NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Dapagliflozin for treating chronic kidney disease [ID3866]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Dapagliflozin for treating chronic kidney disease [ID3866]

Contents:

The following documents are made available to consultees and commentators:

1. **Response to consultee, commentator, and public comments on the Appraisal Consultation Document (ACD)**

2. **Comments on the Appraisal Consultation Document from AstraZeneca**

3. **Consultee and commentator comments on the Appraisal Consultation Document** from:
   a. Kidney Care UK
   b. Royal College of General Practitioners
   c. St. George's University Hospitals NHS Foundation Trust – London Kidney Network
   d. Boehringer-Ingelheim
   e. Novartis

4. **Comments on the Appraisal Consultation Document received through the NICE website**

5. **Evidence Review Group critique of company comments on the ACD**

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

Appraisal title

Single Technology Appraisal

Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)

Type of stakeholder:

Consultees – Organisations that accept an invitation to participate in the appraisal including the companies, national professional organisations, national patient organisations, the Department of Health and Social Care and the Welsh Government and relevant NHS organisations in England. Consultees can make a submission and participate in the consultation on the appraisal consultation document (ACD; if produced). All non-company consultees can nominate clinical experts and/or patient experts to verbally present their personal views to the Appraisal Committee. Company consultees can also nominate clinical experts. Representatives from NHS England and clinical commissioning groups invited to participate in the appraisal may also attend the Appraisal Committee as NHS commissioning experts. All consultees have the opportunity to consider an appeal against the final recommendations, or report any factual errors, within the final appraisal document (FAD).

Clinical and patient experts and NHS commissioning experts – The Chair of the Appraisal Committee and the NICE project team select clinical experts and patient experts from nominations by consultees and commentators. They attend the Appraisal Committee meeting as individuals to answer questions to help clarify issues about the submitted evidence and to provide their views and experiences of the technology and/or condition. Before they attend the meeting, all experts must either submit a written statement (using a template) or indicate they agree with the submission made by their nominating organisation..

Commentators – Commentators can participate in the consultation on the ACD (if produced), but NICE does not ask them to make any submission for the appraisal. Non-company commentator organisations can nominate clinical experts and patient experts to verbally present their personal views to the Appraisal Committee. Commentator organisations representing relevant comparator technology companies can also nominate clinical experts. These organisations receive the FAD and have opportunity to report any factual errors. These organisations include comparator technology companies, Healthcare Improvement Scotland any relevant National Collaborating Centre (a group commissioned by NICE to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups such as the NHS Confederation, the NHS Commercial Medicines Unit, the Scottish Medicines Consortium, the Medicines and Healthcare Products Regulatory Agency, the Department of Health and Social Care, Social Services and Public Safety for Northern Ireland).

Public – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but NICE reserves the right to summarise and edit comments received during consultations, or not to publish them at all, where in the reasonable opinion of NICE, the comments are voluminous, publication would be unlawful or publication would be otherwise inappropriate.

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
1	Company	AstraZeneca	**Summary of Company position** The Company would like to thank the Committee for the opportunity to respond to the Appraisal Consultation Document (ACD) and welcomes the current draft recommendations for dapagliflozin as a treatment for chronic kidney disease (CKD). However, the Company is concerned that the current recommendations set out within the ACD are unnecessarily restrictive with respect to the included urine albumin-creatinine ratio (uACR) thresholds, particularly in light of the clinical and economic evidence presented at the Committee meeting and the current low levels of uACR testing in UK clinical practice. A clear case for cost-effectiveness has been demonstrated for dapagliflozin in patients with CKD and comorbid type 2 diabetes mellitus (T2DM), irrespective of uACR. In light of the clinical data and economic case presented during Technical Engagement and at the Committee meeting, the Company believes that the Committee has not provided a clear and adequate reason for not recommending the use of dapagliflozin in the full population of patients with CKD and comorbid T2DM. As detailed further in Issues 2 and 4 of this response, the restricted recommendation within the T2DM population is unwarranted and is not supported by the clinical and economic evidence presented. It is also likely to further exacerbate inequalities of care by preventing access to dapagliflozin for patients who may benefit from it, based on clinical trial data from the DECLARE-TIMI 58 trial.[1] Within the non-T2DM population, the Company recognises that the clinical data are less certain for patients with a low uACR; however, the Company believes that the response set out in this document under Issue 3 will help to alleviate the concerns raised by the Committee and thereby enable a broader recommendation to be made for this population, irrespective of uACR. The Company urges the Committee to consider the full range of evidence and the points of clarification outlined in this response in the development of their final recommendations. The Company also urges the Committee to carefully consider the appropriateness of constructing further subgroups within populations for which a therapy has already been deemed to be cost-effective, and the implications of applying restrictions based on uACR testing given the potential impact this may have on healthcare inequalities. In light of some of the concerns outlined by the Committee within the ACD, the Company has conducted a number of new analyses that are presented within this response as follows: • An updated Company base case analysis based on the characteristics of patients from a newly-defined Clinical Practice Research Datalink (CPRD) dataset that more closely reflects the patient population	The recommendation in the FAD has been broadened to include people with type 2 diabetes and a uACR of less than 3 mg/mmol. See section 1.1 of the FAD. Dapagliflozin cannot be recommended in people with a uACR of less than 22.6 mg/mmol who do not have type 2 diabetes. See section 3.20 of the FAD. The new analyses were considered by the committee during decision making. See section 3.15 and section 3.19 of the FAD.

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<tr><th>Comment number</th><th>Type of stakeholder</th><th>Organisation name</th><th>Stakeholder comment
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<tr><td></td><td></td><td></td><td>
under appraisal, in line with the Committee's recommended estimated glomerular filtration rate (eGFR) restrictions (Table 1, see Issue 6 for further details)
• Revised scenario analyses based on the characteristics of patients with CKD from the newly-defined CPRD dataset that fall within the expected target populations: Subgroup 1: uACR ≥22.6 mg/mmol (200 mg/g); Subgroup 2: T2DM with a uACR <22.6 mg/mmol (200 mg/g); Subgroup 3: non-T2DM with a uACR <22.6 mg/mmol (200 mg/g) (Scenarios 1–3 in Table 1)
• New scenario analyses within the additional uACR subgroups constructed by the Committee of ≤3 mg/mmol (**A1**: <30 mg/g) and 3–22 mg/mmol (**Modified A2**: 30–199 mg/g [modified at upper bound to mirror the DAPA-CKD trial inclusion criteria, with the true A2 classification being 3–30 mg/mmol {30–300 mg/g}]), in both the T2DM and non-T2DM populations (Scenarios 4–11 in Table 1)
  ○ Scenarios 4, 6, 8 and 10 are based on the characteristics of patients from the newly-defined CPRD dataset, whereas Scenarios 5, 7, 9 and 11 are based on the characteristics of patients from the DECLARE$_{CKD}$ cohort. Both approaches are associated with similar incremental cost-effectiveness ratios (ICERs), demonstrating the robustness of the results with respect to both approaches
• *Note that all analyses have been conducted based on thresholds defined by mg/g values, in line with the DAPA-CKD trial eligibility criteria. For simplicity, all mg/mmol values presented throughout this response have been rounded to align with the uACR categories defined in the draft recommendations where possible*

The results of the new analyses conducted by the Company as part of this response are presented below in Table 1 and described in more detail in Issue 7. These analyses demonstrate that the recommendation to restrict dapagliflozin to use in patients with comorbid T2DM and a uACR ≥3 mg/mmol is inappropriate, and there is sufficient evidence to support the cost-effectiveness of dapagliflozin in both the T2DM and non-T2DM populations irrespective of uACR.

All results fall well below the threshold considered by NICE for a new therapy to be deemed cost-effective. Together with the evidence presented within the original Company submission, at Technical Engagement, and within the Committee meeting itself, the Company believes that the evidence presented within this response provides sufficient certainty in the cost-effectiveness of dapagliflozin, such that the restricted recommendations based on uACR are carefully and appropriately reconsidered by the Committee and removed from the final recommendations for this appraisal.

Table 1: Updated Company base case and scenario analyses conducted as part of this response
<table>
<tr><th>Population</th><th>ΔCosts (£)</th><th>ΔQALYs</th><th>ICER</th></tr>
<tr><td>Updated Company base case: overall population
(risk equations from the DAPA-CKD and DECLARE$_{CKD}$ combined dataset, adjusted to patient characteristics of</td><td>£1,974</td><td>0.332</td><td>£5,948</td></tr>
</table>
</td><td></td></tr>
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Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment

newly-defined CPRD dataset)			
1 **DAPA-CKD like population (uACR ≥22.6 mg/mmol [200 mg/g])**: risk equations from the DAPA-CKD and $DECLARE_{CKD}$ combined dataset, adjusted to patient characteristics from the newly-defined CPRD dataset (uACR ≥22.6 mg/mmol [200 mg/g] subgroup)	−£1,004	0.521	**Dominant**
2 **T2DM low uACR population (uACR <22.6 mg/mmol [200 mg/g])**: risk equations from $DECLARE_{CKD,}$ adjusted to patient characteristics from the newly-defined CPRD dataset (uACR <22.6 mg/mmol [200 mg/g] subgroup)	£2,576	0.430	**£5,990**
3 **Non-T2DM low uACR population (uACR <22.6 mg/mmol [200 mg/g])**: risk equations from $DECLARE_{CKD}$ with non-diabetes correction factor, adjusted to patient characteristics from the newly-defined CPRD dataset (uACR <22.6 mg/mmol [200 mg/g] subgroup)	£1,512	0.088	**£17,139**
New uACR subgroup scenario analyses			
4 **T2DM A1 population**: risk equations from $DECLARE_{CKD,}$ adjusted to patient characteristics from the **newly-defined CPRD dataset** (uACR <3 mg/mmol [<30 mg/g] subgroup)	£2,646	0.433	**£6,112**
5 **T2DM A1 population**: risk equations from $DECLARE_{CKD,}$ adjusted to patient characteristics from the **$DECLARE_{CKD}$ cohort** (uACR <3 mg/mmol [<30 mg/g] subgroup)	£2,603	0.436	**£5,965**
6 **T2DM Modified A2* population**: risk equations from $DECLARE_{CKD,}$ adjusted to patient characteristics from the **newly-defined CPRD dataset** (uACR 3–22 mg/mmol [30–199 mg/g] subgroup)	£2,309	0.412	**£5,599**
7 **T2DM Modified A2* population**: risk equations from $DECLARE_{CKD}$, adjusted to patient characteristics from the **$DECLARE_{CKD}$ cohort** (uACR 3–22 mg/mmol [30–199 mg/g] subgroup)	£2,675	0.421	**£6,352**

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<tr><td></td><td></td><td></td><td>
<table>
<tr><td>8</td><td>Non-T2DM A1 population: risk equations from DECLARE$_{CKD}$ with non-diabetes correction factor, adjusted to patient characteristics from the newly-defined CPRD dataset (uACR <3 mg/mmol [<30 mg/g] subgroup)</td><td>£1,586</td><td>0.095</td><td>£16,684</td></tr>
<tr><td>9</td><td>Non-T2DM A1 population: risk equations from DECLARE$_{CKD}$ with non-diabetes correction factor, adjusted to patient characteristics from the DECLARE$_{CKD}$ cohort (uACR <3 mg/mmol [<30 mg/g] subgroup)</td><td>£1,697</td><td>0.183</td><td>£9,277</td></tr>
<tr><td>10</td><td>Non-T2DM Modified A2* population: risk equations from DECLARE$_{CKD}$ with non-diabetes correction factor, adjusted to patient characteristics from the newly-defined CPRD dataset (uACR 3–22 mg/mmol [30–199 mg/g] subgroup)</td><td>£1,274</td><td>0.065</td><td>£19,532</td></tr>
<tr><td>11</td><td>Non-T2DM Modified A2* population: risk equations from DECLARE$_{CKD}$ with non-diabetes correction factor, adjusted to patient characteristics from the DECLARE$_{CKD}$ cohort (uACR 3–22 mg/mmol [30–199 mg/g] subgroup)</td><td>£1,770</td><td>0.150</td><td>£11,769</td></tr>
</table>
Note: *Modified at upper bound (22 mg/mmol [199 mg/g]) to mirror the DAPA-CKD trial inclusion criteria, with the true A2 classification being 3–30 mg/mmol (30–300 mg/g). These analyses were conducted based on thresholds defined by mg/g values, in line with the DAPA-CKD trial eligibility criteria. For simplicity, all mg/mmol values presented throughout this response have been rounded to align with the categories defined in the draft recommendations where possible.

Abbreviations: CKD: chronic kidney disease; CPRD: Clinical Practice Research Datalink; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year; uACR: urinary albumin creatinine ratio; T2DM: type 2 diabetes mellitus.
</td><td></td></tr>
<tr><td>2</td><td>Company</td><td>AstraZeneca</td><td><u>The recommendation to restrict dapagliflozin to use in patients with T2DM with a uACR ≥3 mg/mmol is inappropriate and does not reflect the available clinical and cost-effectiveness evidence</u>

The restricted recommendation outlined within the ACD for patients with CKD and comorbid T2DM based on a uACR threshold of 3 mg/mmol (30 mg/g) does not reflect the clinical and cost-effectiveness evidence for dapagliflozin provided as part of this appraisal to date. The Company urges the Committee to carefully reconsider this restriction for the following reasons:</td><td>The recommendation in the FAD has been broadened to include people with type 2 diabetes and a uACR of less than 3 mg/mmol. Please see section 1.1 of the FAD.</td></tr>
</table>

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			1. The ACD states that the cost-effectiveness estimate of dapagliflozin plus standard care compared with standard care alone in Subgroup 2 (patients with T2DM with a uACR <22.6 mg/mmol [200 mg/g]) "*is comfortably within what NICE considers an acceptable use of resources*." The Company is therefore extremely concerned as to why a further restriction within this subgroup has been made without any clear rationale, and urges the Committee to base their final recommendations on the clinical and cost-effectiveness evidence presented within this appraisal. 2. The uACR threshold of 3 mg/mmol (30 mg/g) represents an additional subgroup within an already pre-defined subpopulation for which the Committee provide no clear rationale. Despite the inappropriate nature of this further restriction, the Company have conducted additional scenario analyses to demonstrate the cost-effectiveness of dapagliflozin both within the additional subgroup of uACR <3 mg/mmol (<30 mg/g) and within the already recommended uACR subgroup of 3–22 mg/mmol (30–199 mg/g). Results of these scenario analyses are presented below and in further detail under Issue 7, demonstrating that dapagliflozin is cost-effective in subgroups of patients both above and below this additional uACR threshold, with ICERs that fall well below the cost-effectiveness threshold considered by NICE. 3. It is inappropriate to construct further subgroups within subpopulations for which a therapy has already been deemed to be cost-effective. This view is supported by precedent from a prior appraisal appeal (TA504, Pirfenidone for treating idiopathic pulmonary fibrosis)[2, 3] and therefore the Company urges the Committee to carefully and appropriately reconsider this restriction within the development of their final recommendations for this appraisal. 4. Finally, a recommendation which requires uACR testing to be conducted is likely to further exacerbate current inequalities of care within the National Health Service (NHS), as discussed in further detail below in Issue 4. <u>2.1 Dapagliflozin is clinically and cost-effective in patients with T2DM irrespective of uACR</u> Section 3.8 of the ACD states that "*Results from DECLARE-TIMI-58 and DAPA-HF suggested that dapagliflozin plus standard care is more effective than standard care alone across the broad CKD population, regardless of uACR and eGFR levels*". This statement is already clear in its reflection of the evidence provided by the Company to date for the clinical efficacy of dapagliflozin in patients with CKD and comorbid T2DM irrespective of uACR, and in particular the available subgroup analyses of the DECLARE-TIMI 58 trial:[4]}[5] • Subgroup analyses of the DECLARE-TIMI 58 trial presented in the Company submission demonstrate a clear treatment benefit in patients below and above a uACR threshold of **22.6 mg/mmol** (200 mg/g) for the following endpoints:[6] o <u>Renal endpoint</u> (≥40% eGFR decline, end stage kidney disease [ESKD], or death from renal causes); hazard ratio (HR) (95% confidence interval [CI]): [redacted] versus [redacted] for patients with a uACR of <22.6 mg/mmol and ≥22.6 mg/mmol respectively; p value for interaction=[redacted] o <u>Cardiorenal endpoint</u> (≥40% eGFR decline, ESKD, renal death or CV [cardiovascular] death); HR (95% CI): [redacted] versus [redacted] for patients with a <22.6 mg/mmol and	

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≥22.6 mg/mmol respectively; p value for interaction=[redacted]

In addition, analyses presented by Mosenzon et al. 2019 provide further clear evidence of a treatment benefit for dapagliflozin in terms of these endpoints across all uACR subgroups defined according to KDIGO guidelines: A1 (<3mg/mmol [<30 mg/g]), A2 (3–30 mg/mmol [30–300 mg/g]) and A3 (≥30mg/mmol [≥300 mg/g]):[5]

Renal-specific composite outcome (p-value for interaction=0.30)

A1 HR (95% CI): 0.52 (0.37, 0.74)
A2 HR (95% CI): 0.59 (0.39, 0.87)
A3 HR (95% CI): 0.38 (0.25, 0.58)

Cardiorenal composite outcome (p-value for interaction=0.020):

A1 HR (95% CI): 0.89 (0.73, 1.08)
A2 HR (95% CI): 0.73 (0.57, 0.94)
A3 HR (95% CI): 0.52 (0.38, 0.72)

Clinical data from the DECLARE-TIMI 58 trial directly inform the economic model used by both the Company and the Evidence Review Group (ERG) to generate cost-effectiveness estimates for dapagliflozin in patients with CKD and comorbid T2DM and a uACR ranging from 0–22.6 mg/mmol (200 mg/g) (Table 2). Based on the results of these analyses, Section 3.17 of the ACD states that "*the cost-effectiveness estimate of dapagliflozin plus standard care compared with standard care alone in subgroup 2 was comfortably within what NICE considers an acceptable use of NHS resources*". It is therefore unclear why the Committee has made a restricted recommendation for the use of dapagliflozin in only a proportion of this population (those with a uACR 3–22 mg/mmol [30–199 mg/g]), given no cost-effectiveness results have been presented for patients with comorbid T2DM and a uACR above or below 3 mg/mmol (30 mg/g) specifically.

Table 2: Select results from the unified broad population analyses presented at Technical Engagement, for patients with CKD and comorbid T2DM with a uACR <22.6 mg/mmol (<200 mg/g)

Population	ΔCosts (£)	ΔQALYs	ICER
Company analyses, assuming mean age 64	£2,801	0.52	£5,418
ERG analyses, assuming mean age 76.6	£2,245	0.31	£7,189

Abbreviations: ERG: Evidence Review Group; ICER: Incremental Cost-Effectiveness Ratio; QALY: Quality Adjusted Life Years; T2DM: Type 2 diabetes mellitus; uACR: urinary albumin-creatinine ratio.

The Company welcome the Committee's acknowledgement within the ACD that the remit of the Committee is to appraise dapagliflozin based on the evidence submitted within this technology appraisal only, regardless of the recent class-level recommendations for sodium-glucose co-transporter-2 (SGLT2) inhibitors in patients with CKD and comorbid T2DM in NICE guideline 28 (NG28: Type 2 diabetes in adults: management, published 24th November 2021).[7] The recommendations presented in the NICE clinical guideline are informed by a separate economic model based predominantly on data for canagliflozin. This model therefore does not include important data from the DECLARE-TIMI 58 trial in patients with CKD and comorbid T2DM with a uACR <200 mg/mmol, as</td><td></td></tr>
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			these subgroup data are not yet published. As highlighted above, robust clinical trial data for dapagliflozin in patients with CKD and comorbid T2DM with a uACR <22.6 mg/mmol have been provided to the Committee for this appraisal which directly inform the economic model used within the ERG analyses. This economic model produces an ICER that is "*comfortably within that NICE considers an acceptable use of NHS resources*" across the entire subgroup of uACR 0–22.6 mg/mmol (0–200 mg/g), making further subgrouping within this population inappropriate.
			
			Furthermore, the Company would like to highlight to the Committee the recently published, NICE-accredited, UK Kidney Association (UKKA) guidelines which recommend the use of SGLT2 inhibitors to modify cardiovascular risk in patients with CKD and comorbid T2DM across the full uACR spectrum (both above and below 25 mg/mmol):[8]
			• *"In people with T2DM and an eGFR ≥25 mL/min/1.73m^2, we recommend initiating SGLT-2 inhibition in those with:*
			  ○ *uACR of ≥25 mg/mmol attributed to diabetic nephropathy (Grade 1A)*
			  ○ *Established coronary disease or stable symptomatic heart failure (irrespective of ejection fraction) (Grade 1A)*
			• *We suggest initiating SGLT-2 inhibition to modify cardiovascular risk in those with an eGFR 25–60 mL/min/1.73m^2 and uACR <25 mg/mmol, recognising effects on glycaemic control will be limited".*
			
			The UKKA guidelines were developed by leading nephrologists in the UK and state that *"benefits on heart failure hospitalisation and major adverse cardiovascular events (MACE) have been demonstrated in a range of populations at risk, including trials recruiting people with CKD without albuminuria. Therefore, although SGLT-2 inhibitors are not expected to provide important reductions in blood glucose in the presence of CKD and renal benefits are uncertain, we offer a grade 2B Suggestion for Use to modify risk of heart failure, myocardial infarction or cardiovascular death in those with CKD without albuminuria".* The Company therefore urge the Committee to similarly consider the full breadth of the available evidence for the benefits of dapagliflozin regardless of uACR, to avoid any potential inconsistency between this NICE-accredited clinical guideline and the final recommendations for this technology appraisal.
			
			<u>2.2 In response to the ACD, the Company have conducted a number of new scenario analyses that demonstrate dapagliflozin is cost-effective in patients with CKD and comorbid T2DM both above and below the additional 3 mg/mmol (30 mg/g) uACR threshold</u>
			
			In response to the additional uACR restriction included within the ACD for patients with CKD and comorbid T2DM, the Company have conducted four additional scenario analyses to demonstrate the cost-effectiveness of dapagliflozin in patients with CKD and comorbid T2DM both above and below this additional uACR threshold of 3 mg/mmol (30 mg/g) (Table 3):
			• <3 mg/mmol (**A1**: <30 mg/g)
			• 3–22 mg/mmol (**Modified A2**: 30–199 mg/g)	

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The first two analyses are based on the characteristics of patients from the newly-defined CPRD dataset, whereas the second two analyses are based on the characteristics of patients from the DECLARE$_{CKD}$ cohort. The results of these analyses are presented below and demonstrate that dapagliflozin is cost-effective in subgroups of patients both above and below the additional uACR threshold of 3 mg/mmol, with ICERs that fall well below the cost-effectiveness threshold considered by NICE, and with minimal differences observed between the two approaches. Similar ICERs were observed across the A1 and Modified A2 subgroups, which comprise [redacted]% and [redacted]% of patients in the newly-defined CPRD dataset, respectively (see Issue 6).[9]

Table 3: New uACR subgroup scenario analyses for patients with CKD and comorbid T2DM conducted by the Company as part of this response
<table>
<tr><th>Population</th><th>ΔCosts (£)</th><th>ΔQALYs</th><th>ICER</th></tr>
<tr><td colspan="4">Modelled patient characteristics based on the newly-defined CPRD dataset</td></tr>
<tr><td>T2DM A1 population: risk equations from DECLARE$_{CKD,}$ adjusted to patient characteristics from the newly-defined CPRD dataset (uACR <3 mg/mmol [<30 mg/g] subgroup)</td><td>£2,646</td><td>0.433</td><td>£6,112</td></tr>
<tr><td>T2DM Modified A2* population: risk equations from DECLARE$_{CKD,}$ adjusted to patient characteristics from the newly-defined CPRD dataset (uACR 3–22 mg/mmol [30–199 mg/g] subgroup)</td><td>£2,309</td><td>0.412</td><td>£5,599</td></tr>
<tr><td colspan="4">Modelled patient characteristics based on the DECLARE$_{CKD}$ cohort</td></tr>
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Note: *Modified at upper bound (22 mg/mmol [199 mg/g]) to mirror the DAPA-CKD trial inclusion criteria, with the true A2 classification being 3–30 mg/mmol (30–300 mg/g). These analyses were conducted based on thresholds defined by mg/g values, in line with the DAPA-CKD trial eligibility criteria. For simplicity, all mg/mmol values presented throughout this response have been rounded to align with the categories defined in the draft recommendations where possible.
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			Abbreviations: CKD: chronic kidney disease; CPRD: Clinical Practice Research Datalink; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year; uACR: urinary albumin creatinine ratio; T2DM: type 2 diabetes mellitus. 2.3 Irrespective of the cost-effectiveness of dapagliflozin within the additional uACR subgroups, the introduction of further subgroups within pre-defined subpopulations for which a therapy has already been deemed to be cost-effective is inappropriate based on precedent from a prior appraisal appeal Discussion by the NICE Appeals Panel during the appeals process for TA504 (Pirfenidone for treating idiopathic pulmonary fibrosis) clearly specifies the criteria for the appropriateness of considering subgroups within an appraisal and further highlights the inappropriateness of additional subgrouping of the CKD and comorbid T2DM population in the current draft recommendation.[2, 3] The Appeals Panel for TA504 concluded that "*unless a scope specifies otherwise, the Appeal Panel considers that there is a soft presumption that the starting point for any Committee should be consideration of the whole patient group as one, with a view to making one recommendation for that group. Where different recommendations are to be made for different groups of patients, the reason for departing from one recommendation should be clear and adequate*".[2, 3] The NICE final scope for this appraisal of dapagliflozin in CKD does not specify subgroups of patients by uACR status, and lists only people with diabetes, people with cardiovascular disease and people with other causes of CKD as potential subgroups to explore, should the evidence allow. These analyses were presented in the Company submission based on data from the DAPA-CKD trial, and demonstrated the consistency of the dapagliflozin treatment effect in these subgroups.[10, 11] The ACD therefore presents no clear rationale for further dividing patients with CKD and comorbid T2DM using a uACR threshold of 3 mg/mmol (30 mg/g), and this additional subgroup of patients with CKD and comorbid T2DM with a uACR of <3 mg/mmol (<30 mg/g) does not comprise an identifiable patient population which has been defined for a proper purpose or logical reason based on either clinical or economic evidence. The Company strongly believe that the introduction of further subgroups within pre-defined subpopulations for which a therapy has already been deemed to be cost-effective based on the clinical and cost-effectiveness evidence provided as part of the appraisal to date is inappropriate. The Company therefore urges the Committee to carefully and appropriately reconsider this restriction within the development of their final recommendations for this appraisal. 2.4 A recommendation based on uACR measurements is likely to further exacerbate current inequalities of care within the NHS Finally, restricting access to dapagliflozin based on uACR measurements will likely exacerbate current inequalities of care within the NHS related to uACR testing, between both primary and secondary care and between patients with and without comorbid T2DM. These inequalities cause the Company, professional organisations, and patients with CKD grave concern with respect to equitable access to dapagliflozin, and are discussed further in Issue 4.	
3	Company	AstraZeneca	**Dapagliflozin is highly likely to represent a cost-effective treatment option for patients with CKD and a**	The wording of the

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<u>uACR <22.6 mg/mmol (200 mg/g) irrespective of T2DM status</u>

<u>3.1 The available evidence suggests that the treatment effect of dapagliflozin is consistent regardless of T2DM status in patients with a uACR <22.6 mg/mmol (200 mg/g)</u>

The Medicines and Healthcare products Regulatory Agency (MHRA), European Medicines Agency (EMA), and Food and Drug Administration (FDA) all independently granted a marketing authorisation for the use of dapagliflozin to treat adults with CKD without any restrictions based on uACR category or T2DM status.[12-14] This broad label allowing the initiation of dapagliflozin in all eligible patients with CKD Stages 1–4 was granted based on results from the DAPA-CKD trial, the strength of supporting clinical evidence from the DECLARE-TIMI 58 and DAPA-HF trials and the strong mechanistic rationale for the similarity of renal efficacy of dapagliflozin in patients with and without comorbid T2DM – as detailed below.

