the EMPA-KIDNEY study the subgroups by diabetes status showed differing magnitudes of benefit and so it would be pertinent to understand the impact of albuminuria status within the diabetic and non-diabetic groups to examine the clinical and cost effectiveness of empagliflozin in these subgroups. People with CKD often have heart failure and these conditions, and the risk of disease progression is higher with comorbid disease. The benefit of empagliflozin in the subgroup of CKD with and without heart failure is important in evaluating clinical and cost effectiveness for this population of	Comment noted. The appraisal committee will consider all relevant evidence and make recommendations for relevant subgroups where appropriate.

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		patients given that a major driver of benefit and cost effectiveness is hospitalisation for heart failure which will be more frequent in those patients with established heart failure.	
	Kidney Care UK	Progression of CKD has been found to be more rapid in specific groups and it may be necessary to consider these groups separately. eg “Some ethnic groups, particularly Bangladeshi, appear to be more sensitive to the combined effects of proteinuria and hypertension than other ethnic groups. Clinicians need to be aware that younger people with diabetes (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)	Comment noted. The appraisal committee will consider all relevant evidence and make recommendations for relevant subgroups where appropriate.
	Kidney Research UK	The review should consider patients for whom the current dapagliflozin technology appraisal does not recommend treatment. This includes patients with eGFR <25 mL/min/1.73m2, patients without diabetes with ACR <25 mg/mmol and patients not on ACEi or ARB. Empagliflozin has been studied in patients with CKD in whom RAS inhibitors are not tolerated or indicated, so its use in patients with CKD not on RAS inhibitors should be considered by the appraisal.	Comments noted The appraisal committee will consider all relevant evidence and make recommendations for relevant subgroups where appropriate.
	UK Kidney Association	Not beyond those stated in the draft scope	Comment noted. No action required.
Comparators	Boehringer Ingelheim	**The comparators listed in the scope are appropriate.** The EMPA-KIDNEY trial studied patients with CKD, with or without T2D, with an eGFR between 20 and 45 ml/min/1.73m^2, or an eGFR between 45 and 90 ml/min/1.73m^2 with a uACR of at least 200mg/g (22.6 mg/mmol) [1]. BI are seeking a recommendation for empagliflozin for the broad population	Comments noted. No action required.

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		represented in the EMPA-KIDNEY trial. Thus, the appropriate comparator comprises established clinical management for this broad range of patients. BI acknowledges dapagliflozin as a relevant comparator for a specific sub-group of the CKD population, as per the TA775 recommendations. Dapagliflozin is recommended as an option for treating CKD in adults only if [2]: • it is an add-on to optimised standard care including the highest tolerated licensed dose of ACEi or ARBs, unless these are contraindicated, and • people have an eGFR of 25–75 ml/min/1.73 m^2 at the start of treatment and ○ have type 2 diabetes or ○ have a uACR of 22.6 mg/mmol or more. [1] The EMPA-KIDNEY Collaborative Group (2022) Empagliflozin in Patients with Chronic Kidney Disease. *NEJM*. [Online] Accessed 18 November 2022. Available at https://www.nejm.org/doi/10.1056/NEJMoa2204233 [2] NICE (2022) *Dapagliflozin for treating chronic kidney disease (TA775)*. [Online] Accessed 17 November 2022. Available at https://www.nice.org.uk/guidance/ta775/resources/dapagliflozin-for-treating-chronic-kidney-disease-pdf-82611498049477	
	AstraZeneca	**Which treatments are considered to be established clinical practice in the NHS for chronic kidney disease? How often are statins, antiplatelets/anticoagulants, SGLT2 inhibitors given in this population?** In the UK the only licenced SGLT2i recommended by NICE for the treatment of CKD is dapagliflozin in patients with an uACR of >22.6 mg/mmol or type 2 diabetes. ACE inhibitors and ARBs are recommended in patients with a uACR of >70 mg/mmol regardless of underlying comorbidities, and for patients with lower	Comments noted. No action required.

