National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Canagliflozin for treating chronic kidney disease in people with type 2 diabetes

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Comment 1: the draft remit

Section	Consultee/ Commentator	Comments	Action
Appropriateness	Kidney Care UK	Yes	Comment noted. No changes have been made.
	Napp Pharmaceuticals Ltd	Napp believe it is highly appropriate for this topic to be referred to NICE for production of a Single Technology Appraisal for the following reasons: 1. Diabetic Kidney Disease (DKD) in Type 2 Diabetes Mellitus (T2DM) is a distinct clinical entity (ICD10 Code E11.22) with: a. Significant and accelerating incidence and prevalence. b. Limited and insufficient treatment options. i. There are no disease-specific treatments for DKD at present. ii. Current standard of care involves use of a number of T2DM and CKD treatments, which leave a high residual risk and disease burden even in optimally treated DKD patients. ,	Thank you, your comments have been noted. The scope now refers to diabetic kidney disease in adults with type 2 diabetes.

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		c. Significant impact on patient HRQoL, particularly in end-stage renal disease requiring dialysis or transplant, as well as through excess risk of major adverse cardiovascular events. , , d. High management costs, particularly in relation to provision of renal replacement therapy (dialysis or transplant) for end-stage renal disease. 2. Current NICE technology appraisals of canagliflozin (TA315 , TA390) only consider use of the technology as a treatment for T2DM via control of hyperglycaemia. Although all DKD patients must (by definition) suffer from comorbid diabetes, DKD is a physiologically and clinically distinct disease process, requiring additional treatment and management to T2DM alone.7 Treatment of DKD focuses on different outcomes and utilises different interventions than the treatment of T2DM, meaning the currently available TAs for canagliflozin do not provide any relevant guidance for its use in this indication. 3. The published trial data for canagliflozin that support the application for this new indication is: a. From a robust trial design. b. Highly statistically significant. c. Primarily based on “hard” clinical endpoints, e.g. CV mortality and morbidity, incidence of End Stage Kidney Disease (ESKD). d. Clinically relevant on a population health basis. e. Clinically relevant in terms of individual patient HRQoL.	

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		f. Novel – there have not been any successful trials or new treatments licensed for CKD or DKD in approximately 18 years. g. Of great interest to HCPs working in relevant fields as well as patients – there has been notable and ongoing professional and lay press coverage of positive trial results since first released in April 2019.	
	Primary Care Diabetes Society	Yes. However we have some concern that this proposal will only look at the use of canagliflozin within its marketing authorisation (requires eGFR > 60 ml/min/1.73m2 for initiation), yet the published data from the CREDENCE trial suggests that 60% of those recruited had eGFR < 60 ml/min/1.73m2, with the sub analysis suggesting greater benefit in this subgroup. These changes would have a major impact on our patients with CKD and cardiovascular disease.	Thank you for your comment. The appraisal committee will consider the clinical and cost-effectiveness evidence for canagliflozin but will only be able to make recommendations within the licensed marketing authorisation. No changes have been made.
	Association of British Clinical Diabetologists (ABCD), British Renal Society and The Renal Association UK	This is appropriate	Comment noted. No changes have been made.
Wording	Napp Pharmaceuticals Ltd	The wording of the remit is broadly applicable but requires some refinement in line with updates to the latest expected marketing	Thank you for your comment. The remit has been amended in

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		authorisation wording following feedback from EMA/CHMP. Please refer to Comment Section 4 below (not reported here).	line with the trial evidence.
	Primary Care Diabetes Society	The above comment needs taken into consideration and we would value a review of the evidence that considers the use of canagliflozin in those with eGFR in the range 30-60 ml/mi/1.73m2, as the trial data may be suggestive of benefit in this subgroup and we feel this too warrants economic analysis.	Thank you for your comment. Subgroup analyses may be reported but this will depend on the availability of data. The appraisal committee will consider the relevance of subgroups (if the data allows this) but will only be able to make recommendations within the licensed marketing authorisation. No changes have been made.
	Association of British Clinical Diabetologists (ABCD), British Renal Society and The Renal Association UK	This is appropriate	Comment noted. No changes have been made.
Timing Issues	Napp Pharmaceuticals Ltd	There is a high degree of urgency for NICE to issue a technology appraisal on this topic. Using unpublished figures from a UK epidemiological survey conducted by Napp, in conjunction with the	Thank you, your comments have been noted. No changes have been made.