The consistency of the treatment effect of dapagliflozin irrespective of T2DM status was clearly demonstrated in both the DAPA-CKD and DAPA-HF trials. In DAPA-CKD, the effect of dapagliflozin on the primary outcome of a sustained decline in eGFR ≥50%, ESKD or death from renal or CV causes was consistent regardless of T2DM status (Table 4).[10]

Table 4: Subgroup analyses of DAPA-CKD primary endpoint by T2DM status

	Dapagliflozin, n/N	Placebo, n/N	HR (95% CI)	p-value interaction
Primary endpoint (sustained decline in eGFR ≥50%, ESKD or death from renal or CV causes)				
With T2DM	125/1,455	229/1,451	0.64 (0.52, 0.79)	0.24
Without T2DM	45/697	83/701	0.50 (0.35, 0.72)	

Abbreviations: CI: confidence interval; CV: cardiovascular; eGFR: estimated glomerular filtration rate; ESKD: end-stage kidney disease; HR: hazard ratio; T2DM: type 2 diabetes mellitus.
Sources: Wheeler et al. 2020.[15]

Subgroup analyses of the DAPA-HF trial also support the consistency of the dapagliflozin treatment effect across patients with and without T2DM. Dapagliflozin significantly reduced the risk of the primary outcome of worsening HF or CV death and the secondary renal outcome independently of T2DM status (Table 5).[16] Furthermore, in a separate post-hoc analysis of the DAPA-HF trial, the rate of decline in eGFR between day 14 and day 720 in patients with eGFR <60 ml/min/1.73m^2 (n=1,926 [41%]) treated with dapagliflozin or placebo was consistent irrespective of T2DM status (p-value for interaction=0.92).[17]

Table 5: Subgroup analyses of DAPA-HF primary and secondary endpoints by T2DM status

	Dapagliflozin, n/N	Placebo, n/N	HR (95% CI)	p-value interaction

</td><td>

marketing authorisations reflects where regulatory agencies found dapagliflozin to be safe and effective. It does not necessarily reflect where dapagliflozin represents an acceptable use of NHS resources.

The committee considered that the real-world evidence did not robustly resolve the evidence gap in people with low uACR levels with type 2 diabetes. See section 3.10 of the FAD.

The committee agreed with the company's updated mean age of 72.9 years, as it reflected the same CPRD datasets as those used to inform the other patients characteristics. See section 3.16 of the FAD.

The ERG's presentation of alternative ICERs for the subgroup of people with a uACR of less than 22.6 mg/mmol without type 2 diabetes does not represent an implicit acceptance that the available clinical evidence in this subgroup is adequate.

The committee noted that there was no direct

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Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment

Primary endpoint (Cardiovascular death, hospitalization for heart failure, or an urgent heart failure visit[a])					
With T2DM	215/1,075	271/1,064	0.75 (0.63, 0.90)	0.80	
Without T2DM	171/1,298	231/1,307	0.73 (0.60, 0.88)		
Secondary renal endpoint (worsening kidney function[b])					
With T2DM	18/1,075	24/1,064	0.73 (0.39, 1.34)	0.86	
Without T2DM	10/1,298	15/1,307	0.67 (0.30, 1.49)		

Footnotes: [a] Analysed as time to first occurrence of any of these events; an urgent visit was defined as a hospital visit in which intravenous therapy for heart failure was administered. [b] Composite outcome analysed as time to first occurrence of 50% or greater reduction in eGFR sustained for at least 28 days, kidney failure, or death from kidney-related causes. Kidney failure was defined as eGFR less than 15 mL/min/1.73m^2 sustained for at least 28 days, chronic dialysis treatment sustained for at least 28 days, or kidney transplant.
Abbreviations: CI: confidence interval; eGFR: estimated glomerular filtration rate; ESKD: end-stage kidney disease; HR: hazard ratio; T2DM: type 2 diabetes mellitus.
Sources: Petrie et al. 2020.[16]

In addition, the clinical characteristics of CKD are similar irrespective of the presence of comorbid T2DM due to common pathological processes in the kidneys. Dapagliflozin is anticipated to improve renal outcomes via mechanisms independent of blood glucose lowering and also confers benefits to the entire cardiorenal system in the form of reduction of body weight and blood pressure, in patients with CKD both with and without comorbid T2DM.[18, 19]

Overall, the consistency of the dapagliflozin treatment effect in patients with CKD irrespective of T2DM status suggests that the results of the DECLARE-TIMI 58 subgroup analyses by uACR presented in the Company submission and in Issue 2.1 above are likely to also apply to patients with CKD without comorbid T2DM. As such, the treatment effect observed in DAPA-CKD is likely to extend to patients in lower uACR categories than patients enrolled in DAPA-CKD, in patients with and without comorbid T2DM.

Furthermore, direct evidence of the efficacy of dapagliflozin in patients with CKD without T2DM and with a uACR <22.6 mg/mmol (200 mg/g) is provided by a US study of the Truven and Optum databases.[20] The Optum Research Database is an administrative claims database, generalisable to the US population, containing data from 160 million individuals and electronic health records for more than 80 million individuals nationally. The Truven MarketScan database includes administrative claims and electronic health record data for more than 265 million patients across the US. The data includes inpatient and outpatient claims, outpatient prescription claims, clinical utilisation records, and healthcare expenditures.

The results of this study, which evaluated the efficacy of dapagliflozin through assessment of [redacted] in patients with CKD without T2DM and with a [redacted] are presented in Table 6, and [redacted]. Early change in albuminuria is recognised

clinical trial evidence for people with a uACR of less than 22.6 mg/mmol without type 2 diabetes. This generated considerable uncertainty in the plausibility of the cost-effectiveness estimates for this population. The committee noted a consultee's comment that the benefits of dapagliflozin in preventing decline in renal function should be weighed against the potential consequences of overprescribing and drug interactions, particularly in people with milder disease. It also understood from the company at the second appraisal committee meeting that this subgroup is likely to comprise more of the CKD population than the CPRD data suggests. Therefore, the committee considered that the consequence of decision error was likely to be higher. It concluded that dapagliflozin cannot be recommended for these people. See section 3.20 of the FAD.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			by the National Kidney Foundation, the EMA and the FDA as a surrogate endpoint in CKD suitable for use in clinical trials, and these results provide further reassurance that dapagliflozin is effective in patients with CKD without T2DM and with a uACR [redacted][21] **Table 6: Treatment effect of dapagliflozin in patients with CKD without T2DM and a [redacted]** [redacted] **Footnotes**: *After at [redacted] of treatment with dapagliflozin. **Abbreviations**: SD: standard deviation; uACR: urine albumin-to-creatinine ratio. **Source**: AstraZeneca Data on File: Analyses of the Optum and Truven databases, 2021.[20] <u>3.2 The mean patient age used within the economic model is a key driver of the ICER across all economic subgroup analyses. It is therefore critical that a mean age reflective of patients in clinical practice is considered within the base case and all subgroup analyses</u> The mean age considered by the Committee in their economic analyses was derived from the original CPRD analysis conducted by the Company, which included only patients with a formal diagnosis of CKD.[22] The mean age of this cohort is unlikely to be representative of the total population of patients with CKD considered in this appraisal (Stages 1–4) due to under representation of patients with early-stage disease, and likely represents an overestimate for the mean age of the population for the following reasons: • Diagnosis of Stage 1–2 CKD is only possible using an assessment of uACR (as eGFR remains within normal ranges [≥60 ml/min/1.73 m^2]). Rates of uACR testing for patients at high risk of CKD in UK clinical practice are low, and most patients with CKD in the UK are therefore diagnosed at Stage 3 or later[23, 24] • Patients with early-stage CKD are less likely to have a Read code for CKD added to their primary care record, and were therefore less likely to be included in the original CPRD analysis conducted by the Company[25] • Patients with more advanced disease stages (Stages 3–5) are typically older than patients with earlier disease stages (Stages 1–2) given the irreversible, progressive nature of CKD[26 27] As the mean patient age used in the economic model is a key driver of the ICER in both the base case and all scenario analyses, it is vital that the value used is reflective of the target population for this appraisal. The Company has therefore conducted a targeted literature review (TLR) to validate the true mean age of patients with CKD Stages 1–4 in UK clinical practice and to help the Committee further explore an appropriate mean age for this population.	

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			The TLR aimed to identify observational or real-world evidence studies conducted in the UK reporting a mean or median age for adult patients with CKD Stages 1–4. A search strategy was developed for use in the MEDLINE database (including MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R)), which identified 1,055 records for screening. Overall, 172 records were considered for full-text review following abstract review, and a total of 96 records were ultimately included within the TLR. The majority (n=58) of these studies reported on populations with CKD Stages ≥3 only and were therefore deprioritised for extraction, as this patient population is likely to be older than a population including CKD Stages 1–4 due to the progressive nature of CKD. A further nine studies reported on populations of unclear CKD stage and were also deprioritised for extraction. Among the 29 remaining studies that included a proportion of patients with either Stage 1 or Stage 2 CKD, the majority (n=24) recruited only small cohort sizes unlikely to be generalisable to the overall population of patients with CKD. Five studies reported a mean and/or median age for a cohort size of ≥1,000 patients, and were selected for full extraction. Of these, two studies using data from the CPRD dataset reported a **mean** age of: • 68.8 years (SD: 11.3) in a cohort of 85,500 patients with Stage 2–5 CKD with or without T2DM[28] • 64 years (incident diabetic kidney disease [DKD]) and 70 years (prevalent DKD) for a cohort of 60,867 patients with Stage 1–5 DKD.[27] This study also reported a mean age by stage of CKD in both the prevalent and incident populations: o Prevalent DKD: Stage 1: 51 years; Stage 2: 65 years; Stage 3a: 69 years; Stage 3b: 75 years; Stage 4: 78 years; Stage 5: 74 years; Missing eGFR stage: 68 years o Incident DKD: Stage 1: 51 years; Stage 2: 64 years; Stage 3a: 66 years; Stage 3b: 70 years; Stage 4: 74 years; Stage 5: 64 years; Missing eGFR stage: 61 years Four studies reported a **median** age, two of which were based in Scottish centres, with values ranging from 67.6 years (IQR: 53.6–76.9; n=2,950) to 75 years (IQR: 63–84; n=2,236). One study based on the Laboratory Outcomes, Morbidity and Mortality Study-II cohort (n=19,694) reported median age by disease stage as follows: Stages 1–2: 61.0 years (IQR: 49.3–69.8); Stages 3–5: 75.7 years (IQR: 68.5–82.0).[27, 29-31] The results of this TLR indicate that the mean age of a population with Stage 1–4 CKD in UK clinical practice is likely to be lower than the 76.6 years currently assumed by the ERG, particularly as all five studies included some patients (albeit a small proportion) with Stage 5 disease and may therefore over-estimate the true mean age of patients with CKD Stages 1–4. Nevertheless, in light of the Committee comments in relation to mean patient age, the Company have conducted a new analysis of the CPRD dataset to align more closely to the population being considered within this appraisal. Within this newly-defined CPRD dataset, only patients that fall within the Committee's recommended eGFR restrictions (eGFR 25–75 ml/min/1.73 m^2) have been included (see Issue 6). The mean age of the overall patient population included in this analysis was 72.9 years, and this has been used to inform the Company's updated economic analysis (see Issue 7). 3.3 The Committee and the ERG implicitly accept that there is sufficient clinical evidence for dapagliflozin in patients with CKD without comorbid T2DM and a uACR of <22.6 mg/mmol (200 mg/g) by conducting a cost-effectiveness analysis within this population. As such, there is an opportunity for NICE to make a broader	

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<u>recommendation in this population if they are satisfied that an appropriate mean age produces a cost-effective ICER</u>

The ERG were satisfied to generate and present their own ICERs for the subgroup of patients with CKD without T2DM and a uACR <22.6 mg/mmol (200 mg/g), based on their updated assumptions about the mean age of this population. The ERG therefore implicitly accept that the available clinical evidence in this subgroup is adequate to provide plausible cost-effectiveness estimates.

When a mean age which more appropriately reflects patients in UK clinical practice is used to generate cost-effectiveness estimates for this subgroup, dapagliflozin represents a cost-effective use of NHS resources. This is reflected in the Company's updated economic analysis which incorporates the newly-defined CPRD dataset detailed in Issue 6. The results of the updated analysis in the subgroup of patients with CKD without comorbid T2DM and a uACR <22.6 mg/mmol [200 mg/g] are summarised in Table 7 below (Scenario 1).

In order to fully explore the cost-effectiveness of dapagliflozin within this subgroup, and for consistency with the approach taken in the subgroup of patients with CKD and comorbid T2DM and a low uACR, additional analyses have been conducted by the Company to evaluate the cost-effectiveness of dapagliflozin within the A1 and Modified A2 subgroups in patients with CKD without comorbid T2DM. As for the T2DM analysis, two approaches have been taken whereby patient characteristics have been based on both the newly-defined CPRD dataset as well as the DECLARE$_{CKD}$ cohort. The results show that treatment with dapagliflozin in patients falling within the A1 and Modified A2 uACR categories represents a cost-effective use of NHS resources, with ICERs falling below the established willingness-to-pay threshold for both subgroups. Notably, a lower ICER was observed in the A1 subgroup versus the Modified A2 subgroup, which comprises [redacted]% versus [redacted]% of patients in the newly-defined CPRD dataset.[9]

Table 7: New uACR subgroup scenario analyses for patients with CKD without comorbid T2DM conducted by the Company as part of this response
<table>
<tr><th colspan="2">Population</th><th>ΔCosts (£)</th><th>ΔQALYs</th><th>ICER</th></tr>
<tr><td>1</td><td>Non-T2DM low uACR population (uACR <22.6 mg/mmol [200 mg/g]): risk equations from DECLARE$_{CKD}$ with non-diabetes correction factor, adjusted to patient characteristics from the newly-defined CPRD dataset (uACR <22.6 mg/mmol [200 mg/g] subgroup)</td><td>£1,512</td><td>0.088</td><td>£17,139</td></tr>
<tr><td colspan="5">Modelled patient characteristics based on the newly-defined CPRD dataset</td></tr>
<tr><td>2</td><td>Non-T2DM A1 population: risk equations from DECLARE$_{CKD}$ with non-diabetes correction factor, adjusted to patient characteristics from the newly-</td><td>£1,586</td><td>0.095</td><td>£16,684</td></tr>
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Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment

	defined CPRD dataset (uACR <3 mg/mmol [<30 mg/g] subgroup)			
3	**Non-T2DM Modified A2* population**: risk equations from DECLARE$_{CKD}$ with non-diabetes correction factor, adjusted to patient characteristics from the **newly-defined CPRD dataset** (uACR 3–22 mg/mmol [30–199 mg/g] subgroup)	£1,274	0.065	**£19,532**
Modelled patient characteristics based on the DECLARE$_{CKD}$ cohort				
4	**Non-T2DM A1 population**: risk equations from DECLARE$_{CKD}$ with non-diabetes correction factor, adjusted to patient characteristics from the **DECLARE$_{CKD}$ cohort** (uACR <3 mg/mmol [<30 mg/g] subgroup)	£1,697	0.183	**£9,277**
5	**Non-T2DM Modified A2* population**: risk equations from DECLARE$_{CKD}$ with non-diabetes correction factor, adjusted to patient characteristics from the **DECLARE$_{CKD}$ cohort** (uACR 3–22 mg/mmol [30–199 mg/g] subgroup)	£1,770	0.150	**£11,769**

**Note: ***Modified at upper bound (22 mg/mmol [199 mg/g]) to mirror DAPA-CKD trial inclusion criteria, with true A2 classification being 3–30 mg/mmol (30–300 mg/g). These analyses were conducted based on thresholds defined by mg/g values, in line with the DAPA-CKD trial eligibility criteria. For simplicity, all mg/mmol values presented throughout this response have been rounded to align with the categories defined in the draft recommendations where possible.

Abbreviations: CKD: chronic kidney disease; CPRD: Clinical Practice Research Datalink; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year; uACR: urinary albumin creatinine ratio; T2DM: type 2 diabetes mellitus.

The company acknowledges that there is limited direct evidence available on the renal efficacy of dapagliflozin in patients with CKD without comorbid T2DM and with uACR <200 mg/g. However, it is not uncommon for the NICE Committee to consider indirect evidence to inform decision making in line with the NICE Methods guidance that “consideration of a comprehensive evidence base is fundamental to the appraisal process”. In this case, the updated scenario analyses presented by the Company demonstrate that dapagliflozin either dominates standard of care (SOC) or is substantially below the threshold NICE considers cost-effective in this subgroup. Considering the evidence presented, dapagliflozin is very likely to represent a cost-effective use of NHS resources in patients with uACR <22.6 mg/mmol (200 mg/g) regardless of T2DM status when the mean age considered in the analysis more appropriately reflects UK clinical practice.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
4	Company	AstraZeneca	**Recommendations requiring uACR measurement to gain access to dapagliflozin will exacerbate current inequalities of care within the NHS** The clinical and economic evidence presented for dapagliflozin both within this response and within this technology appraisal to date support the cost-effectiveness of dapagliflozin irrespective of uACR in both the T2DM and non-T2DM populations. The Company therefore believe that restricting access to dapagliflozin based on uACR measurement is not necessary and the introduction of such a restriction is likely to exacerbate current inequalities of care within the NHS relating to uACR testing. Together with the results of the scenario analyses presented as part of this response that demonstrate dapagliflozin to be cost-effective both above and below the additional uACR threshold introduced by the Committee, the potential impact on inequalities of care within the NHS are of grave concern to the Company, professional organisations, and patients. The Company urge the Committee to remove the uACR restrictions for the use of dapagliflozin when developing the final recommendations for this technology appraisal. 4.1 Differences in uACR testing rates between secondary and primary care are substantial across the NHS The majority of patients treated with dapagliflozin will be treated in primary care ([redacted]% of patients with Stage 3–5 CKD are currently treated in primary care), and this ratio would not be impacted following the introduction of dapagliflozin.[32] Patients treated in secondary care are more likely to receive a uACR test compared with those in primary care, as they are likely to have a more advanced stage of disease and specialists are more likely to conduct additional testing compared with healthcare professionals in primary care. uACR is tested infrequently within the primary care setting. Therefore, the currently restricted recommendation based on uACR levels risks many patients with elevated uACR that meet the recommendations set out in the ACD not receiving appropriate treatment due to a lack of testing, resulting in poorer disease outcomes. The Company would also like to highlight that the view provided by a patient expert during the Committee meeting and captured in the ACD that they "*would not hesitate to provide a urine sample*" for uACR testing may not accurately reflect the opinion of all patients treated with dapagliflozin. The Company are pleased to hear the patient expert's opinion and are confident the view presented to the Committee accurately reflects their personal opinion; however, the Company would like to highlight that this statement is from a single patient with advanced CKD being treated within secondary care who is engaged with their care and sufficiently informed to participate as a patient expert within the NICE process. The Company therefore believe that this opinion does not represent the view of the majority of patients who would be treated with dapagliflozin for their CKD in clinical practice. Indeed, the results of a survey of 403 UK general practitioners and nurses involved in the treatment of patients with T2DM indicate that many patients may be reluctant to provide a urine sample.[33] The survey, conducted by Napp Pharmaceuticals in 2019, found that 54% of enrolled HCPs did not conduct annual uACR testing, and that the most frequent reason for not conducting a uACR test was that their patient was unwilling to provide a urine sample.[33] 4.2 Inequalities in uACR testing between patients with and without T2DM will lead to unequal access to dapagliflozin based on disease status by restricting access among patients without T2DM uACR testing rates are currently lower in patients with CKD without comorbid T2DM than those with comorbid	The committee acknowledged that uACR testing is not currently implemented consistently in the NHS. If this did not change, limiting dapagliflozin to subgroups based on uACR levels may negatively affect patient access. However, uACR testing is easy to do, has value in identifying people with CKD who are likely to benefit from dapagliflozin, and is recommended in NG203. Therefore the committee concluded that the current low levels of uACR testing should not prevent it from being included as a criterion in recommendations for dapagliflozin. See section 3.6 of the FAD.

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			T2DM. The results of the National Chronic Kidney Disease Audit in 2017 indicate that less than 15% of patients with CKD without T2DM receive annual uACR testing compared to 54% of those with T2DM.[23] Furthermore, within the DAPA-CKD trial similar proportions of patients with and without comorbid T2DM had a uACR of ≥22.6 mg/mmol (200 mg/g) pre-randomisation ([redacted]% and [redacted]% at the first trial visit, respectively), demonstrating that patients with CKD without comorbid T2DM are equally likely to be eligible for dapagliflozin.[34] Patients without comorbid T2DM who meet the criteria set out in the currently restricted recommendation of the ACD are therefore disadvantaged on the basis of their disease status, due to their lower likelihood of being uACR tested compared to patients with CKD and comorbid T2DM. In addition, a retrospective cohort study using CPRD by Feakins *et al.* in 2018 demonstrated that uACR testing rates are lower for patients of black or Asian ethnicity than for those of Caucasian background and therefore a restriction by uACR may be likely to further drive racial inequalities of healthcare across the UK.[35] 4.3 Use of a technology appraisal recommendation to encourage uACR testing is inappropriate The Committee discussion captured within the ACD implies that not including a uACR restriction within the recommendations for this technology appraisal may reduce the motivation to test for uACR in clinical practice. However, uACR testing has already been deprioritised in clinical practice, indicated by its removal from the Quality Outcomes Framework (QOF) in 2013/2014 despite being recommended in the NICE CKD clinical guidelines at the time (CG182).[7] Since the removal of uACR testing from the QOF in 2013/2014, the proportion of patients with CKD with or without T2DM that receive an annual uACR test has reduced substantially within England as shown in Figure 1.[36] It is also likely that there have since been further declines in uACR testing due to the COVID-19 pandemic which have not yet been reversed. The Company consider it unrealistic to expect rates of testing to increase to the point that would allow full access to dapagliflozin for all eligible patients. As such, the inclusion of restrictions based on uACR measurement in the current draft recommendations for this appraisal only serves to unnecessarily prevent access to dapagliflozin. **Figure 1: Analysis of uACR testing indicators no longer in QOF (INLIQ) in England, 2013/14 to 2018/19**	

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			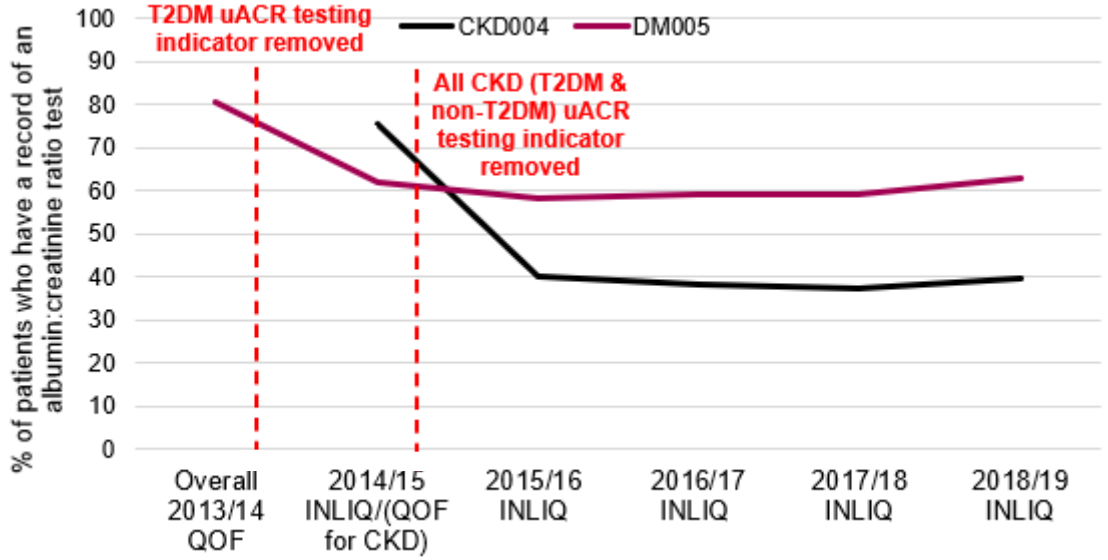 **Footnotes**: CKD004: percentage of patients on the CKD register (with and without T2DM) whose notes have a record of a urine:creatinine ratio (or protein:creatinine ratio) test in the preceding 12 months; DM005: The percentage of patients with diabetes, on the register, who have a record of an albumin:creatinine ratio test in the preceding 12 months **Abbreviations**: CKD: chronic kidney disease; INLIQ: indicators no longer in QOF; QOF: Quality of Outcomes Framework; uACR: urinary albumin creatinine ratio. **Source**: Public Health England, 2020.[36] <u>4.4 The eGFR restrictions included within the draft recommendations define a population at high risk of adverse outcomes who would benefit from additional treatment options, regardless of uACR</u> The draft recommendations currently included within the ACD apply an eGFR restriction of 25–75 ml/min/1.73m^2 for patients with CKD both with and without comorbid T2DM. As indicated in the Kidney Disease Improving Global Outcomes (KDIGO) grid, patients with an eGFR <60 ml/min/1.73m^2 (irrespective of uACR) have an increased risk of disease progression and adverse clinical outcomes, with the risk increasing as eGFR decreases (Figure 2).[37] The current restricted recommendation based on uACR means that patients with decreased renal function (eGFR <60 ml/min/1.73m^2), who either a) meet the uACR criteria but are not tested for uACR or b) have a normal uACR, would not be able to benefit from treatment with dapagliflozin. **Figure 2: Representation of patients with CKD meeting the eGFR criteria set out within the ACD**	