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		levels of albuminuria who have comorbidities such as hypertension (recommended if uACR is >30 mg/mmol) or diabetes (recommended if uACR is >3 mg/mmol), who can tolerate such treatment. Antiplatelets are recommended for the secondary prevention of cardiovascular (CV) disease in patients with established CV disease who have had a CV event in the past. They are not commonly used as primary prevention and are avoided in patients with advanced stages of CKD due to increased risk of bleeding. Statins are recommended for the primary prevention of CV disease in patients who have 10% or greater risk of developing CV disease within the next 10 years or for secondary prevention in patients with established CV disease.[1,2] Preliminary data analyses from the UK Clinical Practice Research Datalink (CPRD) shows that ACE inhibitors are used by [redacted] of patients, ARBs by [redacted] of patients, statins by [redacted] of patients and antiplatelets by [redacted] of patients around the time of CKD diagnosis.[3] Based on UK clinical input, treatment with ACE inhibitors or ARBs is not universal across all CKD patients, in part due to guideline recommendations and in part due to tolerability issues and challenges with repeat appointments for dose titrations which can be difficult for patients to adhere to.[4] In UK clinical practice, all patients with CKD should have their cardiovascular risk managed with a statin for primary and secondary cardiovascular disease prevention. In addition, blood pressure control is fundamental in the management of CKD. In albuminuric patients irrespective of diabetes status Renin-angiotensin-aldosterone system inhibitors (RAASi) at maximum tolerated dose is recommended. ***In clinical practice, would people always be stable on the maximum tolerated dose of ACE inhibitors or ARBs before empagliflozin would be considered?***	

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		A significant consideration to tolerating RAAS inhibition is age, given the majority of the CKD population particularly in non-diabetics have an average age over [redacted] years[5] this can lead to intolerance when up titrating RAASi for example by causing hypotension, dizziness and increasing the risk of falls. As per NICE recommendations, the use of RAASi in CKD is defined by albuminuria status. It is therefore essential that patients are tested to inform prognosis and treatment decision. **Where do you consider empagliflozin will fit into the existing care pathway for chronic kidney disease?** The EMPA-KIDNEY study investigated the cardiovascular and renal benefits of empagliflozin in a broad group of patients with CKD. Whilst the study met its primary endpoint, it may appear that benefit was only seen in those patients with an ACR of 300 mg/g (33.9 mg/mmol). Therefore, empagliflozin would be positioned in patients with CKD on maximum tolerated ACEi or ARB and an ACR>33.9mg/mmol. Whilst the EMPA-REG study may have shown an observed renal benefit in type 2 diabetic patients with lower levels of uACR, this patient population was only representative of type 2 diabetics with atherosclerotic cardiovascular disease and are therefore a population with established cardiovascular disease and therefore inherently at an increased risk of adverse clinical outcomes. This population is not representative of a broader type 2 diabetic CKD population. **In what circumstances would empagliflozin be added to standard care? Would it ever be used to treat people whose CKD is responding to treatment with standard care?** Patients in the EMPA-KIDNEY study were 'required to be taking a clinically appropriate dose of a single-agent RAS inhibitor', unless not indicated or not tolerated. RAAS inhibition is recommended by NICE in patients with a uACR >33.9 mg/mmol, whilst residual risk with RAASi exists, in the EMPA-KIDNEY	

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		study benefit of empagliflozin was seen in patients on RAAS inhibition with few patients not on renin-angiotensin system (RAS) inhibition and benefit not clearly defined with confidence intervals crossing the line of unity.	
	Kidney Care UK	No comment	No action required.
	Kidney Research UK	The appropriate management of patients with chronic kidney disease of any cause includes: ▪ strict blood pressure control ▪ use of a renin-angiotensin system inhibitor if indicated and tolerated (as described in NICE NG203) ▪ statins Anitplatelet/anticoagulant treatments are not indicated in CKD unless there is another clinical indication (and conversely, the presence of CKD should not be a justification for not using such therapy if indicated). Our clinical experts have indicated that the SGLT2 inhibitor (SGLT2i) dapagliflozin is becoming increasingly used following the publication of the DAPA-CKD trial, the update to its marketing authorisation and subsequent NICE appraisal (TA 775).	Comments noted. No action required.
	UK Kidney Association	Agree	Comment noted. No action required.
Outcomes	Boehringer Ingelheim	**The outcomes listed in the scope are appropriate.** The inclusion of outcomes for hospitalisation in addition to cardiovascular outcomes, renal outcomes, and markers of disease progression allow for a holistic view of the total benefits empagliflozin has to offer to a wide population of adults with CKD.	Comment noted. The outcomes listed in the scope are not exhaustive. Companies are encouraged to provide all relevant data, that will be informative for the

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			appraisal. No action required.
	AstraZeneca	The outcomes listed are appropriate for this population in UK clinical practice, however AstraZeneca would like to strongly suggest that the below outcomes are considered: • End stage renal disease (ESRD): Maintenance Dialysis or Kidney transplantation o The main drivers of cost to a healthcare system is renal replacement therapy; namely dialysis and transplantation, therefore endpoints that show delaying the progression to ESRD; the initiation of dialysis and transplantation are the most important and valuable outcomes to evaluate the clinical and cost effectiveness of a new treatment for CKD. Decline in eGFR slope alone is insufficient to evaluate the clinical and cost effectiveness. • Hospitalisation for Heart Failure o People with CKD often have heart failure and these conditions share similar risk factors in terms of hypertension and type 2 diabetes. Hospitalisation for heart failure represents a significant cost to the healthcare system. Therefore, the benefit that empagliflozin has on hospitalisations for heart failure in the broad CKD population studied in the EMPA-KIDNEY trial should be included in the cost effectiveness analysis of empagliflozin. o Whilst the EMPA-REG study showed an observed reduction in hospitalisations for heart failure, this patient population was only representative of type 2 diabetics with atherosclerotic cardiovascular disease and therefore not representative of a broader type 2 diabetic CKD population.	Comments noted. The outcomes listed in the scope are not exhaustive. Kidney replacement to capture disease progression is included in the scope Hospitalisation included as an outcome incorporates all hospitalisations including due to heart failure associated with CKD Companies are encouraged to provide all relevant data that will be informative for the appraisal. No action required.