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		expected new Marketing Authorisation, (MA) we estimate that at minimum: • [redacted] patients will become immediately eligible for treatment within the new MA • An additional [redacted] patients would be eligible following appropriate renal function testing (please refer to response below regarding potential barriers to adoption) Therefore [redacted] UK T2DM/DKD patients could potentially be eligible for canagliflozin treatment in this indication. However, it is important to note that this is a highly conservative estimate, alternative projection methods indicate that there may be more than [redacted] eligible patients. Utilising the conservative estimate of [redacted] patients, over a 12-month period approximately [redacted] of them would be likely to develop renal failure, [redacted] would experience hospitalisation for heart failure, and [redacted] would experience a Major Adverse Cardiovascular Event (MACE). If these patients were all treated with canagliflozin 100 mg for these 12 months (and the (CREDENCE trial efficacy replicated in real-world effectiveness) these event rates would be reduced to approximately [redacted], and [redacted] respectively. I.e. approximately [redacted] incident cases of renal failure would be avoided, [redacted] cases of hospitalisation for heart failure avoided, and [redacted] MACE events also avoided. The MA for canagliflozin in the new T2DM/DKD indication is expected to be granted in [redacted] Ongoing absence of a NICE STA for this indication would significantly contribute to the ongoing accrual of the above adverse clinical outcomes, the rates of which could be greatly decreased with appropriate access to canagliflozin within this population	

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	Primary Care Diabetes Society	As diabetic nephropathy remains the commonest cause of ESRF, with significant impact for affected individuals and cost to the healthcare economy, this warrants timely review.	Thank you, your comments have been noted. No changes have been made.
	Association of British Clinical Diabetologists (ABCD), British Renal Society and The Renal Association UK	There is an urgency to ensure that people with diabetes and CKD are able to access effective treatment for their condition speedily especially with emerging treatment evidence. Delay for these individuals results in loss of their kidney function.	Thank you, your comments have been noted. No changes have been made.
Additional comments on the draft remit	Napp Pharmaceuticals Ltd	No further comments	Noted. No changes have been made.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Kidney Care UK	The background information should include: • The significant burden of treatment options for end stage renal failure, in terms of financial cost to the system and the patient • The burden of treatment and impact on quality of life for patients and their families. • That treatment for kidney failure is the second most expensive complication of type 2 diabetes https://www.ncbi.nlm.nih.gov/pubmed/26773733 .	Thank you for your comments. The background section is intended to give a brief summary of the disease area. An overview of relevant recommendations from CG182 are included and a link has been included for

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		• The increased risk of early death amongst people with diabetes and kidney disease (Diabetic kidney disease shortens lifespan by 16 years compared to diabetes or CKD alone – Wen Kidney Int. 2017 Aug;92(2):388-396) • That awareness of kidney disease as a complication of diabetes is low and particularly that rates of annual testing by GPs are low (Only 54% of people with diabetes are having the NICE recommended regular GP-based urine tests that can enable early identification of kidney disease (HQIP (2017) National Chronic Kidney Disease Audit, London.)	further details. The following changes have been made: • the description of eGFR and ACR categories have been amended in line with table 1 in NICE clinical guideline for Chronic kidney disease in adults: assessment and management • an additional recommendation on target blood pressure has been added from the NICE clinical guideline for Chronic kidney disease in adults: assessment and management • a sentence has been added on the link between chronic kidney

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			disease and cardiovascular disease • the spelling of albumin to creatinine ratio has been corrected • a sentence has been added about survival rates.
	Napp Pharmaceuticals Ltd	• The background section should be revised and expanded to explain the distinction between DKD and CKD. (See response to "appropriateness" above) • Currently no mention is made of NICE Guideline 28 (NG28)[i] or the treatment of hyperglycaemia / T2DM itself, which is a fundamental component of managing DKD. • "albumin to creatine ratio" should be "Urinary Albumin to Creat**ini**ne ratio (uACR) • This section includes a description of albuminuria as (≥3 mg/mmol to <30 mg/mmol "A2"). This should be described as moderate albuminuria, and it would also be useful to include a description of severe albuminuria (≥30 mg/mmol "A3"). • It would be useful to explain within the background that eGFR is a measure of kidney function, and that eGFR loss is essentially irreversible, whilst uACR is a measure of the current 'stress' experienced by the kidney and is highly reversible.[ii] • We suggest that eGFR should be referred to as consisting of five stages rather than six. There are six distinct categories, but two of these are considered a single stage (3a and 3b).	Thank you for your comments. The background section is intended to give a brief summary of the disease area. CG182 are included and a link has been included for further details. The following changes have been made: • the description of eGFR and ACR categories have been amended in line with table 1 in NICE clinical guideline for Chronic kidney disease in adults: assessment and management • an additional recommendation on target blood pressure has