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			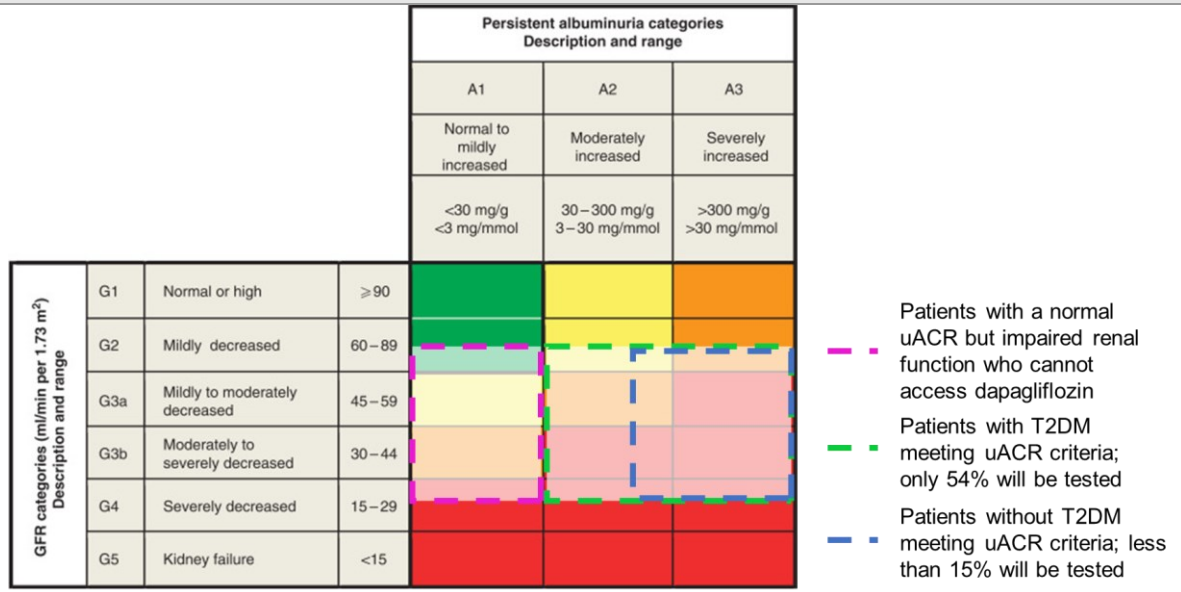 **Footnotes**: Green, low risk of disease progression; yellow, moderately increased risk of disease progression; orange, high risk of disease progression; red, very high risk of disease progression. **Abbreviations:** CKD: chronic kidney disease; GFR: glomerular filtration rate; eGFR: estimated glomerular filtration rate; T2DM: type 2 diabetes mellitus; uACR: urine albumin-to-creatinine ratio. **Source:** KDIGO 2012 ;[38] National CKD Audit 2017.[23] 4.5 The inequalities in care highlighted above directly contradict NICE and the NHS's long-term strategy Finally, the NHS long-term plan highlights a commitment to disease prevention and removing healthcare inequalities.[39] The plan explicitly commits to a more concentrated and systematic approach to reducing health inequalities with a promise that action on health inequalities will be central to the NHS. The recently published NICE 5-year strategy further commits to contributing to reducing healthcare inequalities. Given the highly innovative nature of dapagliflozin for the treatment of patients with CKD, the broad licence granted for dapagliflozin by both the EMA and MHRA, and the highly cost-effective ICER estimates within all patient subgroups, dapagliflozin offers NICE and the NHS an opportunity to reduce healthcare inequalities for patients with CKD by enabling access to dapagliflozin for the full population that need it, without the requirement for a uACR test.	
5	Company	AstraZeneca	**Canagliflozin should not be considered a relevant comparator to dapagliflozin in patients with CKD and**	The committee

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			T2DM The ACD states "*The company did not consider canagliflozin a relevant comparator for dapagliflozin in CKD because it noted that canagliflozin is not widely used for treating CKD with type 2 diabetes in the UK*". The ACD should reflect that canagliflozin was not included in the NICE final scope and therefore the Company were not required to compare to canagliflozin as part of this appraisal. Nevertheless, the Company performed an indirect treatment comparison versus canagliflozin for completeness and transparency. The ACD acknowledges that canagliflozin was recommended for patients with CKD and T2DM as part of a class level recommendation for SGLT2 inhibitors in the NICE CKD clinical guidelines (NG203).[7] However, it is important to emphasise that a recommendation within clinical guidelines does not constitute established clinical practice. The clinical guideline was only published on 25th August 2021, meaning that any impact of the guideline will not yet have translated into UK clinical practice. In addition, clinical guidelines are not associated with the funding mandate of a technology appraisal (a process through which canagliflozin has not undergone in this indication), meaning canagliflozin has not received a recommendation for reimbursement in this population. As a result, the proportion of UK patients with T2DM and CKD Stages 3a or 3b (eGFR 30–59 mL/min/1.73 m^2) who were prescribed canagliflozin increased only slightly from 4.7% in June 2020 (prior to the inclusion of renal data from CREDENCE with the licence update to patients with DKD) to 8.5% in April 2021 (Figure 3).[40] The low uptake of canagliflozin may result from a lack of awareness of the broader population now licensed for treatment, and the fact that physicians in primary care (where the majority of DKD patients would be treated) may typically consider SGLT2 inhibitors as T2DM therapies. Primary care physicians may be less familiar with the cardiorenal benefits of SGLT2 inhibitors in patients with an eGFR <45 mL/min/1.73 m^2 than specialists in secondary care. Nevertheless, the data presented in Figure 3 below represent only a modest increase in canagliflozin uptake for the newly licenced population of patients with DKD and arguably do not represent a level of uptake that would constitute established clinical practice, a criterion required to be met for a therapy to be considered a formal comparator within a technology appraisal. Finally, the Company request that the ACD is updated to reflect that canagliflozin is licenced only for the treatment of patients with DKD specifically (CKD caused by T2DM), whereas dapagliflozin is licenced for the treatment of CKD regardless of diabetes status, including patients with CKD and comorbid T2DM which has not necessarily caused their CKD.[12, 41, 42] The available data for canagliflozin therefore support the clinical efficacy of canagliflozin in patients with DKD only, which comprises a subgroup of patients with CKD and comorbid T2DM. **Figure 3: Uptake of canagliflozin amongst UK patients with DKD Stage 3a and b (eGFR 30–59 mL/min/1.73 m^2)**	considered that, since canagliflozin was recommended in NG28 and is being used to some extent in clinical practice, it represents established clinical practice for people with CKD and type 2 diabetes. It concluded that canagliflozin is a relevant comparator in people with diabetic kidney disease. See section 3.5 of the FAD.

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			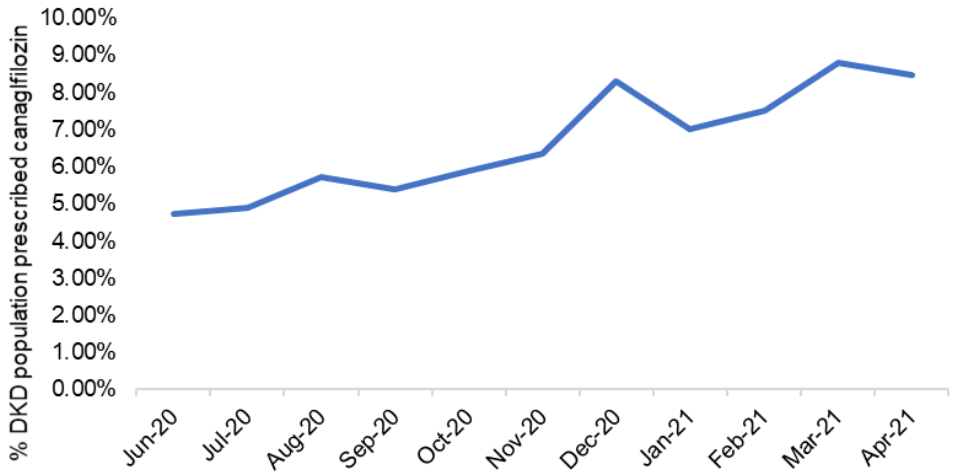 **Abbreviations**: DKD: diabetic kidney disease; eGFR: estimated glomerular filtration rate. **Source**: AstraZeneca Data on File: IQVIA Ltd, incorporating data derived from THIN, A Cegedim Database, Monthly, April 2021.[40]	
6	Company	AstraZeneca	**Revised CPRD dataset** As highlighted above, the Company have updated their base case cost-effectiveness results and scenario analyses using an updated analysis of CPRD data. The overall modelling approach has remained consistent with the approach taken in the Company's updated model submitted at Technical Engagement. However, in line with the draft ACD recommendations restricting dapagliflozin to use in patients with eGFR ≥25 to ≤75 ml/min/1.73 m^2, the Company have updated their analysis of the CPRD dataset to include only patients with eGFR ≥25 to ≤75 ml/min/1.73 m^2 with or without a coded CKD diagnosis. The Company acknowledge that since uACR restrictions were not applied to define this patient population, this analysis will include some patients with an eGFR of 60–75 ml/min/1.73 m^2 that do not have a uACR ≥3 mg/mmol (≥30 mg/g) and therefore would not meet the criteria for a formal diagnosis of CKD. However, given that the rate of uACR testing in the UK is so low, especially in earlier stages of disease, the application of a uACR restriction would serve to exclude many relevant patients due to absent test results. Therefore, in the absence of alternative, more appropriate sources in the literature (see Issue 3.2), this updated analysis of CPRD represents the best available source to characterise the patients in which dapagliflozin will used in clinical practice and therefore inform the patient characteristics within the economic model. The updated CPRD dataset has been used to inform the patient characteristics in the Company's economic model and is associated with a mean age of 72.9 years. Patients identified in the newly-defined CPRD dataset were split into the uACR categories outlined below in Table 8, with the majority of patients falling within the A1	The analyses based on the revised CPRD dataset were considered by committee. See section 3.15 of the FAD. The additional subgroup analyses based on uACR category were considered by committee. See section 3.19 of the FAD.

<table>
<tr><th>Comment number</th><th>Type of stakeholder</th><th>Organisation name</th><th>Stakeholder comment
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Please respond to each comment</th></tr>
<tr><td></td><td></td><td></td><td>category (<3mg/mmol [30 mg/g]). The new ICERs for the base case and scenario analyses generated by the revised economic model are presented throughout this response and summarised below in Issue 7.

Table 8: Proportion of patients in each uACR category in the new CPRD dataset (of patients with a uACR measurement available)
<table>
<tr><th colspan="2">uACR category</th><th>All patients (n=106,675)</th><th>Patients with T2DM (n=72,061)</th><th>Patients without T2DM (n=34,614)</th></tr>
<tr><td>A1</td><td><3 mg/mmol (<30 mg/g)</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Modified A2*</td><td>3–22 mg/mmol (30–199 mg/g)</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>≥22.6 mg/mmol</td><td>≥22.6 mg/mmol (≥200 mg/g)</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
</table>
Note: *Modified at upper bound (22 mg/mmol [199 mg/g]) to mirror the DAPA-CKD trial inclusion criteria, with the true A2 classification being 3–30 mg/mmol (30–300 mg/g). These analyses were conducted based on thresholds defined by mg/g values, in line with the DAPA-CKD trial eligibility criteria. For simplicity, all mg/mmol values presented throughout this response have been rounded to align with the categories defined in the draft recommendations where possible. Patients with missing uACR measurements: n=[redacted] (n=[redacted] and n=[redacted] for patient with and without T2DM, respectively).

Abbreviations: CPRD: Clinical Practice Research Datalink; T2DM: Type 2 diabetes mellitus; uACR: urine albumin-creatinine ratio.</td><td></td></tr>
<tr><td>7</td><td>Company</td><td>AstraZeneca</td><td><u>Summary of the additional analyses conducted by the Company as part of this response</u>

This section provides a full summary of the additional analyses conducted by the Company as part of this response:

• An updated base case analysis based on the characteristics of patients from the newly-defined CPRD dataset detailed above (see Table 7)
  ○ This analysis is entirely consistent with the approach taken within the Company's updated model submitted at Technical Engagement, however, as detailed above in Issue 6, a revised CPRD dataset has been identified to more closely reflect the anticipated patient population for dapagliflozin defined in the ACD. The patient characteristics from this newly-defined CPRD dataset have therefore been used to adjust the risk equations from the DAPA-CKD and DECLARE$_{CKD}$ combined dataset within the updated Company base case. As shown in Table 9, the updated Company base case ICER is very similar to the base case ICER presented at Technical Engagement.
• Revised scenario analyses based on the characteristics of patients from the newly-defined CPRD dataset that fall within the expected target populations (Subgroup 1: uACR ≥22.6 mg/mmol (200 mg/g);</td><td>The new analyses were considered by the committee during decision making. See section 3.15 and section 3.19 of the FAD.</td></tr>
</table>

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<tr><td></td><td></td><td></td><td>
Subgroup 2: T2DM with a uACR <22.6 mg/mmol (200 mg/g); Subgroup 3: non-T2DM with a uACR <22.6 mg/mmol (200 mg/g) (Scenarios 1–3 in Table 7)
○ As with the updated Company base case, these scenario analyses adopt an entirely consistent modelling approach as per the Company's updated model submitted at Technical Engagement. For these scenario analyses, the risk equations from the combined DAPA-CKD and DECLARE$_{CKD}$ dataset have been adjusted using the characteristics from patients within the newly-defined CPRD dataset that fall within the relevant uACR subgroup. As for the analyses conducted at Technical Engagement, all analyses conducted for patients with CKD and without T2DM have included the non-diabetes correction factor.
• New scenario analyses within the additional uACR subgroups constructed by the Committee of <3 mg/mmol (**A1**: <30 mg/g) and 3–22 mg/mmol (**Modified A2**: 30–199 mg/g [modified at upper bound to mirror the DAPA-CKD trial inclusion criteria, with the true A2 classification being 3–30 mg/mmol {30–300 mg/g}]), in both the T2DM and non-T2DM populations (Scenarios 4–11, Table 7)
○ As with the updated Company base case, these scenarios adopt an entirely consistent modelling approach as per the Company's updated model submitted at Technical Engagement.
▪ Scenarios 4, 6, 8 and 10 are based on the characteristics of patients from the **newly-defined CPRD dataset** that fall within the additional uACR-restricted subgroups set out by the Committee
▪ Scenarios 5, 7, 9 and 11 are based on the characteristics of patients from the **DECLARE$_{CKD}$ cohort** that fall within the additional uACR-restricted subgroups set out by the Committee
▪ The two approaches generate similar ICERs, demonstrating the robustness of these results.
○ As for the analyses conducted at Technical Engagement, all analyses conducted for patients with CKD and without T2DM include the non-diabetes correction factor.
As shown in Table 9, the results from all scenario analyses conducted by the Company as part of this response fall well below the threshold considered for the cost-effectiveness of new therapies by NICE. The Company therefore hope that the analyses presented as part of this response serve to alleviate some of the Committee's concerns and allow the Committee to reconsider their draft recommendations.
Table 9: Revised Company base case and scenario analyses conducted as part of this response
<table>
<tr><th>Population</th><th>ΔCosts (£)</th><th>ΔQALYs</th><th>ICER</th></tr>
<tr><td>Updated Company base case: overall population
(risk equations from DAPA-CKD and DECLARE$_{CKD}$</td><td>£1,974</td><td>0.332</td><td>£5,948</td></tr>
</table>
</td><td></td></tr>
</table>

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row				NICE Response Please respond to each comment
			combined dataset, adjusted to patient characteristics of newly-defined CPRD dataset)				
			1	**DAPA-CKD like population (uACR ≥22.6 mg/mmol [200 mg/g])**: risk equations from the DAPA-CKD and DECLARE$_{CKD}$ combined dataset, adjusted to patient characteristics from the newly-defined CPRD dataset (uACR ≥22.6 mg/mmol [200 mg/g] subgroup)	−£1,004	0.521	**Dominant**
			2	**T2DM low uACR population (uACR <22.6 mg/mmol [200 mg/g])**: risk equations from DECLARE$_{CKD,}$ adjusted to patient characteristics from the newly-defined CPRD dataset (uACR <22.6 mg/mmol [200 mg/g] subgroup)	£2,576	0.430	**£5,990**
			3	**Non-T2DM low uACR population (uACR <22.6 mg/mmol [200 mg/g])**: risk equations from DECLARE$_{CKD}$ with non-diabetes correction factor, adjusted to patient characteristics from the newly-defined CPRD dataset (uACR <22.6 mg/mmol [200 mg/g] subgroup)	£1,512	0.088	**£17,139**
			New uACR subgroup scenario analyses				
			4	**T2DM A1 population**: risk equations from DECLARE$_{CKD,}$ adjusted to patient characteristics from the **newly-defined CPRD dataset** (uACR <3 mg/mmol [<30 mg/g] subgroup)	£2,646	0.433	**£6,112**
			5	**T2DM A1 population**: risk equations from DECLARE$_{CKD,}$ adjusted to patient characteristics from the **DECLARE$_{CKD}$ cohort** (uACR <3 mg/mmol [<30 mg/g] subgroup)	£2,603	0.436	**£5,965**
			6	**T2DM Modified A2* population**: risk equations from DECLARE$_{CKD,}$ adjusted to patient characteristics from the **newly-defined CPRD dataset** (uACR 3–22 mg/mmol [30–199 mg/g] subgroup)	£2,309	0.412	**£5,599**
			7	**T2DM Modified A2* population**: risk equations from DECLARE$_{CKD,}$ adjusted to patient characteristics from the **DECLARE$_{CKD}$ cohort**	£2,675	0.421	**£6,352**

<table>
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Please respond to each comment</th></tr>
<tr><td></td><td></td><td></td><td>
<table>
<tr><td></td><td>(uACR 3–22 mg/mmol [30–199 mg/g] subgroup)</td><td></td><td></td><td></td></tr>
<tr><td>8</td><td>Non-T2DM A1 population: risk equations from DECLARE$_{CKD}$ with non-diabetes correction factor, adjusted to patient characteristics from the newly-defined CPRD dataset (uACR <3 mg/mmol [<30 mg/g] subgroup)</td><td>£1,586</td><td>0.095</td><td>£16,684</td></tr>
<tr><td>9</td><td>Non-T2DM A1 population: risk equations from DECLARE$_{CKD}$ with non-diabetes correction factor, adjusted to patient characteristics from the DECLARE$_{CKD}$ cohort (uACR <3 mg/mmol [<30 mg/g] subgroup)</td><td>£1,697</td><td>0.183</td><td>£9,277</td></tr>
<tr><td>10</td><td>Non-T2DM Modified A2* population: risk equations from DECLARE$_{CKD}$ with non-diabetes correction factor, adjusted to patient characteristics from the newly-defined CPRD dataset (uACR 3–22 mg/mmol [30–199 mg/g] subgroup)</td><td>£1,274</td><td>0.065</td><td>£19,532</td></tr>
<tr><td>11</td><td>Non-T2DM Modified A2* population: risk equations from DECLARE$_{CKD}$ with non-diabetes correction factor, adjusted to patient characteristics from the DECLARE$_{CKD}$ cohort (uACR 3–22 mg/mmol [30–199 mg/g] subgroup)</td><td>£1,770</td><td>0.150</td><td>£11,769</td></tr>
</table>
Note: *Modified at upper bound (22 mg/mmol [199 mg/g]) to mirror the DAPA-CKD trial inclusion criteria, with the true A2 classification being 3–30 mg/mmol (30–300 mg/g). These analyses were conducted based on thresholds defined by mg/g values, in line with the DAPA-CKD trial eligibility criteria. For simplicity, all mg/mmol values presented throughout this response have been rounded to align with the categories defined in the draft recommendations where possible.

Abbreviations: CKD: chronic kidney disease; CPRD: Clinical Practice Research Datalink; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year; uACR: urinary albumin creatinine ratio; T2DM: type 2 diabetes mellitus.
</td><td></td></tr>
<tr><td>8</td><td>Company</td><td>AstraZeneca</td><td><u>Additional comments and factual inaccuracies</u>

1. In Section 2.14, when discussing the Public Health England report suggesting that CKD is more prevalent in people aged 75 and over compared with people aged 64 and under, the ACD states “the Committee acknowledged that this report was limited to CKD Stage 3 to 5 and did not fully reflect the target population in the company submission”. The Company request that this sentence is updated to specify exactly the target population in the submission and the likely impact on the applicability of the</td><td>The reference to the Public Health England report has been removed from the FAD.

The changes described in points 2, 3 and 4 have</td></tr>
</table>

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			report (proposed changes in red): "*the Committee acknowledged that this report was limited to CKD Stage 3 to 5 and did not fully reflect the target population in the company submission (CKD Stages 1 to 4, i.e. a patient population with earlier stage disease who would be expected to be younger than patients with Stage 3 to 5 disease)*". 2. In **Section 3.7**, the ACD states "*The clinical experts considered that there would likely be benefits in starting dapagliflozin in people with an eGFR of between 15 ml/min/1.73 m^2 and 25 ml/min/1.73 m^2, despite the lack of clinical evidence. However, they noted the uncertainty in this population, as well as concerns with the impact of a transient decrease in eGFR associated with SGLT2 inhibitors at lower eGFR levels*". The Company do not recall that this was the conclusion made by the three clinical experts during the Committee meeting, and believe this was only mentioned by one expert. The Company disagree that there is uncertainty around the clinical benefit of dapagliflozin in this population: dapagliflozin has received marketing authorisation for the treatment of adults with CKD in addition to SOC (i.e. regardless of uACR or eGFR category), demonstrating that the regulatory body is satisfied with the clinical evidence for dapagliflozin in patients with eGFR 15–25 ml/min/1.73 m^2. The Company request that this sentence is updated accordingly (proposed changes in red) "*The clinical experts considered that there would likely be benefits in starting dapagliflozin in people with an eGFR of between 15 ml/min/1.73 m^2 and 25 ml/min/1.73 m^2, despite the lack of clinical evidence. However, one expert ~~they~~ noted the uncertainty in this population, as well as concerns with the impact of a transient decrease in eGFR associated with SGLT2 inhibitors at lower eGFR levels*" 3. In **Section 3.8**, the ACD states "*7% of people (n=1,100) had an eGFR of less than 60 ml/min/1.73 m^2. DECLARE-TIMI-58 did not restrict inclusion in the trial based on uACR levels*". The Company believe this wording leads readers to incorrectly consider that 1,100 patients is not a large cohort size. Furthermore, the second sentence detailing the DECLARE-TIMI-58 uACR levels should be reworded to reflect the fact that patients in DECLARE-TIMI-58 were included across the full spectrum of uACR ranges. Therefore, the Company request the following wording changes are made (proposed changes in red): "*1,265 (7.4%) ~~7% of people (n=1,100)~~ had an eGFR of less than 60 ml/min/1.73 m^2. DECLARE-TIMI-58 did not restrict inclusion in the trial based on uACR levels and therefore likely enrolled patients across a wide range of uACR levels*". The Company would also like to note the proportion of patients with an eGFR <60 ml/min1.73m^2 in DECLARE-TIMI-58 should be 1,265 (7.4%), which has been corrected above.[1] 4. In **Section 3.8**, the Company request that the sentence "*Both DECLARE-TIMI-58 and DAFA-HF included some people with comorbid CKD*" is updated to include the proportion of patients with comorbid CKD in DECLARE-TIMI-58 and DAPA-HF (34.8% and 40.7%, respectively), and that DAFA-HF is corrected to DAPA-HF, as follows (proposed changes in red): "*Both DECLARE-TIMI-58 and DAPA-HF included some people with comorbid CKD (34.8% and 40.7%, respectively)*".[43, 44] 5. In **Section 3.16**, the ACD states that the exact results of the cost-effectiveness analysis in subgroup 1 are commercial in confidence because they include confidential discounts. The Company are not aware of any commercial in confidence discounts that are considered in the cost-effectiveness model. The results of the cost-effectiveness analysis were presented in the ACM slides and this statement should therefore be removed from the ACD.	been made in the FAD. The ICERs are now reported in sections 3.18 to 3.20 of the FAD.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
9	Comparator	Boehringer-Ingelheim	*BI are pleased that NICE recognise the benefit of a medicine in the SGLT2i class in the treatment of CKD. We understand that this represents good news for both patients and clinicians in providing an additional therapeutic option.'*	Comment noted.
10	Comparator	Novartis	Novartis agrees that the draft recommendation reflects the available evidence relevant to this appraisal. Clarity of the recommendation wording (section 1.1) could be improved by adding the following *italicised text*: "Dapagliflozin is recommended as an option for treating chronic kidney disease (CKD) in adults. It is recommended only if: • it is an add-on to optimised standard care including angiotensin-converting enzyme (ACE) inhibitors or angiotensin-receptor blockers (ARBs) *(titrated to the highest licensed dose that the person can tolerate)*, unless these are contraindicated ~~or not tolerated~~, and • people have an estimated glomerular filtration rate (eGFR) *at treatment initiation* of 25 ml/min/1.73 m^2 to 75 ml/min/1.73 m^2 and [...]" Addition of "titrated to the highest licensed dose that the person can tolerate" would ensure consistency with the wording used in the NICE guidelines 'Chronic kidney disease: assessment and management' (NG203) and 'Type 2 diabetes in adults: management' (NG28) when referring to treatment with an ACE inhibitor or ARB for CKD. By providing greater specificity in terms of defining 'optimised' standard care, the suggested adaptation could contribute to reducing variation in care. It would also be in line with the inclusion criteria of the pivotal DAPA-CKD study ("Stable, and for the patient maximum tolerated labelled daily dose, treatment with ACE-I or ARB for at least 4 weeks before visit 1, if not medically contraindicated")[1] and thus reflect the available evidence. As the aspect of potential intolerance is already covered by the suggested addition, the text "or not tolerated" could be omitted. eGFR thresholds both in the DAPA-CKD trial inclusion criteria[1] and the SmPC[2] refer to eGFR at initiation of dapagliflozin treatment. We propose adding this information in order to avoid misinterpretation that dapagliflozin treatment would need to be stopped once a patient's eGFR declines below 25 ml/min/1.73 m^2. References: [1] A Study to Evaluate the Effect of Dapagliflozin on Renal Outcomes and Cardiovascular Mortality in Patients with Chronic Kidney Disease. Clinical Study Protocol Version 4.0. Published with: Heerspink HJL, Stefánsson BV, Correa-Rotter R, et al. Dapagliflozin in patients with chronic kidney disease. N Engl J Med 2020;383:1436-46. [2] Forxiga 10 mg film-coated tablets. Summary of Product Characteristics. Available at: https://www.medicines.org.uk/emc/product/7607/smpc [Date accessed: 23 November 2021].	The suggested changes have been made to section 1.1 of the FAD.
11	Comparator	Novartis	Novartis agrees with the Committee's conclusion in section 3.6 that it is appropriate to make recommendations for dapagliflozin based on uACR levels. The ACD (section 3.6) notes hesitancy about doing urine tests in secondary care; however, this issue may be more prevalent in primary care. Expert input during the first appraisal committee meeting seemed to suggest that urine tests are done more commonly in specialist renal clinics in secondary care. The current summary in	Section 3.6 of the FAD has been amended to remove the reference to secondary care specifically when

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			the ACD may therefore need to be reconsidered. With regard to testing uACR versus uPCR (ACD section 3.6), the recently updated NICE guideline 'Chronic kidney disease: assessment and management' (NG203) states a preference for using uACR due to greater sensitivity for low levels of proteinuria, with the option to use uPCR as an alternative if uACR is ≥70 mg/mmol. The rationale and impact section of the guideline mentions that the guideline committee found that the recommendation of uACR over uPCR fits well with current practice, which suggests that overall, uACR testing is more widely done. The statement in ACD section 3.6 that uPCR tests are more widely done than uACR tests may therefore not be accurate. However, uPCR is the preferred measure in some CKD aetiologies such as glomerular diseases.[3] Further information on circumstances where uPCR may be considered the more appropriate measure could be added. A recommendation how to convert between uACR and uPCR categories is available, although several limitations are acknowledged.[3, 4] Reference: [3] Kidney Disease Improving Global Outcomes (KDIGO). KDIGO 2021 Clinical Practice Guideline for the Management of Glomerular Diseases. Kidney International 2021;100. [4] Kidney Disease Improving Global Outcomes (KDIGO). KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. Kidney International Supplements 2013;3.	describing the hesitancy around urine tests. Section 3.6 of the FAD has been updated to remove the reference to uACR testing when describing the prevalence of uPCR testing.
12	Comparator	Novartis	Section 3.7 of the ACD states that "DAPA-CKD included people with an eGFR of 25 ml/min/1.73 m^2 to 75 ml/min/1.73 m^2 and a uACR of 22.6 mg/mmol or more." The trial inclusion criteria specified also an upper uACR limit of 5000 mg/g (565 mg/mmol)[1] and the text in section 3.7 should be amended accordingly to reflect this. Reference: [1] A Study to Evaluate the Effect of Dapagliflozin on Renal Outcomes and Cardiovascular Mortality in Patients with Chronic Kidney Disease. Clinical Study Protocol Version 4.0. Published with: Heerspink HJL, Stefánsson BV, Correa-Rotter R, et al. Dapagliflozin in patients with chronic kidney disease. N Engl J Med 2020;383:1436-46.	Section 3.7 of the FAD has been updated in line with this comment.
13	Comparator	Novartis	Section 3.8 of the ACD states that "DECLARE-TIMI-58 included people with type 2 diabetes who had, or were at high risk of, cardiovascular events and had an eGFR of more than 60 ml/min/1.73 m^2. However, 7% of people (n=1,100) had an eGFR of less than 60 ml/min/1.73 m^2." The DECLARE-TIMI-58 exclusion criterion referred to creatinine clearance <60 ml/min, rather than eGFR <60 ml/min/1.73 m^2.[5] We therefore propose that in the above first sentence about people included in the DECLARE-TIMI-58 study, "... and had an eGFR of more than 60 ml/min/1.73 m^2" is replaced with ".... and had a creatinine clearance of 60 ml/min or more". Reference: [5] DECLARE Dapagliflozin Effect on CardiovascuLAR Events. A Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial to Evaluate the Effect of Dapagliflozin 10 mg Once Daily on the Incidence of Cardiovascular Death, Myocardial Infarction or Ischemic Stroke in Patients with Type 2 Diabetes. Revised Clinical Study Protocol, Edition Number 5.0. Available at: https://s3.amazonaws.com/ctr-med-7111/D1693C00001/9c285ea0-c985-475c-9454-693ef18bed8c/7bfad075-4f33-4ef9-9b0b-	Section 3.8 of the FAD has been updated in line with this comment.