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	Kidney Care UK	Yes	Comment noted. No action required.
	Kidney Research UK	The eGFR outcome should be “eGFR slopes” in place of “eGFR”, and in particular the outcome to emphasize are chronic eGFR slopes (which take account of reversible acute dip in eGFR).	Comment noted. The outcomes listed in the scope are not exhaustive. Companies are encouraged to provide all relevant data, that will be informative for the appraisal. No action required.
	UK Kidney Association	Appropriate	Comment noted. No action required.
Equality	Boehringer Ingelheim	**BI believes that a positive recommendation of empagliflozin enabling broad access for patients across primary and secondary care settings and the multidisciplinary care team can help address inequalities of access to care for CKD patients, particularly in areas with limited presence of secondary and specialist care facilities.** Principle 9 of NICE’s Social Value judgements as part of its statement highlights the goal to reduce health inequalities across protected characteristics as well as considering those arising from socioeconomic factors [1]. Socio-economic disparities are associated with health inequalities in England, with more socially advantaged patients often receiving better access to secondary and specialist care in the NHS [2]. Resource constraints in a post-COVID-19 healthcare system may further exacerbate pre-existing inequalities in access to secondary and specialist care in the NHS. Secondary care in CKD is largely focussed on patients with	Comments noted. The appraisal committee will consider all relevant equality issues and make recommendations for specific groups where appropriate.

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		ESKD, and barriers in ease and affordability of travel may further complicate access to these settings. BI therefore propose broad access to empagliflozin for adults with CKD across primary and secondary care settings, as well as across the full multidisciplinary team as CKD patients may be seen by a variety of specialities in clinical practice. Broad access is important for alleviating any health inequalities in terms of access to nephroprotective treatments for CKD patients. [1] NICE (2020) Our principals: The Principals that guide the development of NICE guidance and standards. [Online] Accessed 18 November 2022. Available at https://www.nice.org.uk/about/who-we-are/our-principles [2]. Cookson, R., Propper, C., Asaria, M., Raine, R (2016) Socioeconomic inequalities in health care in England. The Journal of Applied Public Economics, 37(3-4): pp. 371-403. [Online] Accessed 18 November 2022. Available at https://onlinelibrary.wiley.com/doi/epdf/10.1111/j.1475-5890.2016.12109	
	AstraZeneca	No comments	No action required.
	Kidney Care UK	The scope should consider the difference in risk of rapid progression of CKD in different groups with protected characteristics, and consider sub-analysis of these groups. Ethnicity: (see above) Some ethnic groups, particularly Bangladeshi, appear to be more sensitive to the combined effects of proteinuria and hypertension than other ethnic groups. Age: Clinicians need to be aware that younger people with diabetes with CKD (<55 years) are at twice the risk of rapid progression than those > 65 years and thus need closer monitoring, management of risk factors and early specialist review to delay progression.	Comments noted. The appraisal committee will consider all relevant equality issues and make recommendations for specific groups where appropriate.

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	Kidney Research UK	Kidney disease disproportionally impacts people from deprived communities and ethnic minority groups. They are more likely to develop kidney disease, progress faster to renal failure and therefore 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.	Thank you for your comment. The appraisal committee will consider all relevant equality issues and make recommendations for specific groups where appropriate.
	UK Kidney Association	To my knowledge none of these potential issues should be a problem for this appraisal	Comment noted. No action required.
Other considerations	Boehringer Ingelheim	No further considerations.	Comment noted. No action required.
	AstraZeneca	**Intervention/Technology** The current draft scope states that the intervention/technology considered in this appraisal is empagliflozin. AstraZeneca requests that the description of the intervention is updated to “Empagliflozin in combination with optimised standard care (including treatment with an ACE inhibitor or ARB)” in line with the clinical trial of EMPA-KIDNEY and current clinical practice.	Comment noted. The intervention section of the scope has been updated to ‘Empagliflozin in combination with optimised standard care’
	Kidney Care UK	None	No action required.
	Kidney Research UK	The time-horizon of the health economic analyses is crucial as CKD can progress over many years, but still result in kidney failure (which either requires treatment with kidney replacement therapy or is fatal). Kidney transplants are also not permanent, on average lasting 20 years.	Comment noted. The committee will consider a time horizon long enough to reflect all important differences in