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			82b2648b7afb/DECLARE_TIMI_58_D1693C00001-revised-csp_5_Redacted_version-v1.pdf [Date accessed: 23 November 2021].	
14	Professional group	London Kidney Network	**Are the provisional recommendations sound and a suitable basis for guidance to the NHS?** Our view is that the provisional recommendations are implementable in NHS settings. We are pleased to see that there is no longer mention of complex monitoring in primary care after commencement of this treatment, which we felt to be a barrier to implementation – as well as unsupported by the literature. We offer that the guidance should refer to an eGFR greater than 25 rather than 25 where this appears in the document.	The wording of [greater than or equal to] 25 ml/min/1.73 m^2 rather than greater than 25 ml/min/1.73 m^2 has been retained, as this aligns with the inclusion criteria of the DAPA-CKD trial.
15	Professional group	London Kidney Network	**Has all of the relevant evidence been taken into account?** Yes, we consider that it has been.	Comment noted.
16	Professional group	London Kidney Network	**Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?** Yes, we believe they are.	Comment noted.
17	Professional group	London Kidney Network	The key issue as we see it from an equalities point of view, is that the benefits of this drug are so clear that it is more important than ever that it is equitably available to all and particularly to service users who find our services more challenging to engage with.	Dapagliflozin has been recommended in the subgroups in which the committee considered that it represents an acceptable use of NHS resources.
18	Professional group	London Kidney Network	Data from East London supports CKD being more common and severe in Black and South Asian populations, and those in higher deprivation indices. No mention is made of the imperative we have to ensure that traditionally marginalised groups are prescribed this drug, but this may be beyond the remit of this appraisal. It may be that time and close monitoring of prescribing trends will tell us if we are succeeding to do this. SGLT2i have been used in trials when ACE-i/ARB doses are maximised; the use of these drugs is differentially distributed by ethnicity and deprivation. It is therefore possible that the SGLT2-i may be overlooked if a patient is not already on an ACE/ARB. Conversely, the provision of guidance for the use of SGLT2-i may encourage the prescription of ACE/ARB as a first step, bringing about a benefit to this patient group.	The committee noted that CKD disproportionally affects people from black, Asian, and minority ethnic groups and lower socioeconomic backgrounds. People from these groups are also more likely to have CKD that progresses quicker to kidney failure and to die earlier. It also noted that use of ACE inhibitors or ARBs differs by ethnicity and socioeconomic status. However, the committee did not consider these to be equality issues that could be resolved by this appraisal. See section

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				3.22 of the FAD.
19	Professional group	London Kidney Network	We are not entirely clear on how these recommendations may impact people living with disabilities. With the advent of virtual CKD service growing, physical access to nephrologists is less important than it has been to garner a special opinion. That having been said, these drugs should come from primary care, so the question is how patients with disability engage with primary care overall rather than how they access nephrology. It may be beyond the scope of this technological assessment to make recommendations on increasing access to health services.	The committee did not consider that there were any equality issues that could be resolved by this appraisal. See section 3.22 of the FAD.
20	Professional group	London Kidney Network	Proteinuria testing is differential by age/ethnicity (and likely other groups who can't access service to deliver a urine sample) so, if prescription is based on proven presence of proteinuria, this may be a consideration. This will be less relevant if prescribing advice and evidence indicates good effects regardless of proteinuria.	The committee considered that it is appropriate to make recommendations for dapagliflozin based on uACR levels. See section 3.6 of the FAD.
21	Professional group	Royal College of General Practitioners	The RCGP welcome the addition of any new medication to prevent severe CKD and renal failure, however, we believe that making the assumption that "Chronic kidney disease (CKD) is a complex progressive disorder with loss of nephrons causing kidney function to decline over time…. lead(ing). to end-stage renal disease and death" is an extreme position on CKD when looking at primary care patients. Within primary care, the vast majority of people who are diagnosed with CKD will not progress to develop end stage renal disease or subsequently die *from* the condition. Most people who present with CKD within primary care are older adults whose kidneys are not functioning as well as they used to, due to age. These patients die *with* CKD, rather than *from* CKD. Whilst we understand the importance of preventing decline in renal function, this has to be weighed up against the unintended consequences of overprescribing and drug interactions which is key when managing multimorbid disease within primary care, especially in an aging population. The unintended consequences are central to the over prescribing review recently published by DHSC and we believe must be considered when making recommendations for new drugs. (https://www.gov.uk/government/publications/national-overprescribing-review-report)	Section 3.1 of the FAD has been updated to state that CKD can eventually lead to end-stage renal disease and death (rather than that it always does). Section 3.1 has also been updated to state that CKD can have huge implications on a person's quality of life (rather than it always does). Section 3.2 of the FAD has been updated to state that with current best practice CKD can often still progress to end-stage renal disease (rather than it often does). Section 3.20 of the FAD has been updated to note the concerns around the potential consequences of overprescribing and drug interactions, particularly in people with milder

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				disease.
22	Professional group	Royal College of General Practitioners	The recommendation to prescribe this drug to anyone with an eGFR from 25-75 and an ACR >22.6, does not appear to align with the data presented to the committee. The average age of the trial patients was 61, the average eGFR was 43 and the average ACR was greater than 100mg/mol. This trial data therefore represented severe disease, whereas the recommendations provided appear to recommend this medication for patients who have significantly milder disease, very commonly seen in primary care and whose renal function often remains stable for years. Can the committee explain why these cut offs were chosen which do not appear to align with the data presented from the trails and when considering the upper limit of eGFR (currently 75), to add on this medication, consider the unintended consequences of over prescribing in the elderly and those with multiple co morbid disease.	The recommendations in section 1.1 of the FAD align with the available evidence from the DAPA-CKD and DECLARE-TIMI-58 clinical trials.
23	Professional group	Royal College of General Practitioners	Finally, when making the recommendations, it is essential that clear guidance is given to primary care regarding additional monitoring required and that the correct timeline is made clear for the introduction of dapogliflozin. The recommendations currently read as though this is an instant addition of this drug, with an eGFR of 25-75 and ACR of > 22.6, whereas the evidence from the data provided, appears to be “when stabilised” for 3 months on an ARB/ACE. This additional information in the top line recommendations will ensure the medication is added at the right time to the patient medication burden, giving enough time for the renal function to improve on first line drugs as described (ACE and ARB).	Section 3.7 of the FAD has been updated to state that people in the trial had to be stable on a maximum tolerated dose of an ACE inhibitor or ARB for at least 4 weeks before screening, unless medically contraindicated.
24	Patient/carer group	Kidney Care UK	We very much welcome the draft recommendation to offer Dapagliflozin to people with Chronic Kidney Disease (CKD) with and without diabetes. The SGLT2 drugs are an extremely exciting development for the treatment of CKD that could delay the need for the difficult and onerous treatments like dialysis and have the potential to make a huge difference to the lives of kidney patients.	Comment noted.
25	Patient/carer group	Kidney Care UK	We would like to request further clarification on access to the treatment for people with Type 1 diabetes. We understand it has been withdrawn as a treatment for Type 1 diabetes, but it is not clear what the status of it is as a treatment for CKD in people who also have type 1 diabetes. Kidney Care UK has received a number of queries regarding this and we recommend further clarification within the ACD recommendations.	The marketing authorisation for dapagliflozin states that it should not be used in people with type 1 diabetes.
26	Patient/carer group	Kidney Care UK	Kidney Care UK would like to see a specific recommendation that diet and lifestyle advice is provided alongside any prescription of Dapagliflozin, as it is key to empowering patients to take control of their own health. It is important that patients have access to evidence based recommendations that can help them to delay or prevent progression of their kidney disease, alongside pharmaceutical treatments such as a SGLT2 inhibitor.	Section 3.2 of the FAD has been updated to state that NG203 recommends lifestyle advice including dietary interventions for adults with CKD.
27	Patient/carer group	Kidney Care UK	We would like to see a recommendation that prescribing clinicians should make patients aware of the potential side effects and how to reduce the risk of them or how to treat should they occur. Patients have reported unpleasant side effects following treatment with Dapagliflozin. Being made aware of potential side effects enables patients to take action to avoid or identify and treat early, yet not all patients receive this information.	Section 2 of the FAD has a link to regulatory web page for dapagliflozin, including the patient information leaflet that describes the risks and

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				benefits of the medicine.
28	Patient/carer group	Kidney Care UK	We would like to see a research recommendation that evidence should be developed on the benefits of the technology for people with kidney transplants. We have had a number of queries from people with kidney transplants to ask whether the drug would be available to them and it would be helpful to develop an evidence base to inform a recommendation on this.	Section 3.9 has been added to the FAD which states that there is a lack of evidence for dapagliflozin in people with CKD who have had an organ transplant, and there is need for further clinical trials in these people.
29	Web comment	Not applicable	1.1 "Recommended as an option" suggests it's an alternative, but then it's generally meant to be an add-on in the text. "Recommended as an option" is a very weak recommendation to prescribe, when the "option" is not to prescribe it. Suggest remove "as an option" as this attenuates the clear conclusion that the trial shows it's beneficial.	'Recommended as an option' is standard wording used in technology appraisal guidance. This is in contrast to other NICE products like clinical guidelines, which have a different function and therefore use different language. See section 4 of the FAD for details.
30	Web comment	Medicines Optimisation Team, NICE	**1 <u>Recommendations</u>** **Section 1.1:** **Selected text: 'only if'** We had comments on the T2DM integrated guidance work that putting 'only if' can cause a conflict between guideline and TA recs if medicines are recommended in a broader population in the guideline. The COG (content operations group) are working on a solution so it would be good to link in with the work they are doing before publication. **Selected text: '22.6 mg/mmol or more ora uACR of 3 mg/mmol or more and type 2 diabetes.'** Current CKD guideline says offer if ACR more than 30 and T2DM - not sure how this TA aligns with the recs that are being updated but I'm assuming it will be checked for consistency upon publication. **Selected text: '75 ml/min/1.73 m2'** I know the upper limit was in the trial inclusion criteria but I don't think we need to give an upper limit here if they have a diagnosis of CKD.	Comment noted. The committee was aware of the broader context of the NG28 recommendations, but was mindful that its remit was to appraise the clinical and cost effectiveness of dapagliflozin. See section 3.19 of the FAD. The upper eGFR limit of 75 ml/min/1.73 m^2 has been retained to align with the committee's decision, which was made to align with the evidence from the DAPA-CKD trial. See section 3.18 of the FAD.

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NICE National Institute for Health and Care Excellence

Dapagliflozin for treating chronic kidney disease [ID3866]

Consultation on the appraisal consultation document – deadline for comments 5pm on 26 November 2021. Please submit via NICE Docs.

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The appraisal committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	**AstraZeneca**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**
Name of commentator person completing form:	[redacted]

Issue number	Comments
	Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.

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NICE National Institute for Health and Care Excellence

Dapagliflozin for treating chronic kidney disease [ID3866]

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1	**Summary of Company position** The Company would like to thank the Committee for the opportunity to respond to the Appraisal Consultation Document (ACD) and welcomes the current draft recommendations for dapagliflozin as a treatment for chronic kidney disease (CKD). However, the Company is concerned that the current recommendations set out within the ACD are unnecessarily restrictive with respect to the included urine albumin-creatinine ratio (uACR) thresholds, particularly in light of the clinical and economic evidence presented at the Committee meeting and the current low levels of uACR testing in UK clinical practice. A clear case for cost-effectiveness has been demonstrated for dapagliflozin in patients with CKD and comorbid type 2 diabetes mellitus (T2DM), irrespective of uACR. In light of the clinical data and economic case presented during Technical Engagement and at the Committee meeting, the Company believes that the Committee has not provided a clear and adequate reason for not recommending the use of dapagliflozin in the full population of patients with CKD and comorbid T2DM. As detailed further in Issues 2 and 4 of this response, the restricted recommendation within the T2DM population is unwarranted and is not supported by the clinical and economic evidence presented. It is also likely to further exacerbate inequalities of care by preventing access to dapagliflozin for patients who may benefit from it, based on clinical trial data from the DECLARE-TIMI 58 trial.[1] Within the non-T2DM population, the Company recognises that the clinical data are less certain for patients with a low uACR; however, the Company believes that the response set out in this document under Issue 3 will help to alleviate the concerns raised by the Committee and thereby enable a broader recommendation to be made for this population, irrespective of uACR. The Company urges the Committee to consider the full range of evidence and the points of clarification outlined in this response in the development of their final recommendations. The Company also urges the Committee to carefully consider the appropriateness of constructing further subgroups within populations for which a therapy has already been deemed to be cost-effective, and the implications of applying restrictions based on uACR testing given the potential impact this may have on healthcare inequalities. In light of some of the concerns outlined by the Committee within the ACD, the Company has conducted a number of new analyses that are presented within this response as follows: • An updated Company base case analysis based on the characteristics of patients from a newly-defined Clinical Practice Research Datalink (CPRD) dataset that more closely reflects the patient population under appraisal, in line with the Committee's recommended estimated glomerular filtration rate (eGFR) restrictions (Table 1, see Issue 6 for further details) • Revised scenario analyses based on the characteristics of patients with CKD from the newly-defined CPRD dataset that fall within the expected target populations: Subgroup 1: uACR ≥22.6 mg/mmol (200 mg/g); Subgroup 2: T2DM with a uACR <22.6 mg/mmol (200 mg/g); Subgroup 3: non-T2DM with a uACR <22.6 mg/mmol (200 mg/g) (Scenarios 1–3 in Table 1) • New scenario analyses within the additional uACR subgroups constructed by the Committee of <3 mg/mmol (**A1**: <30 mg/g) and 3–22 mg/mmol (**Modified A2**: 30–199 mg/g [modified at upper bound to mirror the DAPA-CKD trial inclusion criteria, with the true A2 classification being 3–30 mg/mmol {30–300 mg/g}]), in both the T2DM and non-T2DM populations (Scenarios 4–11 in Table 1) o Scenarios 4, 6, 8 and 10 are based on the characteristics of patients from the newly-defined CPRD dataset, whereas Scenarios 5, 7, 9 and 11 are based on the characteristics of patients from the $DECLARE_{CKD}$ cohort. Both approaches are

associated with similar incremental cost-effectiveness ratios (ICERs), demonstrating the robustness of the results with respect to both approaches

- *Note that all analyses have been conducted based on thresholds defined by mg/g values, in line with the DAPA-CKD trial eligibility criteria. For simplicity, all mg/mmol values presented throughout this response have been rounded to align with the uACR categories defined in the draft recommendations where possible*

The results of the new analyses conducted by the Company as part of this response are presented below in Table 1 and described in more detail in Issue 7. These analyses demonstrate that the recommendation to restrict dapagliflozin to use in patients with comorbid T2DM and a uACR ≥3 mg/mmol is inappropriate, and there is sufficient evidence to support the cost-effectiveness of dapagliflozin in both the T2DM and non-T2DM populations irrespective of uACR.

All results fall well below the threshold considered by NICE for a new therapy to be deemed cost-effective. Together with the evidence presented within the original Company submission, at Technical Engagement, and within the Committee meeting itself, the Company believes that the evidence presented within this response provides sufficient certainty in the cost-effectiveness of dapagliflozin, such that the restricted recommendations based on uACR are carefully and appropriately reconsidered by the Committee and removed from the final recommendations for this appraisal.

Table 1: Updated Company base case and scenario analyses conducted as part of this response

Population		ΔCosts (£)	ΔQALYs	ICER
Updated Company base case: overall population (risk equations from the DAPA-CKD and $DECLARE_{CKD}$ combined dataset, adjusted to patient characteristics of newly-defined CPRD dataset)		£1,974	0.332	**£5,948**
1	**DAPA-CKD like population (uACR ≥22.6 mg/mmol [200 mg/g])**: risk equations from the DAPA-CKD and $DECLARE_{CKD}$ combined dataset, adjusted to patient characteristics from the newly-defined CPRD dataset (uACR ≥22.6 mg/mmol [200 mg/g] subgroup)	−£1,004	0.521	**Dominant**
2	**T2DM low uACR population (uACR <22.6 mg/mmol [200 mg/g])**: risk equations from $DECLARE_{CKD,}$ adjusted to patient characteristics from the newly-defined CPRD dataset (uACR <22.6 mg/mmol [200 mg/g] subgroup)	£2,576	0.430	**£5,990**
3	**Non-T2DM low uACR population (uACR <22.6 mg/mmol [200 mg/g])**: risk equations from $DECLARE_{CKD}$ with non-diabetes correction factor, adjusted to patient characteristics from the newly-defined CPRD dataset (uACR <22.6 mg/mmol [200 mg/g] subgroup)	£1,512	0.088	**£17,139**
New uACR subgroup scenario analyses				
4	**T2DM A1 population**: risk equations from $DECLARE_{CKD,}$ adjusted to patient characteristics from the **newly-defined CPRD dataset** (uACR <3 mg/mmol [<30 mg/g] subgroup)	£2,646	0.433	**£6,112**

	5	**T2DM A1 population**: risk equations from $DECLARE_{CKD}$, adjusted to patient characteristics from the **$DECLARE_{CKD}$ cohort** (uACR <3 mg/mmol [<30 mg/g] subgroup)	£2,603	0.436	**£5,965**
	6	**T2DM Modified A2* population**: risk equations from $DECLARE_{CKD}$, adjusted to patient characteristics from the **newly-defined CPRD dataset** (uACR 3–22 mg/mmol [30–199 mg/g] subgroup)	£2,309	0.412	**£5,599**
	7	**T2DM Modified A2* population**: risk equations from $DECLARE_{CKD}$, adjusted to patient characteristics from the **$DECLARE_{CKD}$ cohort** (uACR 3–22 mg/mmol [30–199 mg/g] subgroup)	£2,675	0.421	**£6,352**
	8	**Non-T2DM A1 population**: risk equations from $DECLARE_{CKD}$ with non-diabetes correction factor, adjusted to patient characteristics from the **newly-defined CPRD dataset** (uACR <3 mg/mmol [<30 mg/g] subgroup)	£1,586	0.095	**£16,684**
	9	**Non-T2DM A1 population**: risk equations from $DECLARE_{CKD}$ with non-diabetes correction factor, adjusted to patient characteristics from the **$DECLARE_{CKD}$ cohort** (uACR <3 mg/mmol [<30 mg/g] subgroup)	£1,697	0.183	**£9,277**
	10	**Non-T2DM Modified A2* population**: risk equations from $DECLARE_{CKD}$ with non-diabetes correction factor, adjusted to patient characteristics from the **newly-defined CPRD dataset** (uACR 3–22 mg/mmol [30–199 mg/g] subgroup)	£1,274	0.065	**£19,532**
	11	**Non-T2DM Modified A2* population**: risk equations from $DECLARE_{CKD}$ with non-diabetes correction factor, adjusted to patient characteristics from the **$DECLARE_{CKD}$ cohort** (uACR 3–22 mg/mmol [30–199 mg/g] subgroup)	£1,770	0.150	**£11,769**

**Note: ***Modified at upper bound (22 mg/mmol [199 mg/g]) to mirror the DAPA-CKD trial inclusion criteria, with the true A2 classification being 3–30 mg/mmol (30–300 mg/g). These analyses were conducted based on thresholds defined by mg/g values, in line with the DAPA-CKD trial eligibility criteria. For simplicity, all mg/mmol values presented throughout this response have been rounded to align with the categories defined in the draft recommendations where possible.
Abbreviations: CKD: chronic kidney disease; CPRD: Clinical Practice Research Datalink; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year; uACR: urinary albumin creatinine ratio; T2DM: type 2 diabetes mellitus.

2

The recommendation to restrict dapagliflozin to use in patients with T2DM with a uACR ≥3 mg/mmol is inappropriate and does not reflect the available clinical and cost-effectiveness evidence

The restricted recommendation outlined within the ACD for patients with CKD and comorbid T2DM based on a uACR threshold of 3 mg/mmol (30 mg/g) does not reflect the clinical and cost-effectiveness evidence for dapagliflozin provided as part of this appraisal to date. The Company urges the Committee to carefully reconsider this restriction for the following reasons:

1. The ACD states that the cost-effectiveness estimate of dapagliflozin plus standard care compared with standard care alone in Subgroup 2 (patients with T2DM with a uACR <22.6

mg/mmol [200 mg/g]) "*is comfortably within what NICE considers an acceptable use of resources*." The Company is therefore extremely concerned as to why a further restriction within this subgroup has been made without any clear rationale, and urges the Committee to base their final recommendations on the clinical and cost-effectiveness evidence presented within this appraisal.

2. The uACR threshold of 3 mg/mmol (30 mg/g) represents an additional subgroup within an already pre-defined subpopulation for which the Committee provide no clear rationale. Despite the inappropriate nature of this further restriction, the Company have conducted additional scenario analyses to demonstrate the cost-effectiveness of dapagliflozin both within the additional subgroup of uACR <3 mg/mmol (<30 mg/g) and within the already recommended uACR subgroup of 3–22 mg/mmol (30–199 mg/g). Results of these scenario analyses are presented below and in further detail under Issue 7, demonstrating that dapagliflozin is cost-effective in subgroups of patients both above and below this additional uACR threshold, with ICERs that fall well below the cost-effectiveness threshold considered by NICE.
3. It is inappropriate to construct further subgroups within subpopulations for which a therapy has already been deemed to be cost-effective. This view is supported by precedent from a prior appraisal appeal (TA504, Pirfenidone for treating idiopathic pulmonary fibrosis)[2, 3] and therefore the Company urges the Committee to carefully and appropriately reconsider this restriction within the development of their final recommendations for this appraisal.
4. Finally, a recommendation which requires uACR testing to be conducted is likely to further exacerbate current inequalities of care within the National Health Service (NHS), as discussed in further detail below in Issue 4.

2.1 Dapagliflozin is clinically and cost-effective in patients with T2DM irrespective of uACR

Section 3.8 of the ACD states that "*Results from DECLARE-TIMI-58 and DAPA-HF suggested that dapagliflozin plus standard care is more effective than standard care alone across the broad CKD population, regardless of uACR and eGFR levels*". This statement is already clear in its reflection of the evidence provided by the Company to date for the clinical efficacy of dapagliflozin in patients with CKD and comorbid T2DM irrespective of uACR, and in particular the available subgroup analyses of the DECLARE-TIMI 58 trial:[4]}[5]

- Subgroup analyses of the DECLARE-TIMI 58 trial presented in the Company submission demonstrate a clear treatment benefit in patients below and above a uACR threshold of **22.6 mg/mmol** (200 mg/g) for the following endpoints:[6]
  - Renal endpoint (≥40% eGFR decline, end stage kidney disease [ESKD], or death from renal causes); hazard ratio (HR) (95% confidence interval [CI]): [redacted] versus [redacted] for patients with a uACR of <22.6 mg/mmol and ≥22.6 mg/mmol respectively; p value for interaction=[redacted]
  - Cardiorenal endpoint (≥40% eGFR decline, ESKD, renal death or CV [cardiovascular] death); HR (95% CI): [redacted] versus [redacted] for patients with a <22.6 mg/mmol and ≥22.6 mg/mmol respectively; p value for interaction=[redacted]
- In addition, analyses presented by Mosenzon et al. 2019 provide further clear evidence of a treatment benefit for dapagliflozin in terms of these endpoints across all uACR subgroups defined according to KDIGO guidelines: **A1** (**<3mg/mmol** [<30 mg/g]), **A2** (**3–30 mg/mmol** [30–300 mg/g]) and **A3** (**≥30mg/mmol** [≥300 mg/g]):[5]
  - Renal-specific composite outcome (p-value for interaction=0.30)
    - A1 HR (95% CI): 0.52 (0.37, 0.74)
    - A2 HR (95% CI): 0.59 (0.39, 0.87)
    - A3 HR (95% CI): 0.38 (0.25, 0.58)
  - Cardiorenal composite outcome (p-value for interaction=0.020):
    - A1 HR (95% CI): 0.89 (0.73, 1.08)

Dapagliflozin for treating chronic kidney disease [ID3866]

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- A2 HR (95% CI): 0.73 (0.57, 0.94)
- A3 HR (95% CI): 0.52 (0.38, 0.72)

Clinical data from the DECLARE-TIMI 58 trial directly inform the economic model used by both the Company and the Evidence Review Group (ERG) to generate cost-effectiveness estimates for dapagliflozin in patients with CKD and comorbid T2DM and a uACR ranging from 0–22.6 mg/mmol (200 mg/g) (Table 2). Based on the results of these analyses, Section 3.17 of the ACD states that "*the cost-effectiveness estimate of dapagliflozin plus standard care compared with standard care alone in subgroup 2 was comfortably within what NICE considers an acceptable use of NHS resources*". It is therefore unclear why the Committee has made a restricted recommendation for the use of dapagliflozin in only a proportion of this population (those with a uACR 3–22 mg/mmol [30–199 mg/g]), given no cost-effectiveness results have been presented for patients with comorbid T2DM and a uACR above or below 3 mg/mmol (30 mg/g) specifically.

Table 2: Select results from the unified broad population analyses presented at Technical Engagement, for patients with CKD and comorbid T2DM with a uACR <22.6 mg/mmol (<200 mg/g)

Population	ΔCosts (£)	ΔQALYs	ICER
Company analyses, assuming mean age 64	£2,801	0.52	£5,418
ERG analyses, assuming mean age 76.6	£2,245	0.31	£7,189

Abbreviations: ERG: Evidence Review Group; ICER: Incremental Cost-Effectiveness Ratio; QALY: Quality Adjusted Life Years; T2DM: Type 2 diabetes mellitus; uACR: urinary albumin-creatinine ratio.

The Company welcome the Committee's acknowledgement within the ACD that the remit of the Committee is to appraise dapagliflozin based on the evidence submitted within this technology appraisal only, regardless of the recent class-level recommendations for sodium-glucose co-transporter-2 (SGLT2) inhibitors in patients with CKD and comorbid T2DM in NICE guideline 28 (NG28: Type 2 diabetes in adults: management, published 24th November 2021).[7] The recommendations presented in the NICE clinical guideline are informed by a separate economic model based predominantly on data for canagliflozin. This model therefore does not include important data from the DECLARE-TIMI 58 trial in patients with CKD and comorbid T2DM with a uACR <200 mg/mmol, as these subgroup data are not yet published. As highlighted above, robust clinical trial data for dapagliflozin in patients with CKD and comorbid T2DM with a uACR <22.6 mg/mmol have been provided to the Committee for this appraisal which directly inform the economic model used within the ERG analyses. This economic model produces an ICER that is "*comfortably within that NICE considers an acceptable use of NHS resources*" across the entire subgroup of uACR 0–22.6 mg/mmol (0–200 mg/g), making further subgrouping within this population inappropriate.

Furthermore, the Company would like to highlight to the Committee the recently published, NICE-accredited, UK Kidney Association (UKKA) guidelines which recommend the use of SGLT2 inhibitors to modify cardiovascular risk in patients with CKD and comorbid T2DM across the full uACR spectrum (both above and below 25 mg/mmol):[8]

- *"In people with T2DM and an eGFR ≥25 mL/min/1.73m^2, we recommend initiating SGLT-2 inhibition in those with:*
  - *uACR of ≥25 mg/mmol attributed to diabetic nephropathy (Grade 1A)*
  - *Established coronary disease or stable symptomatic heart failure (irrespective of ejection fraction) (Grade 1A)*
- *We suggest initiating SGLT-2 inhibition to modify cardiovascular risk in those with an eGFR 25–60 mL/min/1.73m^2 and uACR <25 mg/mmol, recognising effects on glycaemic control will be limited"*.

The UKKA guidelines were developed by leading nephrologists in the UK and state that *"benefits on heart failure hospitalisation and major adverse cardiovascular events (MACE) have been demonstrated in a range of populations at risk, including trials recruiting people with CKD without albuminuria. Therefore, although SGLT-2 inhibitors are not expected to provide important reductions in blood glucose in the presence of CKD and renal benefits are uncertain, we offer a grade 2B Suggestion for Use to modify risk of heart failure, myocardial infarction or cardiovascular death in those with CKD without albuminuria".* The Company therefore urge the Committee to similarly consider the full breadth of the available evidence for the benefits of dapagliflozin regardless of uACR, to avoid any potential inconsistency between this NICE-accredited clinical guideline and the final recommendations for this technology appraisal.

2.2 In response to the ACD, the Company have conducted a number of new scenario analyses that demonstrate dapagliflozin is cost-effective in patients with CKD and comorbid T2DM both above and below the additional 3 mg/mmol (30 mg/g) uACR threshold

In response to the additional uACR restriction included within the ACD for patients with CKD and comorbid T2DM, the Company have conducted four additional scenario analyses to demonstrate the cost-effectiveness of dapagliflozin in patients with CKD and comorbid T2DM both above and below this additional uACR threshold of 3 mg/mmol (30 mg/g) (Table 3):

- <3 mg/mmol (**A1**: <30 mg/g)
- 3–22 mg/mmol (**Modified A2**: 30–199 mg/g)

The first two analyses are based on the characteristics of patients from the newly-defined CPRD dataset, whereas the second two analyses are based on the characteristics of patients from the $DECLARE_{CKD}$ cohort. The results of these analyses are presented below and demonstrate that dapagliflozin is cost-effective in subgroups of patients both above and below the additional uACR threshold of 3 mg/mmol, with ICERs that fall well below the cost-effectiveness threshold considered by NICE, and with minimal differences observed between the two approaches. Similar ICERs were observed across the A1 and Modified A2 subgroups, which comprise [redacted]% and [redacted]% of patients in the newly-defined CPRD dataset, respectively (see Issue 6).[9]

Table 3: New uACR subgroup scenario analyses for patients with CKD and comorbid T2DM conducted by the Company as part of this response

Population	ΔCosts (£)	ΔQALYs	ICER
Modelled patient characteristics based on the newly-defined CPRD dataset			
T2DM A1 population: risk equations from $DECLARE_{CKD}$, adjusted to patient characteristics from the newly-defined CPRD dataset (uACR <3 mg/mmol [<30 mg/g] subgroup)	£2,646	0.433	**£6,112**
T2DM Modified A2* population: risk equations from $DECLARE_{CKD}$, adjusted to patient characteristics from the newly-defined CPRD dataset (uACR 3–22 mg/mmol [30–199 mg/g] subgroup)	£2,309	0.412	**£5,599**
Modelled patient characteristics based on the $DECLARE_{CKD}$ cohort			
T2DM A1 population: risk equations from $DECLARE_{CKD}$, adjusted to patient characteristics from the $DECLARE_{CKD}$ cohort (uACR <3 mg/mmol [<30 mg/g] subgroup)	£2,603	0.436	**£5,965**

T2DM Modified A2* population: risk equations from $DECLARE_{CKD}$, adjusted to patient characteristics from the $DECLARE_{CKD}$ cohort (uACR 3–22 mg/mmol [30–199 mg/g] subgroup)	£2,675	0.421	**£6,352**

**Note: ***Modified at upper bound (22 mg/mmol [199 mg/g]) to mirror the DAPA-CKD trial inclusion criteria, with the true A2 classification being 3–30 mg/mmol (30–300 mg/g). These analyses were conducted based on thresholds defined by mg/g values, in line with the DAPA-CKD trial eligibility criteria. For simplicity, all mg/mmol values presented throughout this response have been rounded to align with the categories defined in the draft recommendations where possible.
Abbreviations: CKD: chronic kidney disease; CPRD: Clinical Practice Research Datalink; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year; uACR: urinary albumin creatinine ratio; T2DM: type 2 diabetes mellitus.

2.3 Irrespective of the cost-effectiveness of dapagliflozin within the additional uACR subgroups, the introduction of further subgroups within pre-defined subpopulations for which a therapy has already been deemed to be cost-effective is inappropriate based on precedent from a prior appraisal appeal

Discussion by the NICE Appeals Panel during the appeals process for TA504 (Pirfenidone for treating idiopathic pulmonary fibrosis) clearly specifies the criteria for the appropriateness of considering subgroups within an appraisal and further highlights the inappropriateness of additional subgrouping of the CKD and comorbid T2DM population in the current draft recommendation.[2, 3] The Appeals Panel for TA504 concluded that "*unless a scope specifies otherwise, the Appeal Panel considers that there is a soft presumption that the starting point for any Committee should be consideration of the whole patient group as one, with a view to making one recommendation for that group. Where different recommendations are to be made for different groups of patients, the reason for departing from one recommendation should be clear and adequate*".[2, 3]

With respect to TA504, the Appeals Panel concluded that the Committee acted unfairly as the Committee did not demonstrate consideration of the whole population as defined in the NICE scope before considering subgroups. The Appeals Panel further concluded that: "*It would not normally be reasonable to look for subgroups within that population where use was cost ineffective. However, it would go too far to make that a general rule. Hypothetically if a Committee was aware that there existed an identifiable subgroup defined for a proper purpose and in a logical way and in which use was clearly not cost-effective, then it might be difficult to say that taking account of that subgroup was unreasonable*".[2, 3]

The NICE final scope for this appraisal of dapagliflozin in CKD does not specify subgroups of patients by uACR status, and lists only people with diabetes, people with cardiovascular disease and people with other causes of CKD as potential subgroups to explore, should the evidence allow. These analyses were presented in the Company submission based on data from the DAPA-CKD trial, and demonstrated the consistency of the dapagliflozin treatment effect in these subgroups.[10, 11] The ACD therefore presents no clear rationale for further dividing patients with CKD and comorbid T2DM using a uACR threshold of 3 mg/mmol (30 mg/g), and this additional subgroup of patients with CKD and comorbid T2DM with a uACR of <3 mg/mmol (<30 mg/g) does not comprise an identifiable patient population which has been defined for a proper purpose or logical reason based on either clinical or economic evidence.

The Company strongly believe that the introduction of further subgroups within pre-defined subpopulations for which a therapy has already been deemed to be cost-effective based on the clinical and cost-effectiveness evidence provided as part of the appraisal to date is inappropriate. The Company therefore urges the Committee to carefully and appropriately reconsider this restriction within the development of their final recommendations for this appraisal.

2.4 A recommendation based on uACR measurements is likely to further exacerbate current inequalities of care within the NHS

	Finally, restricting access to dapagliflozin based on uACR measurements will likely exacerbate current inequalities of care within the NHS related to uACR testing, between both primary and secondary care and between patients with and without comorbid T2DM. These inequalities cause the Company, professional organisations, and patients with CKD grave concern with respect to equitable access to dapagliflozin, and are discussed further in Issue 4.
3	**Dapagliflozin is highly likely to represent a cost-effective treatment option for patients with CKD and a uACR <22.6 mg/mmol (200 mg/g) irrespective of T2DM status** 3.1 The available evidence suggests that the treatment effect of dapagliflozin is consistent regardless of T2DM status in patients with a uACR <22.6 mg/mmol (200 mg/g) The Medicines and Healthcare products Regulatory Agency (MHRA), European Medicines Agency (EMA), and Food and Drug Administration (FDA) all independently granted a marketing authorisation for the use of dapagliflozin to treat adults with CKD without any restrictions based on uACR category or T2DM status.[12-14] This broad label allowing the initiation of dapagliflozin in all eligible patients with CKD Stages 1–4 was granted based on results from the DAPA-CKD trial, the strength of supporting clinical evidence from the DECLARE-TIMI 58 and DAPA-HF trials and the strong mechanistic rationale for the similarity of renal efficacy of dapagliflozin in patients with and without comorbid T2DM – as detailed below. The consistency of the treatment effect of dapagliflozin irrespective of T2DM status was clearly demonstrated in both the DAPA-CKD and DAPA-HF trials. In DAPA-CKD, the effect of dapagliflozin on the primary outcome of a sustained decline in eGFR ≥50%, ESKD or death from renal or CV causes was consistent regardless of T2DM status (Table 4).[10] **Table 4: Subgroup analyses of DAPA-CKD primary endpoint by T2DM status** **Abbreviations**: CI: confidence interval; CV: cardiovascular; eGFR: estimated glomerular filtration rate; ESKD: end-stage kidney disease; HR: hazard ratio; T2DM: type 2 diabetes mellitus. **Sources**: Wheeler et al. 2020.[15] Subgroup analyses of the DAPA-HF trial also support the consistency of the dapagliflozin treatment effect across patients with and without T2DM. Dapagliflozin significantly reduced the risk of the primary outcome of worsening HF or CV death and the secondary renal outcome independently of T2DM status (Table 5).[16] Furthermore, in a separate post-hoc analysis of the DAPA-HF trial, the rate of decline in eGFR between day 14 and day 720 in patients with eGFR <60 ml/min/1.73m^2 (n=1,926 [41%]) treated with dapagliflozin or placebo was consistent irrespective of T2DM status (p-value for interaction=0.92).[17] **Table 5: Subgroup analyses of DAPA-HF primary and secondary endpoints by T2DM status**

	Dapagliflozin, n/N	Placebo, n/N	HR (95% CI)	p-value interaction
Primary endpoint (sustained decline in eGFR ≥50%, ESKD or death from renal or CV causes)				
With T2DM	125/1,455	229/1,451	0.64 (0.52, 0.79)	0.24
Without T2DM	45/697	83/701	0.50 (0.35, 0.72)	

	Dapagliflozin, n/N	Placebo, n/N	HR (95% CI)	p-value interaction
Primary endpoint (Cardiovascular death, hospitalization for heart failure, or an urgent heart failure visit[a])				
With T2DM	215/1,075	271/1,064	0.75 (0.63, 0.90)	0.80
Without T2DM	171/1,298	231/1,307	0.73 (0.60, 0.88)	
Secondary renal endpoint (worsening kidney function[b])				

With T2DM	18/1,075	24/1,064	0.73 (0.39, 1.34)	0.86
Without T2DM	10/1,298	15/1,307	0.67 (0.30, 1.49)	

Footnotes: [a] Analysed as time to first occurrence of any of these events; an urgent visit was defined as a hospital visit in which intravenous therapy for heart failure was administered. [b] Composite outcome analysed as time to first occurrence of 50% or greater reduction in eGFR sustained for at least 28 days, kidney failure, or death from kidney-related causes. Kidney failure was defined as eGFR less than 15 mL/min/1.73m^2 sustained for at least 28 days, chronic dialysis treatment sustained for at least 28 days, or kidney transplant.
Abbreviations: CI: confidence interval; eGFR: estimated glomerular filtration rate; ESKD: end-stage kidney disease; HR: hazard ratio; T2DM: type 2 diabetes mellitus.
Sources: Petrie et al. 2020.[16]

In addition, the clinical characteristics of CKD are similar irrespective of the presence of comorbid T2DM due to common pathological processes in the kidneys. Dapagliflozin is anticipated to improve renal outcomes via mechanisms independent of blood glucose lowering and also confers benefits to the entire cardiorenal system in the form of reduction of body weight and blood pressure, in patients with CKD both with and without comorbid T2DM.[18, 19]

Overall, the consistency of the dapagliflozin treatment effect in patients with CKD irrespective of T2DM status suggests that the results of the DECLARE-TIMI 58 subgroup analyses by uACR presented in the Company submission and in Issue 2.1 above are likely to also apply to patients with CKD without comorbid T2DM. As such, the treatment effect observed in DAPA-CKD is likely to extend to patients in lower uACR categories than patients enrolled in DAPA-CKD, in patients with and without comorbid T2DM.

Furthermore, direct evidence of the efficacy of dapagliflozin in patients with CKD without T2DM and with a uACR <22.6 mg/mmol (200 mg/g) is provided by a US study of the Truven and Optum databases.[20] The Optum Research Database is an administrative claims database, generalisable to the US population, containing data from 160 million individuals and electronic health records for more than 80 million individuals nationally. The Truven MarketScan database includes administrative claims and electronic health record data for more than 265 million patients across the US. The data includes inpatient and outpatient claims, outpatient prescription claims, clinical utilisation records, and healthcare expenditures.

The results of this study, which evaluated the efficacy of dapagliflozin through assessment of [redacted] in patients with CKD without T2DM and with a [redacted] are presented in Table 6, and demonstrate [redacted] Early change in albuminuria is recognised by the National Kidney Foundation, the EMA and the FDA as a surrogate endpoint in CKD suitable for use in clinical trials, and these results provide further reassurance that dapagliflozin is effective in patients with CKD without T2DM and with a uACR [redacted][21]

Table 6: Treatment effect of dapagliflozin in patients with CKD without T2DM and a [redacted]

	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Footnotes: *After at [redacted] of treatment with dapagliflozin.
Abbreviations: SD: standard deviation; uACR: urine albumin-to-creatinine ratio.
Source: AstraZeneca Data on File: Analyses of the Optum and Truven databases, 2021.[20]

Dapagliflozin for treating chronic kidney disease [ID3866]

Consultation on the appraisal consultation document – deadline for comments 5pm on 26 November 2021. Please submit via NICE Docs.

	3.2 The mean patient age used within the economic model is a key driver of the ICER across all economic subgroup analyses. It is therefore critical that a mean age reflective of patients in clinical practice is considered within the base case and all subgroup analyses
	
	The mean age considered by the Committee in their economic analyses was derived from the original CPRD analysis conducted by the Company, which included only patients with a formal diagnosis of CKD.[22] The mean age of this cohort is unlikely to be representative of the total population of patients with CKD considered in this appraisal (Stages 1–4) due to under representation of patients with early-stage disease, and likely represents an overestimate for the mean age of the population for the following reasons:
	
	• Diagnosis of Stage 1–2 CKD is only possible using an assessment of uACR (as eGFR remains within normal ranges [≥60 ml/min/1.73 m^2]). Rates of uACR testing for patients at high risk of CKD in UK clinical practice are low, and most patients with CKD in the UK are therefore diagnosed at Stage 3 or later[23, 24]
	
	• Patients with early-stage CKD are less likely to have a Read code for CKD added to their primary care record, and were therefore less likely to be included in the original CPRD analysis conducted by the Company[25]
	
	• Patients with more advanced disease stages (Stages 3–5) are typically older than patients with earlier disease stages (Stages 1–2) given the irreversible, progressive nature of CKD[26 27]
	
	As the mean patient age used in the economic model is a key driver of the ICER in both the base case and all scenario analyses, it is vital that the value used is reflective of the target population for this appraisal. The Company has therefore conducted a targeted literature review (TLR) to validate the true mean age of patients with CKD Stages 1–4 in UK clinical practice and to help the Committee further explore an appropriate mean age for this population.
	
	The TLR aimed to identify observational or real-world evidence studies conducted in the UK reporting a mean or median age for adult patients with CKD Stages 1–4. A search strategy was developed for use in the MEDLINE database (including MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R)), which identified 1,055 records for screening. Overall, 172 records were considered for full-text review following abstract review, and a total of 96 records were ultimately included within the TLR. The majority (n=58) of these studies reported on populations with CKD Stages ≥3 only and were therefore deprioritised for extraction, as this patient population is likely to be older than a population including CKD Stages 1–4 due to the progressive nature of CKD. A further nine studies reported on populations of unclear CKD stage and were also deprioritised for extraction.
	
	Among the 29 remaining studies that included a proportion of patients with either Stage 1 or Stage 2 CKD, the majority (n=24) recruited only small cohort sizes unlikely to be generalisable to the overall population of patients with CKD. Five studies reported a mean and/or median age for a cohort size of ≥1,000 patients, and were selected for full extraction. Of these, two studies using data from the CPRD dataset reported a **mean** age of:
	• 68.8 years (SD: 11.3) in a cohort of 85,500 patients with Stage 2–5 CKD with or without T2DM[28]
	• 64 years (incident diabetic kidney disease [DKD]) and 70 years (prevalent DKD) for a cohort of 60,867 patients with Stage 1–5 DKD.[27] This study also reported a mean age by stage of CKD in both the prevalent and incident populations:
	  ○ Prevalent DKD: Stage 1: 51 years; Stage 2: 65 years; Stage 3a: 69 years; Stage 3b: 75 years; Stage 4: 78 years; Stage 5: 74 years; Missing eGFR stage: 68 years
	  ○ Incident DKD: Stage 1: 51 years; Stage 2: 64 years; Stage 3a: 66 years; Stage 3b: 70 years; Stage 4: 74 years; Stage 5: 64 years; Missing eGFR stage: 61 years

Four studies reported a **median** age, two of which were based in Scottish centres, with values ranging from 67.6 years (IQR: 53.6–76.9; n=2,950) to 75 years (IQR: 63–84; n=2,236). One study based on the Laboratory Outcomes, Morbidity and Mortality Study-II cohort (n=19,694) reported median age by disease stage as follows: Stages 1–2: 61.0 years (IQR: 49.3–69.8); Stages 3–5: 75.7 years (IQR: 68.5–82.0).[27, 29-31]

The results of this TLR indicate that the mean age of a population with Stage 1–4 CKD in UK clinical practice is likely to be lower than the 76.6 years currently assumed by the ERG, particularly as all five studies included some patients (albeit a small proportion) with Stage 5 disease and may therefore over-estimate the true mean age of patients with CKD Stages 1–4.

Nevertheless, in light of the Committee comments in relation to mean patient age, the Company have conducted a new analysis of the CPRD dataset to align more closely to the population being considered within this appraisal. Within this newly-defined CPRD dataset, only patients that fall within the Committee's recommended eGFR restrictions (eGFR 25–75 ml/min/1.73 m^2) have been included (see Issue 6). The mean age of the overall patient population included in this analysis was 72.9 years, and this has been used to inform the Company's updated economic analysis (see Issue 7).

3.3 The Committee and the ERG implicitly accept that there is sufficient clinical evidence for dapagliflozin in patients with CKD without comorbid T2DM and a uACR of <22.6 mg/mmol (200 mg/g) by conducting a cost-effectiveness analysis within this population. As such, there is an opportunity for NICE to make a broader recommendation in this population if they are satisfied that an appropriate mean age produces a cost-effective ICER

The ERG were satisfied to generate and present their own ICERs for the subgroup of patients with CKD without T2DM and a uACR <22.6 mg/mmol (200 mg/g), based on their updated assumptions about the mean age of this population. The ERG therefore implicitly accept that the available clinical evidence in this subgroup is adequate to provide plausible cost-effectiveness estimates.

When a mean age which more appropriately reflects patients in UK clinical practice is used to generate cost-effectiveness estimates for this subgroup, dapagliflozin represents a cost-effective use of NHS resources. This is reflected in the Company's updated economic analysis which incorporates the newly-defined CPRD dataset detailed in Issue 6. The results of the updated analysis in the subgroup of patients with CKD without comorbid T2DM and a uACR <22.6 mg/mmol [200 mg/g] are summarised in Table 7 below (Scenario 1).

In order to fully explore the cost-effectiveness of dapagliflozin within this subgroup, and for consistency with the approach taken in the subgroup of patients with CKD and comorbid T2DM and a low uACR, additional analyses have been conducted by the Company to evaluate the cost-effectiveness of dapagliflozin within the A1 and Modified A2 subgroups in patients with CKD without comorbid T2DM. As for the T2DM analysis, two approaches have been taken whereby patient characteristics have been based on both the newly-defined CPRD dataset as well as the $DECLARE_{CKD}$ cohort. The results show that treatment with dapagliflozin in patients falling within the A1 and Modified A2 uACR categories represents a cost-effective use of NHS resources, with ICERs falling below the established willingness-to-pay threshold for both subgroups. Notably, a lower ICER was observed in the A1 subgroup versus the Modified A2 subgroup, which comprises [redacted]% versus [redacted]% of patients in the newly-defined CPRD dataset.[9]

Dapagliflozin for treating chronic kidney disease [ID3866]

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Table 7: New uACR subgroup scenario analyses for patients with CKD without comorbid T2DM conducted by the Company as part of this response

Population		ΔCosts (£)	ΔQALYs	ICER
1	**Non-T2DM low uACR population (uACR <22.6 mg/mmol [200 mg/g])**: risk equations from $DECLARE_{CKD}$ with non-diabetes correction factor, adjusted to patient characteristics from the **newly-defined CPRD dataset** (uACR <22.6 mg/mmol [200 mg/g] subgroup)	£1,512	0.088	**£17,139**
Modelled patient characteristics based on the newly-defined CPRD dataset				
2	**Non-T2DM A1 population**: risk equations from $DECLARE_{CKD}$ with non-diabetes correction factor, adjusted to patient characteristics from the **newly-defined CPRD dataset** (uACR <3 mg/mmol [<30 mg/g] subgroup)	£1,586	0.095	**£16,684**
3	**Non-T2DM Modified A2* population**: risk equations from $DECLARE_{CKD}$ with non-diabetes correction factor, adjusted to patient characteristics from the **newly-defined CPRD dataset** (uACR 3–22 mg/mmol [30–199 mg/g] subgroup)	£1,274	0.065	**£19,532**
Modelled patient characteristics based on the $DECLARE_{CKD}$ cohort				
4	**Non-T2DM A1 population**: risk equations from $DECLARE_{CKD}$ with non-diabetes correction factor, adjusted to patient characteristics from the **$DECLARE_{CKD}$ cohort** (uACR <3 mg/mmol [<30 mg/g] subgroup)	£1,697	0.183	**£9,277**
5	**Non-T2DM Modified A2* population**: risk equations from $DECLARE_{CKD}$ with non-diabetes correction factor, adjusted to patient characteristics from the **$DECLARE_{CKD}$ cohort** (uACR 3–22 mg/mmol [30–199 mg/g] subgroup)	£1,770	0.150	**£11,769**

Note: *Modified at upper bound (22 mg/mmol [199 mg/g]) to mirror DAPA-CKD trial inclusion criteria, with true A2 classification being 3–30 mg/mmol (30–300 mg/g). These analyses were conducted based on thresholds defined by mg/g values, in line with the DAPA-CKD trial eligibility criteria. For simplicity, all mg/mmol values presented throughout this response have been rounded to align with the categories defined in the draft recommendations where possible.
Abbreviations: CKD: chronic kidney disease; CPRD: Clinical Practice Research Datalink; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year; uACR: urinary albumin creatinine ratio; T2DM: type 2 diabetes mellitus.