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		Delaying progression is very valuable to patients and the NHS and this must be considered when assessing SGLT2i in people with more slowly-progressive CKD. SGLT2i also reduces risk of hospitalisation (of any cause). We believe that a discounting rate of 1.5% should be presented, per NICE's view that there is an evidence-based case for change from 3.5%, to adequately consider the long term value of the treatment. Cost effectiveness analyses need to consider not just Quality of Life, but also savings from a reduction in hospitalisation and lower risk of the need for dialysis or transplantation. The review should also consider revising NICE guidelines on the use of SGLT2 inhibitors in terms of monitoring after initiation. EMPA-KIDNEY did not remeasure kidney function until 2 months after starting empagliflozin and was found to be safe. Unlike starting RAS inhibitors, there is no proven risk of acute kidney injury or hyperkalaemia on starting SGLT2 inhibitors. Simplified recommendations on how to initiate SGLT2 inhibitors would help ensure more rapid implementation in those who will benefit. This would be a barrier to implementation, with primary care services reluctant to start enacting upon a recommendation if there is burden of extra, unnecessary monitoring.	costs or outcomes between the technologies being compared. The committee may consider analyses using a non-reference-case discount rate of 1.5% per year for both costs and health effects, if, in the committee's considerations, all of the following criteria are met: • The technology is for people who would otherwise die or have a very severely impaired life. • It is likely to restore them to full or near-full health. • The benefits are likely to be sustained over a very long period.

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			The committee will consider all potential resource costs and savings that would be expected from introducing Empagliflozin for chronic kidney disease.
	UK Kidney Association	Nil additional suggested	Comment noted. No action required.
Questions for consultation	Boehringer Ingelheim	**Which treatments are considered to be established clinical practice in the NHS for chronic kidney disease?** Treatment for CKD aims to prevent or delay progression of CKD, reduce the risk of complications, and reduce the risk of cardiovascular disease. Established clinical practice in the NHS is very much individually optimised for each patient. In line with the NG203 recommendations, treatments for patients with CKD may include [1]: - CVD risk management treatments including statins, antiplatelets, and anticoagulants - Management of comorbid conditions and risk factors for progression such as T2D and hypertension - ACEi or ARBs (as per criteria detailed below) - SGLT2i (as per criteria detailed below) - Additional treatments for the management of complications such as anaemia	Comments noted. No action required.

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		NG203 recommends that ACEi or ARBs should be added to standard of care (titrated at the highest licensed dose that the patient can tolerate) in adults with either [1]: • Hypertension and an ACR above 30 mg/mmol • Concurrent T2D and an ACR above 3 mg/mmol • An ACR above 70 mg/mmol (without concurrent T2D). SGLT2is are recommended to patients with CKD as an add-on to the above optimised standard of care. They can be added for adults with concurrent T2D who are taking an ACEi or ARB (titrated to the highest licensed dose that they can tolerate) if [2]: • ACR is above 30 mg/mmol; and • The patient meets the criteria in the drugs relevant marketing authorisation (including eGFR thresholds). Specifically, dapagliflozin can be added for adults who are taking an ACEi or ARB (titrated to the highest licensed dose that they can tolerate) if [3]: • The patient has an eGFR between 25 and 75 ml/min/1.73 m^2; and • They have T2D or a uACR 22.6 mg/mmol or more. Although recommended within NG203, it should be noted that ACEi or ARBs do not always feature within 'individually optimised standard care'. [redacted] suggest that approximately [redacted] of CKD patients in England currently receive an ACEi or ARB. DISCOVER CKD, an observational cohort study investigating treatment patterns in patients with CKD, demonstrated that only 51.5% of patients were prescribed an ACEi or ARB in the UK CPRD cohort [4]. The limited uptake of ACEi or ARBs seen in clinical practice is aligned with the background standard care received in EMPA-KIDNEY, in which approximately 85% of patients received an ACEi or ARB [5]. In EMPA-KIDNEY, standard care was the responsibility of doctors who were asked to	

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		ensure individualized standard of care, including management of cardiovascular risk factors and other existing comorbidities (e.g. hypertension, diabetes etc.), and to prescribe an appropriate dose of a RAS-inhibitor (ACEi or ARB), unless such treatment was either not tolerated or not indicated. [1] NICE (2021) *Chronic kidney disease: assessment and management* (NG203). [Online] Accessed 17 November 2022. Available at https://www.nice.org.uk/guidance/ng203/resources/chronic-kidney-disease-assessment-and-management-pdf-66143713055173 [2] NICE (2015) *Type 2 diabetes in adults: management (NG28).* [Online] Accessed 17 November 2022. Available at https://www.nice.org.uk/guidance/ng28/resources/type-2-diabetes-in-adults-management-pdf-1837338615493 [3] NICE (2022) *Dapagliflozin for treating chronic kidney disease (TA775).* [Online] Accessed 17 November 2022. Available at https://www.nice.org.uk/guidance/ta775/resources/dapagliflozin-for-treating-chronic-kidney-disease-pdf-82611498049477 [4] James, et al. (2022) Low adherence to kidney disease: improving global outcomes 2012 CKD clinical practice guidelines despite clear evidence of utility. *Kidney International Reports*, 7(9):pp 2059-2070. [Online] Accessed 21 November 2022. Available at https://www.sciencedirect.com/science/article/pii/S2468024922014358 [5] The EMPA-KIDNEY Collaborative Group (2022) Empagliflozin in Patients with Chronic Kidney Disease. *NEJM*. [Online] Accessed 18 November 2022. Available at https://www.nejm.org/doi/10.1056/NEJMoa2204233 **How often are statins, antiplatelets/anticoagulants, SGLT2 inhibitors given in this population?** **Statins** DISCOVER CKD, an observational cohort study in patients with CKD, reported that 52.9% of patients were prescribed statins in the UK CPRD cohort [1]. Further, a London based multi-ethnic cohort reported that statins are presribed in 54.9% and 23.3% of CKD patients with and without hypertension, respectively [2].	

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		SGLT2i [redacted] suggest SGLT2i are prescribed in [redacted] of all CKD patients, [redacted] in CKD patients with comorbid T2D. **Anticoagulants/antiplatets.** BI does not currently have data on the use of anticoagulants/antiplatets for the management of cormobid CVD among patients with CKD. [redacted] [1] James, et al. (2022) Low adherence to kidney disease: improving global outcomes 2012 CKD clinical practice guidelines despite clear evidence of utility. *Kidney International Reports*, 7(9):pp 2059-2070. [Online] Accessed 21 November 2022. Available at https://www.sciencedirect.com/science/article/pii/S2468024922014358 [2] Carpio, et al. (2021) Hypertension and cardiovascular risk factor management in a multi-ethnic cohort of adults with CKD: a cross sectional study in general practice. *Journal of Nephrology*, 35:pp 901-910. [Online] Accessed 21 November 2022. Available at https://link.springer.com/article/10.1007/s40620-021-01149-0 **In clinical practice, would people always be stable on the maximum tolerated dose of ACE inhibitors or ARBs before empagliflozin would be considered?** No. As discussed above, in clinical practice (and also in the EMPA-KIDNEY trial population [1]) not all CKD patients receive ACEi or ARBs. Reasons for non-universal uptake in clinical practice include issues with tolerability and	

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		contraindications (especially in patients at risk of hypotension or hyperkalaemia), which are well known [2]. Among those who do receive an ACEi or ARB, dosing may be suboptimal. Clinical experts have indicated that while traditional advice is to titrate and stabilise on the maximum tolerated dose before adding another treatment option, there are patients for whom this is not possible. Furthermore, clinical experts have highlighted that in the treatment of heart failure, clinical practice has recently evolved so that different pillars of care – including both ACEi/ARBs and SGLT2i – are initiated as soon as possible, without any delay to titrate to maximum tolerated doses. It is the view of some clinical experts that the treatment of CKD is likely to evolve in a similar way due to emerging evidence of the benefits of SGLT2i. The EMPA-KIDNEY trial demonstrates empagliflizon offers benefits to patients irrespective of whether or not background therapy includes ACEi or ARBs [1]. [1] The EMPA-KIDNEY Collaborative Group (2022) Empagliflozin in Patients with Chronic Kidney Disease. *NEJM*. [Online] Accessed 18 November 2022. Available at https://www.nejm.org/doi/10.1056/NEJMoa2204233 [2] The ONTARGET Investigators (2008) Telmisartan, ramipril, or both in patients in patients at high risk for vascular events. *NEJM*, 358:pp 1547-1559. [Online] Accessed 23 November 2022. Available at https://www.nejm.org/doi/full/10.1056/NEJMoa0801317 **Where do you consider empagliflozin will fit into the existing care pathway for chronic kidney disease?** Empagliflozin should be considered at the earliest possible point in all patients at risk of CKD disease progression and can be used in combination with individually optimised standard of care (which may or may not include ACEi or ARB treatment).	