The company acknowledges that there is limited direct evidence available on the renal efficacy of dapagliflozin in patients with CKD without comorbid T2DM and with uACR <200 mg/g. However, it is not uncommon for the NICE Committee to consider indirect evidence to inform decision making in line with the NICE Methods guidance that "consideration of a comprehensive evidence base is fundamental to the appraisal process". In this case, the updated scenario analyses presented by the Company demonstrate that dapagliflozin either dominates standard of care (SOC) or is substantially below the threshold NICE considers cost-effective in this subgroup. Considering the evidence presented, dapagliflozin is very likely to represent a cost-effective use of NHS resources

	in patients with uACR <22.6 mg/mmol (200 mg/g) regardless of T2DM status when the mean age considered in the analysis more appropriately reflects UK clinical practice.
4	**Recommendations requiring uACR measurement to gain access to dapagliflozin will exacerbate current inequalities of care within the NHS** The clinical and economic evidence presented for dapagliflozin both within this response and within this technology appraisal to date support the cost-effectiveness of dapagliflozin irrespective of uACR in both the T2DM and non-T2DM populations. The Company therefore believe that restricting access to dapagliflozin based on uACR measurement is not necessary and the introduction of such a restriction is likely to exacerbate current inequalities of care within the NHS relating to uACR testing. Together with the results of the scenario analyses presented as part of this response that demonstrate dapagliflozin to be cost-effective both above and below the additional uACR threshold introduced by the Committee, the potential impact on inequalities of care within the NHS are of grave concern to the Company, professional organisations, and patients. The Company urge the Committee to remove the uACR restrictions for the use of dapagliflozin when developing the final recommendations for this technology appraisal. 4.1 Differences in uACR testing rates between secondary and primary care are substantial across the NHS The majority of patients treated with dapagliflozin will be treated in primary care ([redacted]% of patients with Stage 3–5 CKD are currently treated in primary care), and this ratio would not be impacted following the introduction of dapagliflozin.[32] Patients treated in secondary care are more likely to receive a uACR test compared with those in primary care, as they are likely to have a more advanced stage of disease and specialists are more likely to conduct additional testing compared with healthcare professionals in primary care. uACR is tested infrequently within the primary care setting. Therefore, the currently restricted recommendation based on uACR levels risks many patients with elevated uACR that meet the recommendations set out in the ACD not receiving appropriate treatment due to a lack of testing, resulting in poorer disease outcomes. The Company would also like to highlight that the view provided by a patient expert during the Committee meeting and captured in the ACD that they "*would not hesitate to provide a urine sample*" for uACR testing may not accurately reflect the opinion of all patients treated with dapagliflozin. The Company are pleased to hear the patient expert's opinion and are confident the view presented to the Committee accurately reflects their personal opinion; however, the Company would like to highlight that this statement is from a single patient with advanced CKD being treated within secondary care who is engaged with their care and sufficiently informed to participate as a patient expert within the NICE process. The Company therefore believe that this opinion does not represent the view of the majority of patients who would be treated with dapagliflozin for their CKD in clinical practice. Indeed, the results of a survey of 403 UK general practitioners and nurses involved in the treatment of patients with T2DM indicate that many patients may be reluctant to provide a urine sample.[33] The survey, conducted by Napp Pharmaceuticals in 2019, found that 54% of enrolled HCPs did not conduct annual uACR testing, and that the most frequent reason for not conducting a uACR test was that their patient was unwilling to provide a urine sample.[33] 4.2 Inequalities in uACR testing between patients with and without T2DM will lead to unequal access to dapagliflozin based on disease status by restricting access among patients without T2DM uACR testing rates are currently lower in patients with CKD without comorbid T2DM than those with comorbid T2DM. The results of the National Chronic Kidney Disease Audit in 2017 indicate that less than 15% of patients with CKD without T2DM receive annual uACR testing compared to 54% of those with T2DM.[23] Furthermore, within the DAPA-CKD trial similar proportions of patients with and without comorbid T2DM had a uACR of ≥22.6 mg/mmol (200 mg/g) pre-randomisation ([redacted]% and [redacted]% at the first trial visit, respectively), demonstrating that patients with CKD without comorbid T2DM are equally likely to be eligible for dapagliflozin.[34] Patients without comorbid T2DM who meet

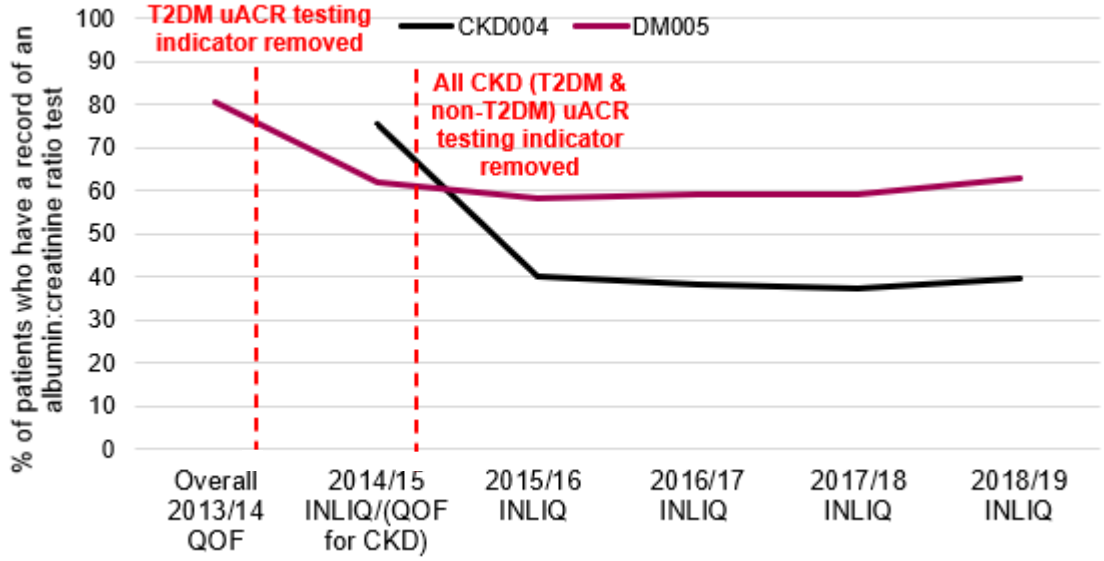
the criteria set out in the currently restricted recommendation of the ACD are therefore disadvantaged on the basis of their disease status, due to their lower likelihood of being uACR tested compared to patients with CKD and comorbid T2DM.

In addition, a retrospective cohort study using CPRD by Feakins *et al.* in 2018 demonstrated that uACR testing rates are lower for patients of black or Asian ethnicity than for those of Caucasian background and therefore a restriction by uACR may be likely to further drive racial inequalities of healthcare across the UK.[35]

4.3 Use of a technology appraisal recommendation to encourage uACR testing is inappropriate

The Committee discussion captured within the ACD implies that not including a uACR restriction within the recommendations for this technology appraisal may reduce the motivation to test for uACR in clinical practice. However, uACR testing has already been deprioritised in clinical practice, indicated by its removal from the Quality Outcomes Framework (QOF) in 2013/2014 despite being recommended in the NICE CKD clinical guidelines at the time (CG182).[7] Since the removal of uACR testing from the QOF in 2013/2014, the proportion of patients with CKD with or without T2DM that receive an annual uACR test has reduced substantially within England as shown in Figure 1.[36] It is also likely that there have since been further declines in uACR testing due to the COVID-19 pandemic which have not yet been reversed. The Company consider it unrealistic to expect rates of testing to increase to the point that would allow full access to dapagliflozin for all eligible patients. As such, the inclusion of restrictions based on uACR measurement in the current draft recommendations for this appraisal only serves to unnecessarily prevent access to dapagliflozin.

Figure 1: Analysis of uACR testing indicators no longer in QOF (INLIQ) in England, 2013/14 to 2018/19



Footnotes: CKD004: percentage of patients on the CKD register (with and without T2DM) whose notes have a record of a urine:creatinine ratio (or protein:creatinine ratio) test in the preceding 12 months; DM005: The percentage of patients with diabetes, on the register, who have a record of an albumin:creatinine ratio test in the preceding 12 months
Abbreviations: CKD: chronic kidney disease; INLIQ: indicators no longer in QOF; QOF: Quality of Outcomes Framework; uACR: urinary albumin creatinine ratio.
Source: Public Health England, 2020.[36]

4.4 The eGFR restrictions included within the draft recommendations define a population at high risk of adverse outcomes who would benefit from additional treatment options, regardless of uACR

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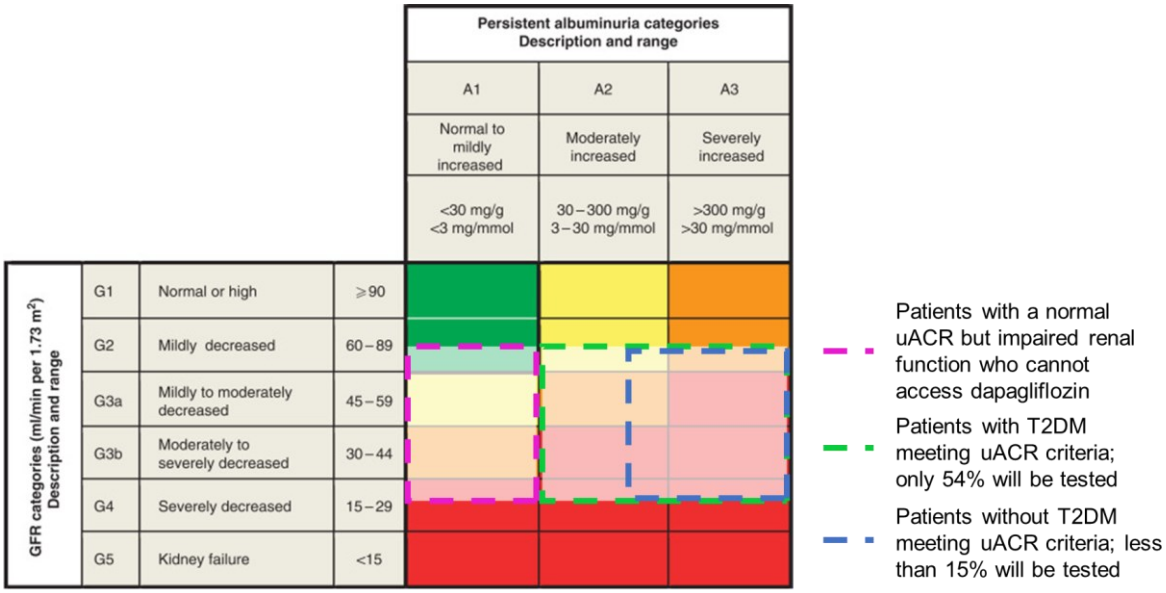
	The draft recommendations currently included within the ACD apply an eGFR restriction of 25–75 ml/min/1.73m^2 for patients with CKD both with and without comorbid T2DM. As indicated in the Kidney Disease Improving Global Outcomes (KDIGO) grid, patients with an eGFR <60 ml/min/1.73m^2 (irrespective of uACR) have an increased risk of disease progression and adverse clinical outcomes, with the risk increasing as eGFR decreases (Figure 2).[37] The current restricted recommendation based on uACR means that patients with decreased renal function (eGFR <60 ml/min/1.73m^2), who either a) meet the uACR criteria but are not tested for uACR or b) have a normal uACR, would not be able to benefit from treatment with dapagliflozin. **Figure 2: Representation of patients with CKD meeting the eGFR criteria set out within the ACD**  **Footnotes**: Green, low risk of disease progression; yellow, moderately increased risk of disease progression; orange, high risk of disease progression; red, very high risk of disease progression. **Abbreviations:** CKD: chronic kidney disease; GFR: glomerular filtration rate; eGFR: estimated glomerular filtration rate; T2DM: type 2 diabetes mellitus; uACR: urine albumin-to-creatinine ratio. **Source:** KDIGO 2012 ;[38] National CKD Audit 2017.[23] <u>4.5 The inequalities in care highlighted above directly contradict NICE and the NHS's long-term strategy</u> Finally, the NHS long-term plan highlights a commitment to disease prevention and removing healthcare inequalities.[39] The plan explicitly commits to a more concentrated and systematic approach to reducing health inequalities with a promise that action on health inequalities will be central to the NHS. The recently published NICE 5-year strategy further commits to contributing to reducing healthcare inequalities. Given the highly innovative nature of dapagliflozin for the treatment of patients with CKD, the broad licence granted for dapagliflozin by both the EMA and MHRA, and the highly cost-effective ICER estimates within all patient subgroups, dapagliflozin offers NICE and the NHS an opportunity to reduce healthcare inequalities for patients with CKD by enabling access to dapagliflozin for the full population that need it, without the requirement for a uACR test.
5	**<u>Canagliflozin should not be considered a relevant comparator to dapagliflozin in patients with CKD and T2DM</u>** The ACD states "*The company did not consider canagliflozin a relevant comparator for dapagliflozin in CKD because it noted that canagliflozin is not widely used for treating CKD with type 2 diabetes in the UK*". The ACD should reflect that canagliflozin was not included in the NICE final scope and

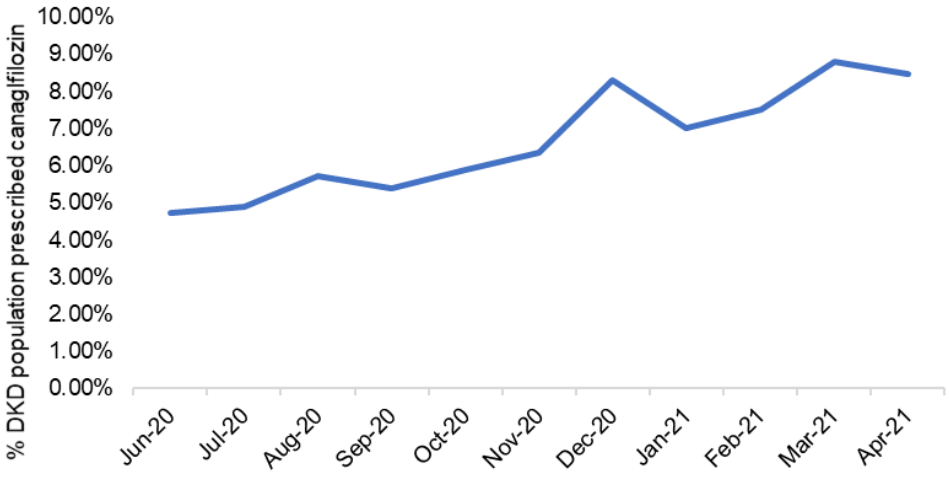
therefore the Company were not required to compare to canagliflozin as part of this appraisal. Nevertheless, the Company performed an indirect treatment comparison versus canagliflozin for completeness and transparency.

The ACD acknowledges that canagliflozin was recommended for patients with CKD and T2DM as part of a class level recommendation for SGLT2 inhibitors in the NICE CKD clinical guidelines (NG203).[7] However, it is important to emphasise that a recommendation within clinical guidelines does not constitute established clinical practice. The clinical guideline was only published on 25th August 2021, meaning that any impact of the guideline will not yet have translated into UK clinical practice. In addition, clinical guidelines are not associated with the funding mandate of a technology appraisal (a process through which canagliflozin has not undergone in this indication), meaning canagliflozin has not received a recommendation for reimbursement in this population. As a result, the proportion of UK patients with T2DM and CKD Stages 3a or 3b (eGFR 30–59 mL/min/1.73 m^2) who were prescribed canagliflozin increased only slightly from 4.7% in June 2020 (prior to the inclusion of renal data from CREDENCE with the licence update to patients with DKD) to 8.5% in April 2021 (Figure 3).[40]

The low uptake of canagliflozin may result from a lack of awareness of the broader population now licensed for treatment, and the fact that physicians in primary care (where the majority of DKD patients would be treated) may typically consider SGLT2 inhibitors as T2DM therapies. Primary care physicians may be less familiar with the cardiorenal benefits of SGLT2 inhibitors in patients with an eGFR <45 mL/min/1.73 m^2 than specialists in secondary care. Nevertheless, the data presented in Figure 3 below represent only a modest increase in canagliflozin uptake for the newly licenced population of patients with DKD and arguably do not represent a level of uptake that would constitute established clinical practice, a criterion required to be met for a therapy to be considered a formal comparator within a technology appraisal.

Finally, the Company request that the ACD is updated to reflect that canagliflozin is licenced only for the treatment of patients with DKD specifically (CKD caused by T2DM), whereas dapagliflozin is licenced for the treatment of CKD regardless of diabetes status, including patients with CKD and comorbid T2DM which has not necessarily caused their CKD.[12, 41, 42] The available data for canagliflozin therefore support the clinical efficacy of canagliflozin in patients with DKD only, which comprises a subgroup of patients with CKD and comorbid T2DM.

Figure 3: Uptake of canagliflozin amongst UK patients with DKD Stage 3a and b (eGFR 30–59 mL/min/1.73 m^2)



Abbreviations: DKD: diabetic kidney disease; eGFR: estimated glomerular filtration rate.
Source: AstraZeneca Data on File: IQVIA Ltd, incorporating data derived from THIN, A Cegedim Database, Monthly, April 2021.[40]

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6 **Revised CPRD dataset**

As highlighted above, the Company have updated their base case cost-effectiveness results and scenario analyses using an updated analysis of CPRD data. The overall modelling approach has remained consistent with the approach taken in the Company's updated model submitted at Technical Engagement. However, in line with the draft ACD recommendations restricting dapagliflozin to use in patients with eGFR ≥25 to ≤75 ml/min/1.73 m^2, the Company have updated their analysis of the CPRD dataset to include only patients with eGFR ≥25 to ≤75 ml/min/1.73 m^2 with or without a coded CKD diagnosis. The Company acknowledge that since uACR restrictions were not applied to define this patient population, this analysis will include some patients with an eGFR of 60–75 ml/min/1.73 m^2 that do not have a uACR ≥3 mg/mmol (≥30 mg/g) and therefore would not meet the criteria for a formal diagnosis of CKD. However, given that the rate of uACR testing in the UK is so low, especially in earlier stages of disease, the application of a uACR restriction would serve to exclude many relevant patients due to absent test results. Therefore, in the absence of alternative, more appropriate sources in the literature (see Issue 3.2), this updated analysis of CPRD represents the best available source to characterise the patients in which dapagliflozin will used in clinical practice and therefore inform the patient characteristics within the economic model.

The updated CPRD dataset has been used to inform the patient characteristics in the Company's economic model and is associated with a mean age of 72.9 years. Patients identified in the newly-defined CPRD dataset were split into the uACR categories outlined below in Table 8, with the majority of patients falling within the A1 category (<3mg/mmol [30 mg/g]). The new ICERs for the base case and scenario analyses generated by the revised economic model are presented throughout this response and summarised below in Issue 7.

Table 8: Proportion of patients in each uACR category in the new CPRD dataset (of patients with a uACR measurement available)

uACR category		All patients (n=106,675)	Patients with T2DM (n=72,061)	Patients without T2DM (n=34,614)
A1	<3 mg/mmol (<30 mg/g)	[redacted]	[redacted]	[redacted]
Modified A2*	3–22 mg/mmol (30–199 mg/g)	[redacted]	[redacted]	[redacted]
≥22.6 mg/mmol	≥22.6 mg/mmol (≥200 mg/g)	[redacted]	[redacted]	[redacted]

Note: *Modified at upper bound (22 mg/mmol [199 mg/g]) to mirror the DAPA-CKD trial inclusion criteria, with the true A2 classification being 3–30 mg/mmol (30–300 mg/g). These analyses were conducted based on thresholds defined by mg/g values, in line with the DAPA-CKD trial eligibility criteria. For simplicity, all mg/mmol values presented throughout this response have been rounded to align with the categories defined in the draft recommendations where possible. Patients with missing uACR measurements: n=[redacted] (n=[redacted] and n=[redacted] for patient with and without T2DM, respectively).
Abbreviations: CPRD: Clinical Practice Research Datalink; T2DM: Type 2 diabetes mellitus; uACR: urine albumin-creatinine ratio.
Source: AstraZeneca Data on File: newly-defined CPRD dataset, 2021.[9]

7 **Summary of the additional analyses conducted by the Company as part of this response**

This section provides a full summary of the additional analyses conducted by the Company as part of this response:

- An updated base case analysis based on the characteristics of patients from the newly-defined CPRD dataset detailed above (see Table 7)
    - This analysis is entirely consistent with the approach taken within the Company's updated model submitted at Technical Engagement, however, as detailed above in Issue 6, a revised CPRD dataset has been identified to more closely reflect the

anticipated patient population for dapagliflozin defined in the ACD. The patient characteristics from this newly-defined CPRD dataset have therefore been used to adjust the risk equations from the DAPA-CKD and $DECLARE_{CKD}$ combined dataset within the updated Company base case. As shown in Table 9, the updated Company base case ICER is very similar to the base case ICER presented at Technical Engagement.

- Revised scenario analyses based on the characteristics of patients from the newly-defined CPRD dataset that fall within the expected target populations (Subgroup 1: uACR ≥22.6 mg/mmol (200 mg/g); Subgroup 2: T2DM with a uACR <22.6 mg/mmol (200 mg/g); Subgroup 3: non-T2DM with a uACR <22.6 mg/mmol (200 mg/g) (Scenarios 1–3 in Table 7)
    - As with the updated Company base case, these scenario analyses adopt an entirely consistent modelling approach as per the Company's updated model submitted at Technical Engagement. For these scenario analyses, the risk equations from the combined DAPA-CKD and $DECLARE_{CKD}$ dataset have been adjusted using the characteristics from patients within the newly-defined CPRD dataset that fall within the relevant uACR subgroup. As for the analyses conducted at Technical Engagement, all analyses conducted for patients with CKD and without T2DM have included the non-diabetes correction factor.
- New scenario analyses within the additional uACR subgroups constructed by the Committee of <3 mg/mmol (**A1**: <30 mg/g) and 3–22 mg/mmol (**Modified A2**: 30–199 mg/g [modified at upper bound to mirror the DAPA-CKD trial inclusion criteria, with the true A2 classification being 3–30 mg/mmol {30–300 mg/g}]), in both the T2DM and non-T2DM populations (Scenarios 4–11, Table 7)
    - As with the updated Company base case, these scenarios adopt an entirely consistent modelling approach as per the Company's updated model submitted at Technical Engagement.
        - Scenarios 4, 6, 8 and 10 are based on the characteristics of patients from the **newly-defined CPRD dataset** that fall within the additional uACR-restricted subgroups set out by the Committee
        - Scenarios 5, 7, 9 and 11 are based on the characteristics of patients from the **$DECLARE_{CKD}$ cohort** that fall within the additional uACR-restricted subgroups set out by the Committee
        - The two approaches generate similar ICERs, demonstrating the robustness of these results.
    - As for the analyses conducted at Technical Engagement, all analyses conducted for patients with CKD and without T2DM include the non-diabetes correction factor.

As shown in Table 9, the results from all scenario analyses conducted by the Company as part of this response fall well below the threshold considered for the cost-effectiveness of new therapies by NICE. The Company therefore hope that the analyses presented as part of this response serve to alleviate some of the Committee's concerns and allow the Committee to reconsider their draft recommendations.

Table 9: Revised Company base case and scenario analyses conducted as part of this response

Population	ΔCosts (£)	ΔQALYs	ICER
Updated Company base case: overall population (risk equations from DAPA-CKD and $DECLARE_{CKD}$	£1,974	0.332	**£5,948**

	combined dataset, adjusted to patient characteristics of newly-defined CPRD dataset)				
	1	**DAPA-CKD like population (uACR ≥22.6 mg/mmol [200 mg/g])**: risk equations from the DAPA-CKD and DECLARE$_{CKD}$ combined dataset, adjusted to patient characteristics from the newly-defined CPRD dataset (uACR ≥22.6 mg/mmol [200 mg/g] subgroup)	−£1,004	0.521	**Dominant**
	2	**T2DM low uACR population (uACR <22.6 mg/mmol [200 mg/g])**: risk equations from DECLARE$_{CKD}$, adjusted to patient characteristics from the newly-defined CPRD dataset (uACR <22.6 mg/mmol [200 mg/g] subgroup)	£2,576	0.430	**£5,990**
	3	**Non-T2DM low uACR population (uACR <22.6 mg/mmol [200 mg/g])**: risk equations from DECLARE$_{CKD}$ with non-diabetes correction factor, adjusted to patient characteristics from the newly-defined CPRD dataset (uACR <22.6 mg/mmol [200 mg/g] subgroup)	£1,512	0.088	**£17,139**
	New uACR subgroup scenario analyses				
	4	**T2DM A1 population**: risk equations from DECLARE$_{CKD}$, adjusted to patient characteristics from the **newly-defined CPRD dataset** (uACR <3 mg/mmol [<30 mg/g] subgroup)	£2,646	0.433	**£6,112**
	5	**T2DM A1 population**: risk equations from DECLARE$_{CKD}$, adjusted to patient characteristics from the **DECLARE$_{CKD}$ cohort** (uACR <3 mg/mmol [<30 mg/g] subgroup)	£2,603	0.436	**£5,965**
	6	**T2DM Modified A2* population**: risk equations from DECLARE$_{CKD}$, adjusted to patient characteristics from the **newly-defined CPRD dataset** (uACR 3–22 mg/mmol [30–199 mg/g] subgroup)	£2,309	0.412	**£5,599**
	7	**T2DM Modified A2* population**: risk equations from DECLARE$_{CKD}$, adjusted to patient characteristics from the **DECLARE$_{CKD}$ cohort** (uACR 3–22 mg/mmol [30–199 mg/g] subgroup)	£2,675	0.421	**£6,352**
	8	**Non-T2DM A1 population**: risk equations from DECLARE$_{CKD}$ with non-diabetes correction factor, adjusted to patient characteristics from the **newly-defined CPRD dataset** (uACR <3 mg/mmol [<30 mg/g] subgroup)	£1,586	0.095	**£16,684**
	9	**Non-T2DM A1 population**: risk equations from DECLARE$_{CKD}$ with non-diabetes correction factor, adjusted to patient characteristics from the **DECLARE$_{CKD}$ cohort** (uACR <3 mg/mmol [<30 mg/g] subgroup)	£1,697	0.183	**£9,277**
	10	**Non-T2DM Modified A2* population**: risk equations from DECLARE$_{CKD}$ with non-diabetes correction factor, adjusted to patient characteristics from the **newly-defined CPRD**	£1,274	0.065	**£19,532**

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		dataset (uACR 3–22 mg/mmol [30–199 mg/g] subgroup)			
	11	**Non-T2DM Modified A2* population**: risk equations from $DECLARE_{CKD}$ with non-diabetes correction factor, adjusted to patient characteristics from the **$DECLARE_{CKD}$ cohort** (uACR 3–22 mg/mmol [30–199 mg/g] subgroup)	£1,770	0.150	**£11,769**

Note: *Modified at upper bound (22 mg/mmol [199 mg/g]) to mirror the DAPA-CKD trial inclusion criteria, with the true A2 classification being 3–30 mg/mmol (30–300 mg/g). These analyses were conducted based on thresholds defined by mg/g values, in line with the DAPA-CKD trial eligibility criteria. For simplicity, all mg/mmol values presented throughout this response have been rounded to align with the categories defined in the draft recommendations where possible.
Abbreviations: CKD: chronic kidney disease; CPRD: Clinical Practice Research Datalink; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year; uACR: urinary albumin creatinine ratio; T2DM: type 2 diabetes mellitus.