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		The EMPA-KIDNEY trial added empagliflozin 10mg to optimised standard of care, which included ACEi or ARBs (unless contraindicated or not tolerated), CV risk management treatments, antihypertensive treatments, and antidiabetic treatments. The trial included patients with or without T2D and included a wider range of eGFR and uACR levels than in other SGLT2i trials [1]. Thus, BI suggest that empagliflozin should be considered in all patients at risk of CKD disease progression in addition to their current individually optimised care. Empagliflozin offers a new treatment option across the full breadth of the CKD population. [1] The EMPA-KIDNEY Collaborative Group (2022) Empagliflozin in Patients with Chronic Kidney Disease. *NEJM*. [Online] Accessed 18 November 2022. Available at https://www.nejm.org/doi/10.1056/NEJMoa2204233 **In what circumstances would empagliflozin be added to standard care? Would it ever be used to treat people whose CKD is responding to treatment with standard care?** CKD is a complex and progressive disease that is classified by KDIGO categories (considering both eGFR and uACR) [1]. There is no standard criteria of response for CKD management; all CKD patients across all KDIGO categories maintain a residual risk of disease progression and other adverse outcomes. Results from the EMPA-KIDNEY trial demonstrate a significant treatment benefit for empagliflozin as compared to placebo, which was optimised standard of care comprising a combination of treatments [2]. Therefore, BI suggest that empagliflozin should be added to current individually optimised care for all patients at risk of progression of their CKD, in order to reduce their residual risk of progression and adverse outcomes. [1] NICE (2021) *Chronic kidney disease: assessment and management (NG203).* [Online] Accessed 17 November 2022. Available at	

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		https://www.nice.org.uk/guidance/ng203/resources/chronic-kidney-disease-assessment-and-management-pdf-66143713055173 [2] The EMPA-KIDNEY Collaborative Group (2022) Empagliflozin in Patients with Chronic Kidney Disease. *NEJM*. [Online] Accessed 18 November 2022. Available at https://www.nejm.org/doi/10.1056/NEJMoa2204233 **Would empagliflozin be a candidate for managed access?** No. **Do you consider that the use of empagliflozin can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation?** No. **Please identify the nature of the data which you understand to be available to enable the committee to take account of these benefits.** Not applicable. **NICE intends to evaluate this technology through its Single Technology Appraisal process. We welcome comments on the appropriateness of appraising this topic through this process. (Information on NICE's health technology evaluation processes is available at https://www.nice.org.uk/about/what-we-do/our-programmes/nice-guidance/nice-technology-appraisal-guidance/changes-to-health-technology-evaluation).** The proposed evaluation route (STA) is appropriate. **NICE's health technology evaluations: the manual states the methods to be used where a cost comparison case is made. Would it be appropriate to use the cost-comparison methodology for this topic?**	

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		BI believes cost-comparison methodology is appropriate for the comparison vs dapagliflozin, within the population in which dapagliflozin is recommended, specifically in adults only if [1]:
		• it is an add-on to optimised standard care including the highest tolerated licensed dose of ACEi or ARBs, unless these are contraindicated, and
		• people have an eGFR of 25–75 ml/min/1.73 m^2 at the start of treatment and
		  ○ have type 2 diabetes or
		  ○ have a uACR of 22.6 mg/mmol or more.
		
		Within this population, clinical expert opinion has indicated that empagliflozin and dapagliflozin are likely to provide similar health benefits (and similar costs).
		For the comparison vs established clinical practice (without dapagliflozin), a cost-utility approach is appropriate and so the STA route remains appropriate for this topic.
		
		Is the new technology likely to be similar in its clinical efficacy and resource use to any of the comparators?
		As noted above, clinical expert opinion has indicated that empagliflozin and dapagliflozin are likely to provide similar health benefits (and similar costs) among the population in which dapagliflozin is recommended [1].
		A qualitative comparison shows that the clinical efficacy of empagliflozin in terms of the primary outcome in the EMPA-KIDNEY trial is similar to that for dapagliflozin in the DAPA-CKD trial. However, important differences exist that cannot be fully adjusted for within the evidence network:	

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		• EMPA-KIDNEY included patients with varying levels of albuminuria, whereas DAPA-CKD only included patients with uACR ≥200 mg/g (≥22.6 mg/mmol) • EMPA-KIDNEY included patients with a broad range of eGFR, from 20 to 90 ml/min/1.73m^2, including 34.5% with an eGFR <30 ml/min/1.73m^2, whereas DAPA-CKD only included patients with an eGFR between 25 and 75 ml/min/1.73m^2 • EMPA-KIDNEY included a smaller proportion of patients with T2D vs DAPA-CKD (46% vs 67.5%) • EMPA-KIDNEY included a smaller proportion of patients with a history of CVD vs DAPA-CKD (26.7% vs 37.4%) BI does not expect an indirect treatment comparison (ITC) approach will reduce uncertainty in the comparative effectiveness between empagliflozin and dapagliflozin due to important differences in their respective trial designs and populations, which include substantial differences in baseline risk of key outcomes. Given the difficulty in providing a meaningful comparison with dapagliflozin with available technical tools, consideration should be given to a cost-comparison approach for the economic evaluation in comparison with dapagliflozin in the shared eligible population. [1] NICE (2022) Dapagliflozin for treating chronic kidney disease (TA775). [Online] Accessed 17 November 2022. Available at https://www.nice.org.uk/guidance/ta775/resources/dapagliflozin-for-treating-chronic-kidney-disease-pdf-82611498049477 [2] The EMPA-KIDNEY Collaborative Group (2022) Empagliflozin in Patients with Chronic Kidney Disease. *NEJM*. [Online] Accessed 18 November 2022. Available at https://www.nejm.org/doi/10.1056/NEJMoa2204233 [3] Heerspink, et al. (2020) Dapagliflozin in patients with chronic kidney disease. *NEJM*. [Online] Accessed 18 November 2022. Available at	

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		https://www.nejm.org/doi/10.1056/NEJMoa2024816?url_ver=Z39.88-2003&rfr_id=ori%3Arid%3Acrossref.org&rfr_dat=cr_pub++0pubmed **Is the primary outcome that was measured in the trial or used to drive the model for the comparator(s) still clinically relevant?** Yes, the primary outcome in DAPA-CKD remains clinically relevant. The primary outcome of the DAPA-CKD trial was a composite, assessed in time-to-event analysis, of the first occurrence of either: a decline of ≥50% in eGFR (confirmed by a second serum creatinine measurement after ≥28 days), the onset of ESKD (defined as maintenance dialysis for ≥28 days, kidney transplantation, or an eGFR of <15 ml/min/1.73 m^2 confirmed by a second measurement after ≥28 days), or death from renal or CV causes [1]. This outcome is similar to that of EMPA-KIDNEY, however there are some important differences: The primary outcome of the EMPA-KIDNEY trial was a composite of progression of kidney disease (defined as ESKD, a sustained decrease in eGFR to <10 ml/min/1.73 m^2, a sustained decrease in eGFR of ≥40% from baseline, or death from renal causes) or death from CV causes [2]. [1] Heerspink, et al. (2020) Dapagliflozin in patients with chronic kidney disease. *NEJM*. [Online] Accessed 18 November 2022. Available at https://www.nejm.org/doi/10.1056/NEJMoa2024816?url_ver=Z39.88-2003&rfr_id=ori%3Arid%3Acrossref.org&rfr_dat=cr_pub++0pubmed [2] The EMPA-KIDNEY Collaborative Group (2022) Empagliflozin in Patients with Chronic Kidney Disease. *NEJM*. [Online] Accessed 18 November 2022. Available at https://www.nejm.org/doi/10.1056/NEJMoa2204233 **Is there any substantial new evidence for the comparator technology/ies that has not been considered? Are there any important ongoing trials reporting in the next year?** BI are not aware of any new evidence that would be available at the time of the appraisal of this topic.	

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	AstraZeneca	**Would empagliflozin be a candidate for managed access?** No comments **Do you consider that the use of empagliflozin can result in any potential substantial health-related benefits that are unlikely to be included in the quality adjusted life year (QALY) calculation?** No, AstraZeneca does not consider the use of empagliflozin to result in any benefits that cannot be captured in the QALY calculation. **Would it be appropriate to use the cost-comparison methodology for this topic? Is the new technology likely to be similar in its clinical efficacy and resource use to any of the comparators?** A cost comparison case can be made if a health 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. AstraZeneca therefore do not deem it appropriate to use the cost comparison methodology for this topic for the following reasons: **DAPA-CKD trial outcomes differ to that of EMPA-KIDNEY:** *Primary endpoint:* The primary endpoint in the DAPA-CKD trial was a composite of ≥50% sustained eGFR decline, ESKD (dialysis/transplantation/ sustained eGFR decline<15), renal or CV death. Whilst the endpoint for EMPA-KIDNEY was a composite of ≥40% sustained eGFR decline, ESKD (dialysis/transplantation/ sustained eGFR decline<10), renal or CV death.	Comments noted. No action required.