8

Additional comments and factual inaccuracies

1. In **Section 2.14**, when discussing the Public Health England report suggesting that CKD is more prevalent in people aged 75 and over compared with people aged 64 and under, the ACD states "*the Committee acknowledged that this report was limited to CKD Stage 3 to 5 and did not fully reflect the target population in the company submission*". The Company request that this sentence is updated to specify exactly the target population in the submission and the likely impact on the applicability of the report (proposed changes in red): "*the Committee acknowledged that this report was limited to CKD Stage 3 to 5 and did not fully reflect the target population in the company submission (CKD Stages 1 to 4, i.e. a patient population with earlier stage disease who would be expected to be younger than patients with Stage 3 to 5 disease)*".
2. In **Section 3.7**, the ACD states "*The clinical experts considered that there would likely be benefits in starting dapagliflozin in people with an eGFR of between 15 ml/min/1.73 m^2 and 25 ml/min/1.73 m^2, despite the lack of clinical evidence. However, they noted the uncertainty in this population, as well as concerns with the impact of a transient decrease in eGFR associated with SGLT2 inhibitors at lower eGFR levels*". The Company do not recall that this was the conclusion made by the three clinical experts during the Committee meeting, and believe this was only mentioned by one expert. The Company disagree that there is uncertainty around the clinical benefit of dapagliflozin in this population: dapagliflozin has received marketing authorisation for the treatment of adults with CKD in addition to SOC (i.e. regardless of uACR or eGFR category), demonstrating that the regulatory body is satisfied with the clinical evidence for dapagliflozin in patients with eGFR 15–25 ml/min/1.73 m^2. The Company request that this sentence is updated accordingly (proposed changes in red) "*The clinical experts considered that there would likely be benefits in starting dapagliflozin in people with an eGFR of between 15 ml/min/1.73 m^2 and 25 ml/min/1.73 m^2, despite the lack of clinical evidence. However, one expert ~~they~~ noted the uncertainty in this population, as well as concerns with the impact of a transient decrease in eGFR associated with SGLT2 inhibitors at lower eGFR levels*"
3. In **Section 3.8**, the ACD states "*7% of people (n=1,100) had an eGFR of less than 60 ml/min/1.73 m^2. DECLARE-TIMI-58 did not restrict inclusion in the trial based on uACR levels*". The Company believe this wording leads readers to incorrectly consider that 1,100 patients is not a large cohort size. Furthermore, the second sentence detailing the DECLARE-TIMI-58 uACR levels should be reworded to reflect the fact that patients in DECLARE-TIMI-58 were included across the full spectrum of uACR ranges. Therefore, the Company request the following wording changes are made (proposed changes in red): "*1,265 (7.4%) ~~7% of people (n=1,100)~~ had an eGFR of less than 60 ml/min/1.73 m^2. DECLARE-TIMI-58 did not restrict inclusion in the trial based on uACR levels and therefore*

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	likely enrolled patients across a wide range of uACR levels". The Company would also like to note the proportion of patients with an eGFR <60 ml/min1.73m^2 in DECLARE-TIMI-58 should be 1,265 (7.4%), which has been corrected above.[1] 4. In **Section 3.8**, the Company request that the sentence "*Both DECLARE-TIMI-58 and DAFA-HF included some people with comorbid CKD*" is updated to include the proportion of patients with comorbid CKD in DECLARE-TIMI-58 and DAPA-HF (34.8% and 40.7%, respectively), and that DAFA-HF is corrected to DAPA-HF, as follows (proposed changes in red): "*Both DECLARE-TIMI-58 and DAPA-HF included some people with comorbid CKD (34.8% and 40.7%, respectively)*".[43, 44] 5. In **Section 3.16**, the ACD states that the exact results of the cost-effectiveness analysis in subgroup 1 are commercial in confidence because they include confidential discounts. The Company are not aware of any commercial in confidence discounts that are considered in the cost-effectiveness model. The results of the cost-effectiveness analysis were presented in the ACM slides and this statement should therefore be removed from the ACD.

Insert extra rows as needed

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- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
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- Please underline all confidential information, and separately highlight information that is submitted under [redacted] and all information submitted under [redacted]. If confidential information is submitted, please also send a 2nd version of your comment with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the Guide to the processes of technology appraisal (section 3.1.23 to 3.1.29) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
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Dapagliflozin for treating chronic kidney disease [ID3866]

Consultation on the appraisal consultation document – deadline for comments 5pm on 26 November 2021. Please submit via NICE Docs.

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Kidney Care UK
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	[redacted]

Comment number	Comments Insert each comment in a new row.

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	Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	We very much welcome the draft recommendation to offer Dapagliflozin to people with Chronic Kidney Disease (CKD) with and without diabetes. The SGLT2 drugs are an extremely exciting development for the treatment of CKD that could delay the need for the difficult and onerous treatments like dialysis and have the potential to make a huge difference to the lives of kidney patients.
2	We would like to request further clarification on access to the treatment for people with Type 1 diabetes. We understand it has been withdrawn as a treatment for Type 1 diabetes, but it is not clear what the status of it is as a treatment for CKD in people who also have type 1 diabetes. Kidney Care UK has received a number of queries regarding this and we recommend further clarification within the ACD recommendations.
3	Kidney Care UK would like to see a specific recommendation that diet and lifestyle advice is provided alongside any prescription of Dapagliflozin, as it is key to empowering patients to take control of their own health. It is important that patients have access to evidence based recommendations that can help them to delay or prevent progression of their kidney disease, alongside pharmaceutical treatments such as a SGLT2 inhibitor.
4	We would like to see a recommendation that prescribing clinicians should make patients aware of the potential side effects and how to reduce the risk of them or how to treat should they occur. Patients have reported unpleasant side effects following treatment with Dapagliflozin. Being made aware of potential side effects enables patients to take action to avoid or identify and treat early, yet not all patients receive this information.
5	We would like to see a research recommendation that evidence should be developed on the benefits of the technology for people with kidney transplants. We have had a number of queries from people with kidney transplants to ask whether the drug would be available to them and it would be helpful to develop an evidence base to inform a recommendation on this.
6	

Insert extra rows as needed

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- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise and all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a 2nd version of your comment with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the Guide to the processes of technology appraisal (section 3.1.23 to 3.1.29) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Royal College of General Practitioners
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	[redacted]

Comment number	Comments Insert each comment in a new row.

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	Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	The RCGP welcome the addition of any new medication to prevent severe CKD and renal failure, however, we believe that making the assumption that "Chronic kidney disease (CKD) is a complex progressive disorder with loss of nephrons causing kidney function to decline over time…. lead(ing). to end-stage renal disease and death" is an extreme position on CKD when looking at primary care patients. Within primary care, the vast majority of people who are diagnosed with CKD will not progress to develop end stage renal disease or subsequently die *from* the condition. Most people who present with CKD within primary care are older adults whose kidneys are not functioning as well as they used to, due to age. These patients die *with* CKD, rather than *from* CKD. Whilst we understand the importance of preventing decline in renal function, this has to be weighed up against the unintended consequences of overprescribing and drug interactions which is key when managing multimorbid disease within primary care, especially in an aging population. The unintended consequences are central to the over prescribing review recently published by DHSC and we believe must be considered when making recommendations for new drugs. (https://www.gov.uk/government/publications/national-overprescribing-review-report)
2	The recommendation to prescribe this drug to anyone with an eGFR from 25-75 and an ACR >22.6, does not appear to align with the data presented to the committee. The average age of the trial patients was 61, the average eGFR was 43 and the average ACR was greater than 100mg/mol. This trial data therefore represented severe disease, whereas the recommendations provided appear to recommend this medication for patients who have significantly milder disease, very commonly seen in primary care and whose renal function often remains stable for years. Can the committee explain why these cut offs were chosen which do not appear to align with the data presented from the trails and when considering the upper limit of eGFR (currently 75), to add on this medication, consider the unintended consequences of over prescribing in the elderly and those with multiple co morbid disease.
3	Finally, when making the recommendations, it is essential that clear guidance is given to primary care regarding additional monitoring required and that the correct timeline is made clear for the introduction of dapogliflozin. The recommendations currently read as though this is an instant addition of this drug, with an eGFR of 25-75 and ACR of > 22.6, whereas the evidence from the data provided, appears to be "when stabilised" for 3 months on an ARB/ACE. This additional information in the top line recommendations will ensure the medication is added at the right time to the patient medication burden, giving enough time for the renal function to improve on first line drugs as described (ACE and ARB).

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	[London Kidney Network]
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	[Nil]
Name of commentator person completing form:	[redacted]

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	Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	**Are the provisional recommendations sound and a suitable basis for guidance to the NHS?** Our view is that the provisional recommendations are implementable in NHS settings. We are pleased to see that there is no longer mention of complex monitoring in primary care after commencement of this treatment, which we felt to be a barrier to implementation – as well as unsupported by the literature. We offer that the guidance should refer to an eGFR greater than 25 rather than 25 where this appears in the document.
2	**Has all of the relevant evidence been taken into account?** Yes, we consider that it has been.
3	**Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?** Yes, we believe they are.
4	The key issue as we see it from an equalities point of view, is that the benefits of this drug are so clear that it is more important than ever that it is equitably available to all and particularly to service users who find our services more challenging to engage with.
5	Data from East London supports CKD being more common and severe in Black and South Asian populations, and those in higher deprivation indices. No mention is made of the imperative we have to ensure that traditionally marginalised groups are prescribed this drug, but this may be beyond the remit of this appraisal. It may be that time and close monitoring of prescribing trends will tell us if we are succeeding to do this. SGLT2i have been used in trials when ACE-i/ARB doses are maximised; the use of these drugs is differentially distributed by ethnicity and deprivation. It is therefore possible that the SGLT2-i may be overlooked if a patient is not already on an ACE/ARB. Conversely, the provision of guidance for the use of SGLT2-i may encourage the prescription of ACE/ARB as a first step, bringing about a benefit to this patient group.
6	We are not entirely clear on how these recommendations may impact people living with disabilities. With the advent of virtual CKD service growing, physical access to nephrologists is less important than it has been to garner a special opinion. That having been said, these drugs should come from primary care, so the question is how patients with disability engage with primary care overall rather than how they access nephrology. It may be beyond the scope of this technological assessment to make recommendations on increasing access to health services.
7	Proteinuria testing is differential by age/ethnicity (and likely other groups who can't access service to deliver a urine sample) so, if prescription is based on proven presence of proteinuria, this may be a consideration. This will be less relevant if prescribing advice and evidence indicates good effects regardless of proteinuria.

Insert extra rows as needed

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Boehringer-Ingelheim
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**
Name of commentator person completing form:	[redacted]

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Example 1	We are concerned that this recommendation may imply that ……..
1	*BI are pleased that NICE recognise the benefit of a medicine in the SGLT2i class in the treatment of CKD. We understand that this represents good news for both patients and clinicians in providing an additional therapeutic option.'*
2	
3	
4	
5	
6	

Insert extra rows as needed

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	**Novartis Pharmaceuticals UK Limited**

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Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	Since April 2005 Novartis has exclusively licensed glycopyrronium bromide and certain intellectual property relating to its use and formulation from Vectura and its co-development partner, Sosei Heptares. The following inhaled medications are comprised of, or contain glycopyrronium bromide: • Seebri® Beezhaler® (glycopyrronium bromide) (used as a maintenance treatment for Chronic Obstructive Pulmonary Disease (COPD)) • Ultibro® Breezhaler® (indacaterol/glycopyrronium bromide) is used as a maintenance treatment for COPD • Enerzair® Breezhaler® (indacaterol/glycopyrronium bromide/mometasone furoate) is used as a maintenance treatment for asthma uncontrolled with LABA/ICS. Phillip Morris International (a tobacco company) is currently in the process of acquiring Vectura Group plc.
Name of commentator person completing form:	[redacted]

Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	Novartis agrees that the draft recommendation reflects the available evidence relevant to this appraisal. Clarity of the recommendation wording (section 1.1) could be improved by adding the following *italicised text*: "Dapagliflozin is recommended as an option for treating chronic kidney disease (CKD) in adults. It is recommended only if: • it is an add-on to optimised standard care including angiotensin-converting enzyme (ACE) inhibitors or angiotensin-receptor blockers (ARBs) *(titrated to the highest licensed dose that the person can tolerate)*, unless these are contraindicated ~~or not tolerated~~, and • people have an estimated glomerular filtration rate (eGFR) *at treatment initiation* of 25 ml/min/1.73 m^2 to 75 ml/min/1.73 m^2 and [...]" Addition of "titrated to the highest licensed dose that the person can tolerate" would ensure consistency with the wording used in the NICE guidelines 'Chronic kidney disease: assessment and management' (NG203) and 'Type 2 diabetes in adults: management' (NG28) when referring to treatment with an ACE inhibitor or ARB for CKD. By providing greater specificity in terms of defining 'optimised' standard care, the suggested adaptation could contribute to reducing variation in care. It would also be in line with the inclusion criteria of the pivotal DAPA-CKD study ("Stable, and for the patient maximum tolerated labelled daily dose, treatment with ACE-I or ARB for at least 4 weeks before visit 1, if not medically contraindicated")[1] and thus reflect the available evidence. As the aspect of potential intolerance is already covered by the suggested addition, the text "or not tolerated" could be omitted. eGFR thresholds both in the DAPA-CKD trial inclusion criteria[1] and the SmPC[2] refer to eGFR at initiation of dapagliflozin treatment. We propose adding this information in order to avoid

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Consultation on the appraisal consultation document – deadline for comments 5pm on 26 November 2021. Please submit via NICE Docs.

	misinterpretation that dapagliflozin treatment would need to be stopped once a patient's eGFR declines below 25 ml/min/1.73 m^2. References: [1] A Study to Evaluate the Effect of Dapagliflozin on Renal Outcomes and Cardiovascular Mortality in Patients with Chronic Kidney Disease. Clinical Study Protocol Version 4.0. Published with: Heerspink HJL, Stefánsson BV, Correa-Rotter R, et al. Dapagliflozin in patients with chronic kidney disease. N Engl J Med 2020;383:1436-46. [2] Forxiga 10 mg film-coated tablets. Summary of Product Characteristics. Available at: https://www.medicines.org.uk/emc/product/7607/smpc [Date accessed: 23 November 2021].
2	Novartis agrees with the Committee's conclusion in section 3.6 that it is appropriate to make recommendations for dapagliflozin based on uACR levels. The ACD (section 3.6) notes hesitancy about doing urine tests in secondary care; however, this issue may be more prevalent in primary care. Expert input during the first appraisal committee meeting seemed to suggest that urine tests are done more commonly in specialist renal clinics in secondary care. The current summary in the ACD may therefore need to be reconsidered. With regard to testing uACR versus uPCR (ACD section 3.6), the recently updated NICE guideline 'Chronic kidney disease: assessment and management' (NG203) states a preference for using uACR due to greater sensitivity for low levels of proteinuria, with the option to use uPCR as an alternative if uACR is ≥70 mg/mmol. The rationale and impact section of the guideline mentions that the guideline committee found that the recommendation of uACR over uPCR fits well with current practice, which suggests that overall, uACR testing is more widely done. The statement in ACD section 3.6 that uPCR tests are more widely done than uACR tests may therefore not be accurate. However, uPCR is the preferred measure in some CKD aetiologies such as glomerular diseases.[3] Further information on circumstances where uPCR may be considered the more appropriate measure could be added. A recommendation how to convert between uACR and uPCR categories is available, although several limitations are acknowledged.[3, 4] Reference: [3] Kidney Disease Improving Global Outcomes (KDIGO). KDIGO 2021 Clinical Practice Guideline for the Management of Glomerular Diseases. Kidney International 2021;100. [4] Kidney Disease Improving Global Outcomes (KDIGO). KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. Kidney International Supplements 2013;3.
3	Section 3.7 of the ACD states that "DAPA-CKD included people with an eGFR of 25 ml/min/1.73 m^2 to 75 ml/min/1.73 m^2 and a uACR of 22.6 mg/mmol or more." The trial inclusion criteria specified also an upper uACR limit of 5000 mg/g (565 mg/mmol)[1] and the text in section 3.7 should be amended accordingly to reflect this. Reference: [1] A Study to Evaluate the Effect of Dapagliflozin on Renal Outcomes and Cardiovascular Mortality in Patients with Chronic Kidney Disease. Clinical Study Protocol Version 4.0. Published with: Heerspink HJL, Stefánsson BV, Correa-Rotter R, et al. Dapagliflozin in patients with chronic kidney disease. N Engl J Med 2020;383:1436-46.
4	Section 3.8 of the ACD states that "DECLARE-TIMI-58 included people with type 2 diabetes who had, or were at high risk of, cardiovascular events and had an eGFR of more than 60 ml/min/1.73 m^2. However, 7% of people (n=1,100) had an eGFR of less than 60 ml/min/1.73 m^2." The DECLARE-TIMI-58 exclusion criterion referred to creatinine clearance <60 ml/min, rather than eGFR <60 ml/min/1.73 m^2.[5] We therefore propose that in the above first sentence about people included in the DECLARE-TIMI-58 study, "... and had an eGFR of more than 60 ml/min/1.73 m^2" is replaced with ".... and had a creatinine clearance of 60 ml/min or more". Reference:

NICE National Institute for Health and Care Excellence

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	[5] DECLARE Dapagliflozin Effect on CardiovascuLAR Events. A Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial to Evaluate the Effect of Dapagliflozin 10 mg Once Daily on the Incidence of Cardiovascular Death, Myocardial Infarction or Ischemic Stroke in Patients with Type 2 Diabetes. Revised Clinical Study Protocol, Edition Number 5.0. Available at: https://s3.amazonaws.com/ctr-med-7111/D1693C00001/9c285ea0-c985-475c-9454-693ef18bed8c/7bfad075-4f33-4ef9-9b0b-82b2648b7afb/DECLARE_TIMI_58_D1693C00001-revised-csp_5_Redacted_version-v1.pdf [Date accessed: 23 November 2021].

Insert extra rows as needed

Checklist for submitting comments

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- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
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- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise and all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a 2nd version of your comment with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the Guide to the processes of technology appraisal (section 3.1.23 to 3.1.29) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
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- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the appraisal consultation document, please submit these separately.

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Comments on the ACD received from the public through the NICE Website

Name	[redacted]
Organisation	N/A
Conflict	N/A
Comments on the ACD:	
1.1 "Recommended as an option" suggests it's an alternative, but then it's generally meant to be an add-on in the text. "Recommended as an option" is a very weak recommendation to prescribe, when the "option" is not to prescribe it. Suggest remove "as an option" as this attenuates the clear conclusion that the trial shows it's beneficial.	
Name	[redacted]
Organisation	Medicines Optimisation Team, NICE
Conflict	N/A
Comments on the ACD:	

1 Recommendations

Section 1.1:

Selected text: 'only if'

We had comments on the T2DM integrated guidance work that putting 'only if' can cause a conflict between guideline and TA recs if medicines are recommended in a broader population in the guideline. The COG (content operations group) are working on a solution so it would be good to link in with the work they are doing before publication.

Selected text: '22.6 mg/mmol or more ora uACR of 3 mg/mmol or more and type 2 diabetes.'

Current CKD guideline says offer if ACR more than 30 and T2DM - not sure how this TA aligns with the recs that are being updated but I'm assuming it will be checked for consistency upon publication.

Selected text: '75 ml/min/1.73 m2'

I know the upper limit was in the trial inclusion criteria but I don't think we need to give an upper limit here if they have a diagnosis of CKD.

Dapagliflozin for treating chronic kidney disease: A Technology Appraisal

Addendum: ERG comments on the company's ACD response

Produced by	School of Health and Related Research (ScHARR), The University of Sheffield
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Date completed	6th December 2021

1. Introduction

In October 2021, the National Institute for Health and Care Excellence (NICE) issued its Appraisal Consultation Document (ACD) on the use of dapagliflozin for the treatment of chronic kidney disease (CKD).[1] Section 1.1 of the ACD makes the following recommendations:

"Dapagliflozin is recommended as an option for treating chronic kidney disease (CKD) in adults. It is recommended only if:

- *it is an add-on to optimised standard care including angiotensin converting enzyme (ACE) inhibitors or angiotensin-receptor blockers (ARBs), unless these are contraindicated or not tolerated, 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 and:*
    - *a urine albumin-to-creatinine ratio (uACR) of 22.6mg/mmol or more or*
    - *a uACR of 3mg/mmol or more and type 2 diabetes."*

In November 2021, the company submitted its response to the NICE ACD.[2] The company's ACD response included a written response document and an updated executable economic model. Some additional evidence is presented within the written response document to support the clinical effectiveness of dapagliflozin in people with Type 2 diabetes mellitus (T2DM) with a uACR of <3mg/mmol and in people without T2DM with a uACR of <22.6mg/mmol. The company's ACD response also reports the results of additional economic analyses which include the use of a new analysis of the Clinical Practice Research Datalink (CPRD),[3] which is used to inform patient characteristics and to adjust event risks for the same subgroups presented in the company's earlier technical engagement (TE) response,[4] as well as additional subgroup analyses by uACR level (<3mg/mmol and 3-22mg/mmol) for people with or without T2DM.

This Evidence Review Group (ERG) addendum provides a summary and critique of the company's ACD response.[2] Section 2 provides a broad overview of the arguments raised in the company's ACD response, the additional clinical effectiveness evidence used to support them, and the results of the additional economic analyses undertaken using the updated post-ACD model. Section 3 provides a more detailed description of the company's concerns together with a brief critique from the ERG.

2. Overview of the company's ACD response

2.1 Overview of company's key arguments

Overall, the company's ACD response[2] argues that:

- The recommendations provided in the NICE ACD[1] are unnecessarily restrictive with respect to uACR thresholds

- The Appraisal Committee has not provided a clear and adequate justification for not recommending dapagliflozin in the full population of patients with CKD and T2DM
- The recommendations, which are conditional on uACR levels, are likely to further exacerbate existing inequalities of care related to uACR testing
- The Appraisal Committee is inappropriately constructing subgroups
- Canagliflozin should not be considered to be a comparator for dapagliflozin.

2.2 Overview of additional evidence supporting the clinical effectiveness of dapagliflozin for restricted subgroups

The company's ACD response[2] (Section 2) refers to the following sources to support the effectiveness of dapagliflozin in people with T2DM:

- Unpublished *post hoc* subgroup analyses by uACR status for the composite renal endpoint (≥40% eGFR decline, end stage kidney disease [ESKD] or death from renal causes) and the cardiorenal endpoint (≥40% eGFR decline, ESKD, renal death or cardiovascular [CV] death) in DECLARE-TIMI 58[5]
- Published subgroup analyses by uACR status defined by KDIGO guidelines A1: <3mg/mmol, A2: 3–30 mg/mmol and A3: ≥30mg/mmol (Mosenzen *et al.*[6])

With respect to patients without T2DM with a uACR of <22.mg/mmol, the company's ACD response (Section 3) refers to the following sources:

- DAPA-CKD – the main trial of dapagliflozin for the treatment of CKD[7]
- An unpublished US study of the Truven and Optum databases.

The company's ACD response (Section 3) also includes brief details of a targeted literature review on the average age of patients with CKD; this is not used in the company's additional economic analyses.

2.3 Summary of additional economic analyses presented in the company's ACD response

The additional economic analyses presented in the company's ACD response[2] are summarised in Table 1. These analyses follow the same subgrouping approach as that presented in the company's TE response,[4] whereby the overall target population for dapagliflozin is divided into three subgroups:

- Subgroup 1: Patients with a uACR of ≥22.6mg/mmol, with or without T2DM (Analysis 1 in Table 1)
    - Overall survival (OS) based on multivariable Weibull model fitted to data from DAPA-CKD and $DECLARE_{CKD}$, adjusted to new CPRD dataset
    - Transition probabilities informed by DAPA-CKD, not adjusted

- Subgroup 2: Patients with a uACR of <22.6mg/mmol with T2DM (Analysis 2 in Table 1)
    - OS based on multivariable Weibull model fitted to DAPA-CKD and $DECLARE_{CKD}$, adjusted to new CPRD dataset
    - Transition probabilities out of CKD stages 1-3 informed by $DECLARE_{CKD}$, transitions out of CKD stages 4-5 informed by DAPA-CKD, not adjusted
- Subgroup 3: Patients with a uACR of <22.6mg/mmol without T2DM (Analysis 3 in Table 1).
    - Same as Subgroup 2 (T2DM) but including non-T2DM mortality adjustment factor based on DAPA-CKD.

The main amendment applied in the company's post-ACD model is the inclusion of a new analysis of the CPRD.[3] The company's earlier TE model assumed a mean age of 64 years, based on a CPRD query including people with eGFR <90 ml/min/1.73cm^2, without the requirement of a formal diagnosis of CKD; other patient characteristics were based on a separate CPRD query relating to a different patient population with CKD. The company's post-ACD model now reflects patients in CPRD with an eGFR ≥25 to ≤75 ml/min/1.73 m^2 with or without a coded CKD diagnosis (mean age = 72.9 years).[2] The ERG believes that all patients in this newly defined CPRD dataset were also receiving ACE inhibitor or ARB therapy, although this is not clearly stated in the company's ACD response.

The results of the company's updated base case analysis are presented as a weighted incremental cost-effectiveness ratio (ICER) for Subgroups 1-3 (Table 1, Analyses 1-3), with weightings derived from the company's updated CPRD analysis.[3] Further subgroup analyses are presented for people with T2DM with a uACR of <3mg/mmol (A1) or a uACR of 3-22mg/mmol (A2* [modified to reflect the lower bound of uACR of 22mg/mmol in DAPA-CKD, rounded down]) (Table 1, Analyses 4-7). The equivalent subgroup analyses are also presented for people without T2DM and with a uACR of <3mg/mmol (A1) or a uACR of 3-22mg/mmol (A2*) (Table 1, Analyses 8-11).