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		The ESKD endpoint alone (not in the primary composite) is different between DAPA-CKD (eGFR <15, dialysis or transplant) and EMPA-KIDNEY (dialysis and transplant (no eGFR <15)) so comparison is difficult. *Key additional endpoints:* In the DAPA-CKD trial, dapagliflozin demonstrated statistical significance in relative risk reduction of all cause death, composite of CV death or hHF and all cause hospitalisations. EMPA-KIDNEY has demonstrated statistical significance in all cause-hospitalisation but not all cause death and composite of CV death or hHF. **Evidence of differentiation for dapagliflozin versus empagliflozin:** Although no head-to-head or indirect treatment comparison data exists in CKD at this moment in time, there is clear evidence across the entire evidence base that there is clinical differentiation between dapagliflozin and empagliflozin as shown in other disease areas (heart failure), creating uncertainty in a class effect. In DAPA-CKD, dapagliflozin has demonstrated consistent benefits across all primary and secondary endpoints and consistent benefits across subgroups. Dapagliflozin has demonstrated statistical significance in reducing CV death in patients with reduced ejection fraction (DAPA-HF) whilst in its own trial (EMPEROR-Reduced), empagliflozin failed to reach statistical significance. In a pooled analysis, from DAPA-HF and DELIVER, dapagliflozin has demonstrated to be statistically significant in reducing CV death/hHF and CV death whilst pooled data from the EMPEROR studies (EMPEROR - PRESERVED, EMPEROR-RESERVED) have only demonstrated statistical significance in reducing the composite of CV death and hHF but not the component of the CV death alone. Although there are no head-to-head data available, this variation seen in the clinical trial data sets suggests there is a clinical variation seen in the SGLT2	

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		class and so a full cost utility analysis should be carried out for this technology to ensure that the evidence base is fully evaluated. **Is the primary outcome that was measured in the trial or used to drive the model for the comparator(s) still clinically relevant?** AstraZeneca considers the primary outcome measured in the trial still clinically relevant. **Is there any substantial new evidence for the comparator technology/ies that has not been considered? Are there any important ongoing trials reporting in the next year?** [redacted]	
	Kidney Care UK	None	No action required.
	Kidney Research UK	The relevant data is the 13 large randomized controlled trials of SGLT2i in various patient populations and their meta-analysis (eg, https://doi.org/10.1016/S0140-6736(22)02164-X). There is also data from the EMPEROR-PRESERVED trial which is relevant alongside EMPA-KIDNEY trial results (particularly with respect of cardiovascular benefits). Half of that trial cohort had an eGFR less than 60 ml/min/1.73m2. In response to the question of - 'in clinical practice, would people always be stable on the maximum tolerated dose of ACE inhibitors or ARBs before empagliflozin would be considered?' - the answer is no. The EMPA-KIDNEY trial did not mandate use of ACEi or ARB as it recognised that they are not always indicated and tolerated in patients with CKD at risk of progression. Approximately 15% of the trial population were not taking one at the start of	Comments noted. No action required.

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		the trial, and the proportional benefit of treatment was similar in such participants to those taking an ACEi or ARB.	
	UK Kidney Association	NA	No action required.
Additional comments on the draft scope	Boehringer Ingelheim	None	No action required.
	AstraZeneca	**Any additional comments on the draft scope** AstraZeneca requests the following related technology appraisals are added into the “Related NICE Recommendations” section: • Dapagliflozin for treating heart failure with reduced ejection fraction (2021) NICE technology appraisal 679. Review date 2024. • Dapagliflozin in combination therapy for treating type 2 diabetes (2013, update 2016) NICE technology appraisal 288. Review date 2017. • Dapagliflozin in triple therapy for treating type 2 diabetes (2016) NICE technology appraisal 418. Review date 2019. • Empagliflozin for treating chronic heart failure with reduced ejection fraction • Technology appraisal guidance [TA773] Published: 09 March 2022 • Empagliflozin in combination therapy for treating type 2 diabetes • Technology appraisal guidance [TA336] Published: 25 March 2015 AstraZeneca requests the following related appraisals in development are added into the “Related NICE Recommendations” section:	Comments noted. Only recommendations relevant to the condition are included in this section. All relevant recommendations for ‘chronic kidney disease’ have already been included in the scope. No action required.

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		• Dapagliflozin for treating chronic heart failure with preserved or mildly reduced ejection fraction [ID1648] In development [GID-TA10942] Expected publication date: TBC • Empagliflozin for treating chronic heart failure with preserved or mildly reduced ejection fraction [ID3945] In development [GID-TA10946] Expected publication date: TBC • Finerenone for treating chronic kidney disease in people with type 2 diabetes [ID3773] Expected publication date: March 2023	
	Kidney Care UK	Kidney Care UK believes it's vital that people are provided with lifestyle and diet advice so they can take action to reduce their risk of further kidney damage, and it is important that any NICE guidance resulting from this review recommends the provision of suitable advice	Thank you for your comment. Where appropriate, the committee will reference relevant NICE guidance on lifestyle and diet advice for people with chronic kidney disease.
	Kidney Research UK	None	No action required.
	UK Kidney Association	None	No action required.

The following stakeholders indicated that they had no comments on the draft remit and/or the draft scope

None