Table 1: Summary of additional analyses presented by the company

Analysis no.	Company's analysis description	Additional ERG comments
N/a	Updated base case - overall target population	Weighted ICER from Analyses 1, 2 and 3. Weightings from company's new CPRD analysis (Subgroup 1 = [redacted]%; Subgroup 2 = [redacted]%; Subgroup 3 = [redacted]%)
Updated analyses of TE Subgroups 1-3 using new CPRD dataset		
1	"DAPA-CKD like" population (uACR ≥22.6mg/mmol)	Same as TE model Subgroup 1, with adjustment to new CPRD dataset. OS from combined multivariable model using DAPA-CKD and $DECLARE_{CKD}$. Transitions from DAPA-CKD (unadjusted).
2	T2DM low uACR population (uACR <22.6mg/mmol)	Same as TE model Subgroup 2, with adjustment to new CPRD dataset. OS from combined multivariable model using DAPA-CKD and $DECLARE_{CKD}$. Transitions from combined dataset of DAPA-CKD and $DECLARE_{CKD}$ (unadjusted).
3	Non-T2DM low uACR population (uACR <22.6mg/mmol)	Same as TE model Subgroup 3,with adjustment to new CPRD dataset. Virtually identical to Analysis 2, but with non-T2DM mortality adjustment factor of [redacted].
New analyses of TE Subgroup 2 (low uACR, T2DM) with or without CPRD adjustment – including further subgrouping by uACR level		
4	T2DM A1 population (uACR <3mg/mmol) CPRD-adjusted	Same as Analysis 2 with CPRD characteristics for uACR <3mg/mmol subgroup
5	T2DM A1 population (uACR <3mg/mmol) unadjusted	Equivalent to Analysis 4 without CPRD adjustment, baseline characteristics from uACR<3mg/mmol subgroup in $DECLARE_{CKD}$
6	T2DM Modified A2* population (uACR 3-22mg/mmol) CPRD-adjusted	Same as Analysis 2 with CPRD characteristics for uACR 3-22mg/mmol subgroup*
7	T2DM Modified A2* population (uACR 3-22mg/mmol) unadjusted	Equivalent to Analysis 6 without CPRD adjustment, baseline characteristics from uACR 3-22mg/mmol subgroup in $DECLARE_{CKD}$
New analyses of TE Subgroup 3 (low uACR, no T2DM) with or without CPRD adjustment – including further subgrouping by uACR level		
8	Non-T2DM A1 population (uACR <3mg/mmol) CPRD-adjusted	Equivalent to Analysis 4 in non-T2DM subgroup
9	Non-T2DM A1 population (uACR <3mg/mmol) unadjusted	Equivalent to Analysis 5 in non-T2DM subgroup
10	Non-T2DM Modified A2* population (uACR 3-22mg/mmol) CPRD-adjusted	Equivalent to Analysis 6 in non-T2DM subgroup
11	Non-T2DM Modified A2* population (uACR 3-22mg/mmol) unadjusted	Equivalent to Analysis 7 in non-T2DM subgroup

ERG - Evidence Review Group; N/a - not applicable; CPRD - Clinical Practice Research Datalink; TE - technical engagement; T2DM - Type 2 diabetes mellitus; uACR - urine albumin-creatinine ratio

The results of the company's new economic analyses using the post-ACD model are presented in Table 2.

Table 2: Results of all additional economic analyses presented in company's ACD response (generated by the ERG using the company's post-ACD model)

Option	LYGs*	QALYs	Costs	Inc. LYGs*	Inc. QALYs	Inc. Costs	ICER
Updated base case – overall target population (weighted ICER from Analyses 1-3)							
Dapagliflozin	12.06	6.94	£25,023	2.85	0.33	£1,974	**£5,948**
SoC	9.21	6.61	£23,048	-	-	-	-
Analysis 1: "DAPA-CKD like" population (uACR ≥22.6mg/mmol)							
Dapagliflozin	10.89	6.17	£50,741	0.96	0.52	-£1,004	**Dominating**
SoC	9.94	5.65	£51,745	-	-	-	-
Analysis 2: T2DM low uACR population (uACR <22.6mg/mmol)							
Dapagliflozin	11.79	6.82	£22,310	3.06	0.43	£2,576	**£5,990**
SoC	8.73	6.39	£19,734	-	-	-	-
Analysis 3: Non-T2DM low uACR population (uACR <22.6mg/mmol)							
Dapagliflozin	12.89	7.37	£24,043	2.91	0.09	£1,512	**£17,139**
SoC	9.98	7.28	£22,531	-	-	-	-
Analysis 4: T2DM A1 population (uACR <3mg/mmol) CPRD-adjusted							
Dapagliflozin	12.03	6.93	£22,353	3.16	0.43	£2,646	**£6,112**
SoC	8.88	6.50	£19,708	-	-	-	-
Analysis 5: T2DM A1 population (uACR <3mg/mmol) unadjusted							
Dapagliflozin	15.37	8.30	£27,596	4.56	0.44	£2,603	**£5,965**
SoC	10.81	7.86	£24,993	-	-	-	-
Analysis 6: T2DM Modified A2* population (uACR 3-22mg/mmol) CPRD-adjusted							
Dapagliflozin	11.06	6.48	£22,243	2.76	0.41	£2,309	**£5,599**
SoC	8.30	6.07	£19,934	-	-	-	-
Analysis 7: T2DM Modified A2* population (uACR 3-22mg/mmol) unadjusted							
Dapagliflozin	15.92	8.54	£27,262	4.77	0.42	£2,675	**£6,352**
SoC	11.16	8.12	£24,587	-	-	-	-
Analysis 8: Non-T2DM A1 population (uACR <3mg/mmol) CPRD-adjusted							
Dapagliflozin	13.19	7.50	£24,221	3.04	0.10	£1,586	**£16,684**
SoC	10.16	7.41	£22,635	-	-	-	-
Analysis 9: Non-T2DM A1 population (uACR <3mg/mmol) unadjusted							
Dapagliflozin	16.94	9.01	£30,184	4.76	0.18	£1,697	**£9,277**
SoC	12.18	8.83	£28,487	-	-	-	-
Analysis 10: Non-T2DM Modified A2* population (uACR 3-22mg/mmol) CPRD-adjusted							
Dapagliflozin	11.94	6.93	£23,389	2.53	0.07	£1,274	**£19,532**
SoC	9.41	6.87	£22,115	-	-	-	-
Analysis 11: Non-T2DM Modified A2* population (uACR 3-22mg/mmol) unadjusted							
Dapagliflozin	17.34	9.18	£29,436	4.89	0.15	£1,770	**£11,769**
SoC	12.45	9.03	£27,666	-	-	-	-

LYG - life year gained; QALY - quality-adjusted life year gained; ICER - incremental cost-effectiveness ratio; SoC - standard of care; uACR - urine albumin-creatinine ratio; T2DM - Type 2 diabetes mellitus

** Undiscounted*

3. Company's main arguments and ERG critique

3.1 Company's concerns regarding the restricted recommendation in patients with T2DM and a uACR of <3mg/mmol (TE Subgroup 2)

3.2.1 Company's arguments

With respect to the restricted recommendation for patients with T2DM and a uACR of <3mg/mmol (TE Subgroup 2), the company's ACD response[2] makes the following main arguments:

- The ACD states that the ICER for dapagliflozin *"is comfortably within what NICE considers an acceptable use of resources"* (ACD,[1] Section 3.17). Hence, the company states that they are *"extremely concerned as to why a further restriction within this subgroup has been made without any clear rationale, and urges the Committee to base their final recommendations on the clinical and cost-effectiveness evidence presented within this appraisal"* (Company's ACD response,[2] page 5).
- The company's ACD response[2] refers to unpublished *post hoc* subgroup analyses of DECLARE-TIMI 58 for people with a uACR level above or below a threshold of 22.6mg/mmol, which indicate a consistent treatment effect for dapagliflozin for renal and cardiorenal endpoints;[5] these data were previously presented in Figure 17 of the company's submission (CS).[8] The company's ACD response also refers to published subgroup analyses of DECLARE-TIMI 58, which indicate a consistent treatment effect for dapagliflozin for renal-specific and cardiorenal composite endpoints across KDIGO uACR thresholds A1, A2 and A3 (Mosenzon *et al*.[6]).
- The uACR threshold of 3mg/mmol represents an additional subgroup for which the Appraisal Committee has not provided a clear rationale. Prior to the release of the ACD,[1] no cost-effectiveness results had been presented for patients with comorbid T2DM and a uACR level above or below 3mg/mmol. The company notes that the economic analysis for Subgroup 2 presented at TE was based on people in DECLARE-TIMI 58 with a uACR level ranging from 0-22.6/mmol.
- Despite disagreeing with the restriction by uACR level, the company's ACD response[2] includes further economic subgroup analyses for: (a) patients with T2DM and a uACR of <3mg/mmol (KDIGO A1) and (b) patients with T2DM and a uACR of 3-22mg/mmol (KDIGO A2*; see Table 1, Analyses 4-7). These additional economic analyses suggest ICERs which are below £7,000 per quality-adjusted life year (QALY) gained in both of these more granular uACR subgroups, irrespective of whether modelled risks are adjusted using the new CPRD dataset (see Table 2, Analyses 4-7). The company highlights that these ICERs are below NICE's usual cost-effectiveness thresholds.

- It is inappropriate to construct further subgroups within subpopulations for which a therapy has already been deemed to be cost-effective. The company cites the appeal following the NICE technology appraisal of pirfenidone for treating idiopathic pulmonary fibrosis (TA504).[9]
- A recommendation which requires uACR testing to be conducted is likely to further exacerbation existing inequalities of care within the NHS.

The above bullet-points represent a condensed summary of the company's arguments relating to this subgroup; further detail can be found in Section 2 of the company's ACD response.[2]

3.2.2 ERG's comments

The ERG believes that the restriction of the ACD recommendation to those individuals with T2DM with a uACR of ≥3mg/mmol was made for consistency with the draft recommendations on the use of sodium glucose cotransporter 2 (SGLT2) inhibitors set out in the NICE guideline on T2DM in adults.[10] The final guideline, which was published by NICE in November 2021, states that for adults with T2DM and CKD who are taking an ARB or an ACE inhibitor (titrated to the highest licensed dose that they can tolerate), SGLT2 inhibitors may be offered (in addition to the ARB or ACE inhibitor) if the patient's ACR is over 30mg/mmol, or considered if their ACR is between 3mg/mmol and 30mg/mmol. The guideline states that *"The committee made a recommendation for research on the effectiveness of SGLT2 inhibitors for people with a baseline ACR of less than 3mg/mol, because there was no evidence looking specifically at this group"* (NICE Guideline NG28,[10] page 32). The evidence review for the guideline included published subgroup analyses of both DAPA-CKD and DECLARE-TIMI 58, but did not find relevant evidence from these studies to support the use of dapagliflozin in the <3mg/mmol subgroup. The ACD also highlights that Subgroup 2 represents a large proportion of the costs and QALYs in the company's weighted economic analysis and so the consequences of decision error were high.

The ERG notes that the supporting evidence from the subgroup analyses of DECLARE-TIMI 58 (the unpublished subgroup analyses[5] and Mosenzon *et al.*[6]) reported in the company's ACD response[2] relate to the whole population of the trial, rather than the subgroup of patients who had T2DM with comorbid CKD. The ERG does not believe that the company has presented any subgroup analyses to support the clinical effectiveness of dapagliflozin specifically in people with T2DM with comorbid CKD who have a uACR of <3mg/mmol. As demonstrated by the final guideline recommendation, this lack of evidence was a concern for the NICE T2DM guideline developers.

The ERG believes that the appeal in TA504[9] reflects a different situation to this appraisal, as there was evidence to support the clinical effectiveness of pirfenidone across all subgroups, yet the technology was considered to be cost-effective in some subgroups but not others. This appraisal differs in that the

Appraisal Committee has not been presented with evidence to support the relative clinical effectiveness of dapagliflozin versus standard care in the relevant uACR <3mg/mmol subgroup with T2DM and CKD and no evidence for this subgroup was identified by the evidence review for the NICE T2DM guideline.

The company's additional economic analyses suggest that the ICER for dapagliflozin is estimated to be less than £7,000 per QALY gained. However, the ERG has some concerns regarding the company's economic analyses for Subgroup 2:

- The ERG's clinical advisors commented that the company's new CPRD dataset, which restricts the population to people with an eGFR ≥25 to ≤75ml/min/1.73m^2 with or without a coded CKD diagnosis, would include a large number of people who do not have CKD. One of the ERG's advisors commented that the majority of people with an eGFR of 60-75ml/min/1.73m^2, which will represent a large proportion of this population, do not have other markers of CKD.
- At the TE stage, the company's economic analyses for Subgroups 1, 2 and 3 were adjusted using distinct CPRD analyses which were intended to reflect the characteristics of patients in the CPRD in those subgroups. In the company's updated post-ACD model, the economic analyses of Subgroups 2 and 3 are based on a single CPRD population in which approximately 67% of people had T2DM and 33% did not (see Appendix 1, Table 4, columns 3 and 4, T2DM values highlighted in bold). Thus, whilst the economic analysis for Subgroup 2 is intended to reflect a subgroup of patients who all have T2DM, one third of patients in the CPRD dataset applied in the modelled subgroup analysis do not have T2DM. The ERG is unclear why these data have not been stratified by T2DM status in the post-ACD model and the impact of this stratification on the ICER for dapagliflozin, had it been included, is unclear.
- The transition probabilities and OS models applied in the uACR <3mg/mmol and 3-22mg/mmol subgroups (Table 1, Analyses 4-7) reflect the overall DECLARE$_{CKD}$ and DAPA-CKD datasets, rather than the specific subgroups defined by these more granular uACR intervals. It is likely that these other model parameters would differ between the subgroups which leads to further uncertainty around the results of the company's post-ACD analyses for Subgroup 2.

Overall, the ERG believes that it would be reasonable either:

- For NICE to amend the ACD to provide a clearer justification for the restriction of the recommendation in the T2DM subgroup to include only those patients with a uACR of ≥3mg/mmol, or
- For the company to provide additional clinical evidence from DECLARE-TIMI 58[11] which demonstrates the relative effectiveness of dapagliflozin in the subgroup of patients with T2DM and a uACR of <3mg/mmol. Specifically, this might be done using the DECLARE$_{CKD}$ dataset

introduced by the company at the TE stage. The ERG also believes that any economic analyses for this subgroup should better reflect the characteristics of the patients included within it (in particular, with respect to the CPRD patient characteristics and the transition probabilities applied in the model).

3.2 Company's concerns regarding the absence of a positive recommendation in patients with a uACR of <22.6mg/mmol without T2DM (TE Subgroup 3)

3.2.1 Company's arguments

With respect to the absence of a positive ACD recommendation in patients without T2DM and with a uACR of <22.6mg/mmol (TE Subgroup 3), the company's ACD response[2] makes the following main arguments:

- The Medicines and Healthcare products Regulatory Agency (MHRA), the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA) have each granted marketing authorisations for dapagliflozin which are broad and which are not restricted by uACR or T2DM status.
- The consistency of the relative treatment effect for dapagliflozin was clearly demonstrated irrespective of T2DM status in both DAPA-CKD[7] and DAPA-HF.[12] The consistency of the relative treatment effect is also likely to apply to patients with lower uACR levels with and without T2DM.
- Further direct evidence of the efficacy of dapagliflozin in people with CKD without T2DM and with a uACR of <22.6mg/mmol is provided from new analyses of the Truven and Optum databases.

  [redacted] ([redacted]). The company claims that *"these results provide further reassurance that dapagliflozin is effective in patients with CKD without T2DM and with a uACR [redacted]"* (Company's ACD response,[2] page 10).
- The mean age in the CPRD dataset[3] is not representative of the age of the total CKD target population for dapagliflozin. The company's ACD response[2] provides brief details of a targeted literature review to validate the true mean age of patients with CKD stages 1-4. Five studies were identified which reported a mean or median age for a cohort with at least 1,000 patients. Mean age was reported as 68.8 years in one cohort with or without T2DM, and 64 and 70 years in incident and prevalent diabetic kidney disease (DKD) cohorts with CKD stages 1-5. Median age was reported in four studies, with estimates ranging from 67.6 years to 75 years. The company argues that a value of 76.6 years, as applied in the ERG's TE addendum[13] (which was based on the company's CPRD analysis for all other patient characteristics) may overestimate

the true mean age. These estimates are not used in the updated economic analyses; instead, age is based on the new CPRD dataset in all updated economic analyses presented in Table 2.

- The Appraisal Committee and the ERG have implicitly accepted that there is sufficient clinical evidence for dapagliflozin in the subgroup of patients with a uACR of <22.6mg/mmol and without T2DM because they conducted a cost-effectiveness analysis in this population.
- Dapagliflozin is very likely to represent a cost-effective use of NHS resources in patients with a uACR of <22.6mg/mmol, regardless of T2DM status when the mean age considered in the analysis more appropriately reflects UK clinical practice. The company's ACD response[2] includes further subgroup analyses for patients without T2DM with a uACR of <3mg/mmol and for those without T2DM with a uACR of 3-22mg/mmol (see Table 1, Analyses 8-11). These additional subgroup analyses result in ICERs which are less than £20,000 per QALY gained in both subgroups, irrespective of whether modelled risks are adjusted using the new CPRD dataset (see Table 2, Analyses 8-11).

The above bullet-points represent a condensed summary of the company's arguments; further detail can be found in Section 3 of the company's ACD response.[2]

3.2.2 ERG's comments

The ERG's concerns regarding Subgroup 3 have not changed since the TE stage of this appraisal.[13] There is no direct comparative evidence to support the relative clinical effectiveness of dapagliflozin versus standard of care (SoC) in people without T2DM who have a uACR of <22.6mg/mmol.

The additional evidence presented from the analysis of the Truven and Optum databases is limited in that: (a) they include very small sample sizes (N=[redacted] and N=[redacted], respectively); (b) they indicate only the [redacted] - a surrogate for hard clinical outcomes; (c) and the data are observational in nature. In contrast, the evidence supporting the clinical effectiveness of dapagliflozin in Subgroups 1 and 2 is based on large randomised controlled trials using relevant final endpoints (DAPA-CKD,[7] N=4,304; DECLARE-TIMI 58,[11] N=17,160). The ERG's clinical advisors did not believe that the Optum and Truven database analyses provide sufficient evidence to demonstrate that dapagliflozin is clinically effective in this subgroup. Overall, the ERG believes that the Optum and Truven database analyses might support a hypothesis that dapagliflozin could have an effect in this subgroup, but the extent to which any conclusions can be drawn from the available data is limited. The ERG also notes that based on the company's new CPRD analysis, Subgroup 3 represents [redacted]% of the total target population for dapagliflozin and the economic model assumes the same relative treatment effect for dapagliflozin in Subgroup 3 as that in Subgroup 2. This is a strong assumption and the potential consequences of decision error are high.

As discussed in the ERG's TE addendum,[13] the ERG had concerns that the company's TE model used one CPRD query to generate patient characteristics for the subgroups, and a separate CPRD query relating to a much broader population to estimate the mean age for that same subgroup. The company's ACD response[2] includes brief details of published studies reporting the average age of CKD patients, but the results of this review are not used in the company's post-ACD economic analyses. The ERG believes that the company's post-ACD approach of drawing all patient characteristics from a single CPRD query is more appropriate. The ERG notes however that the company's argument about the CPRD population not being representative of the target population due to their older age also applies to all of the other CPRD patient characteristics used in the model. This raises broader questions about the appropriateness of including the CPRD adjustment.

The ERG does not agree that presenting cost-effectiveness results for Subgroup 3 reflects either an implicit or explicit acceptance that the clinical evidence of relative efficacy for this subgroup is sufficient. The ERG presented a revised economic analysis for Subgroup 3 in the TE addendum[13] to demonstrate that even if the company's assumption of relative efficacy did hold for this subgroup, despite the absence of evidence to support it, applying the mean age from the same CPRD dataset[3] which was used to inform all other patient characteristics substantially increased the ICER for dapagliflozin compared with the company's TE analysis for Subgroup 3. The ERG's decision to present this analysis in the TE addendum is unrelated to any judgement about the robustness the clinical evidence used to inform it.

In addition to the lack of evidence to demonstrate the relative effectiveness of dapagliflozin versus SoC in people without T2DM and with a uACR of <22.6mg/mmol, the ERG has a number of other concerns regarding the robustness of the results of the company's post-ACD economic analyses for Subgroup 3:

- As discussed in Section 3.2.2, the company's updated CPRD dataset is likely to include a large proportion of people who do not have CKD.
- As discussed in Section 3.2.2, the company's post-ACD economic analyses of Subgroups 2 and 3 are based on the same CPRD dataset, in which around 67% of people had T2DM and 33% did not (see Appendix 1, Table 4, columns 3 and 4). Thus, whilst the company's post-ACD economic analysis for Subgroup 3 is intended to reflect patients who do not have T2DM, two-thirds of patients in the new CPRD dataset used in this subgroup analysis did have T2DM. The ERG is unclear why these data have not been stratified by T2DM status and the impact of this stratification on the ICER for dapagliflozin, had it been included, is unclear.
- As discussed in the ERG's TE addendum,[13] the transition probabilities and OS models for this subgroup do not reflect the characteristics of the subgroup – they are assumed to be the same as those for the T2DM uACR<22.6mg/mmol subgroup (Subgroup 2), albeit with the inclusion

of a non-T2DM mortality adjustment factor (adjustment factor = [redacted]). The ERG's clinical advisors commented that rapid CKD progression is more common in people with T2DM than people without T2DM.

- The ERG notes that the difference in OS and QALYs between Subgroups 2 and 3 is almost entirely attributable to the non-T2DM mortality adjustment factor (see Table 3) and that most of the clinical inputs for Subgroup 3, including relative treatment effects on CKD transitions and OS, are informed by study populations in which the majority of patients (DAPA-CKD), or all patients ($DECLARE_{CKD}$), had T2DM.

As a consequence of these issues, the ERG believes that any ICERs estimated for people with CKD without T2DM and with a uACR of <22.6mg/mmol should be interpreted with considerable caution.

Table 3: Modelled survival and QALYs for Subgroup 2 versus Subgroup 3 with/without the non-T2DM mortality adjustment factor

Subgroup	Life years			QALYs		
	Dapagliflozin	SoC	Inc.	Dapagliflozin	SoC	Inc.
Subgroup 2 - T2DM uACR<22.6mg/mmol	11.79	8.73	3.06	6.82	6.39	0.43
Subgroup 3 - No T2DM <22.6mg/mmol	12.89	9.98	2.91	7.37	7.28	0.09
Subgroup 3 - No T2DM <22.6mg/mmol excluding non-T2DM factor	11.79	8.73	3.06	6.82	6.39	0.43

QALY - quality-adjusted life year; T2DM - type 2 diabetes mellitus; SoC - standard of care; Inc. - incremental; uACR - urine-albumin-creatinine ratio

3.3 Company's concerns that restricted recommendations by uACR level will increase health inequalities

3.3.1 Company's arguments

The company's ACD response[2] raises concerns that restricting the recommendations for dapagliflozin by uACR level will increase existing health inequalities due to low rates of uACR testing in clinical practice in the NHS. In particular, the company argues that existing inequalities in uACR testing between people with and without T2DM will lead to unequal access to dapagliflozin, and that it is inappropriate to use a technology appraisal recommendation to encourage the wider use of uACR testing. These arguments are not presented in detail here, but further detail can be found in Section 4 of the company's ACD response.

3.3.2 ERG's view

The ERG believes that this is a matter for the Appraisal Committee to consider, rather than the ERG. However, the ERG believes that it is usual for NICE recommendations to relate only to those

population(s) for whom the evidence suggests that the technology is both clinically and cost-effective. In this case, evidence is lacking particularly for patients without T2DM and with a uACR of <22.6mg/mmol; hence, it would seem reasonable for the recommendations to reflect this.

3.4 Company's concerns that canagliflozin should not be considered as a comparator

3.4.1 Company's arguments

The company's ACD response[2] makes the following arguments:

- Canagliflozin should not be considered as a comparator
- The ACD should reflect that canagliflozin was not included in the scope for the appraisal;[14] hence, the company were not required to compare dapagliflozin against canagliflozin
- Whilst canagliflozin was recommended as part of a class-level recommendation for SGLT2 inhibitors in NICE Guideline NG203,[15] it does not reflect current practice and its current usage is low
- Canagliflozin is licenced only for the treatment of patients with DKD (CKD caused by T2DM), which comprises a subgroup of patients with CKD and comorbid T2DM.

3.4.2 ERG's view

The CS[8] argued that canagliflozin is not a comparator for this appraisal. However, the CS presented matching-adjusted indirect comparisons (MAICs) between dapagliflozin and canagliflozin and included economic scenario analyses comparing these treatments in people with T2DM based on an assumption of equivalent clinical outcomes and costs. The ERG considers that:

- It is reasonable to include canagliflozin as a comparator within the subgroup of patients with T2DM, where the licensed indications for both treatments overlap (i.e. within DKD).
- On the basis of the company's MAICs, it is reasonable to assume that dapagliflozin and canagliflozin are likely to be equally effective within this DKD subgroup
- If usage of canagliflozin remains low, including canagliflozin as a comparator in the appraisal should be of little consequence for dapagliflozin
- Given the above assumptions, the ACD statement relating to the use of the least expensive option seems reasonable.

3.5 Additional comments from the ERG

The ERG notes that the company's updated base case in their ACD response[2] weights the ICERs for Subgroups 1-3 according to their prevalence in the new CPRD dataset[3] (see Table 2). The ERG does not believe that the company's weighted base case is appropriate. Instead, the ERG believes that it would be more appropriate to consider the cost-effectiveness of dapagliflozin within the individual

subgroups which together make up the company's overall proposed target population. This position was also taken by the Appraisal Committee in the ACD.[2]

The ERG was able to generate the post-ACD results for Subgroups 1-3 using the previous version of the company's model submitted at the TE stage. This provides some reassurance that no other aspect of the company's model has been changed except for the patient characteristics from the CPRD analysis.

4. References

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15. National Institute for Health and Care Excellence. NICE Guideline NG203 - Chronic kidney disease: assessment and management. London, UK; 2021.

Table 4: CPRD/trial patient covariates included in company's additional economic analyses

Characteristic \ Analysis no.	1	2	3	4	5	6	7	8	9	10	11
Age (years)											
Female											
BMI (kg/m2)											
Race: White											
Race: Black or African American											
Race: Other											
Smoker											
CKD 1											
CKD 2											
CKD 3a											
CKD 3b											
CKD 4											
CKD 5 (pre-RRT)											
Dialysis											
Transplant											
UACR: 30-300 mg/g											
UACR: >=300 mg/g											
Type 2 diabetes											
Glomerulonephritis											
ACE											
ARB											
MRA											
Diuretic											
Potassium											
Systolic blood pressure											
Haemoglobin											
Prior HF											
Prior MI											
Prior Stroke											