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		• We suggest that the three uACR categories would be best described as “categories” or “severities” rather than “stages”, as the latter term somewhat implies irreversibility. • The statement *“For both eGFR and ACR, a higher stage* [suggest “category” here] *indicates more severe kidney disease”* is correct but could be subject to misinterpretation. Although a higher eGFR category represents more severe kidney disease, a lower numerical value of eGFR reading represents more severe kidney disease. E.g. a potential alternative way of wording this would be *“As the measured eGFR declines, the eGFR category progresses from G1 to G5 – where G1 represents normal kidney function and G5 represents kidney failure”* • Napp suggest that a paragraph regarding the strong association between CKD/DKD and cardiovascular mortality and morbidity (heart failure; myocardial infarction; stroke) should be added. This relationship is very well established, and kidney-related CV mortality represents a far more likely outcome for an individual person than does ESKD. See outcomes section for more details. • The section describing CG182**Error! Bookmark not defined.** does not explain that the recommendation for RAAS inhibition is based on the direct intrarenal haemodynamic effect of these medicines. The section describing CG182 does not include the important recommendation regarding systemic hypertension control for reducing the progression of CKD/DKD.	been added from the NICE clinical guideline for Chronic kidney disease in adults: assessment and management • a sentence has been added on the link between chronic kidney disease and cardiovascular disease • the spelling of albumin to creatinine ratio has been corrected • a sentence has been added about survival rates.
	Primary Care Diabetes Society	As detail above, whilst this TA is welcomed, we would also welcome the opportunity to consider the benefits in a wider context, including those with e GFR in the range 30-60 mls/min/1.73m2 because the evidence from the published trial data might imply greater benefit for this subgroup, although we acknowledge that, at present, the marketing	Thank you for your comment. The appraisal committee will consider the clinical and cost-effectiveness evidence for canagliflozin but will only be

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		authorisation is for initiation in those with eGFR > 60 mls/min/1.73m2. Many other international guidelines are now recommending SGLT2i down to an eGFR of 30.	able to make recommendations within the licensed marketing authorisation. No changes have been made.
	Association of British Clinical Diabetologists (ABCD), British Renal Society and The Renal Association UK	• There is a need to highlight the inadequacy of current standard of care. Inhibition of the Renin Angiotensin System (RAS) which is now the recommended treatment results in a hazard ratio reduction of only 16 to 20%. The established benefits of canagliflozin are additional to those from RAS inhibition. • Also it needs to be stressed that because there are a growing number of people with diabetes and considering it takes approximately 10 years to develop kidney disease there is likely to be a significant increase in the number of people with diabetes and CKD in the next 5 years.	Thank you for your comment. The background section is intended to give a brief summary of the disease area. The background section has been amended to include an additional recommendation from the NICE clinical guideline for Chronic kidney disease in adults: assessment and management.
The technology/ intervention	Napp Pharmaceuticals Ltd	The wording *(Invokana, Janssen-Cilag, UK commercialisation by Napp Pharmaceuticals Ltd)* should be amended to (Invokana, Napp Pharmaceuticals Ltd). Janssen-Cilag are the legal MA holder, but Napp are the sole and exclusive distributor and executor of all canagliflozin related activity in the UK, and as such Janssen-Cilag should not be referred to. We would strongly suggest that it would be appropriate for this section to specifically state that the canagliflozin / metformin fixed dose combination is not included within the scope of this assessment, nor the 300 mg single-entity formulation of canagliflozin. (Please see section 4 comment on remit)	Noted, this has been corrected. The scope does not currently include details on the formulation or doses. It is anticipated that this will be included in the company's submission. The committee will only be able to make recommendations within the licensed marketing authorisation.

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		It should be noted that the glomerular afferent arteriolar vasoconstriction hypothesis described in this section has not been empirically confirmed, and there are several other plausible hypotheses that could also account in whole or in part for the renoprotective effects demonstrated, e.g. reduction in renal hypoxia due to decreased requirement for active transport of sodium.[19]	
	Primary Care Diabetes Society	With the above caveats, the proposed TA is considered otherwise appropriate.	Thank you, your comments have been noted. No changes have been made.
	Association of British Clinical Diabetologists (ABCD), British Renal Society and The Renal Association UK	This is accurate	Thank you, your comments have been noted. No changes have been made.
Population	Kidney Care UK	Progression of CKD has been found to be more rapid in specific groups and it may be necessary to consider these groups separately. eg “Some ethnic groups, particularly Bangladeshi, appear to be more sensitive to the combined effects of proteinuria and hypertension than other ethnic groups. Clinicians need to be aware that younger people with diabetes (<55 years) with CKD are at twice the risk of rapid progression of CKD compared with those >65 years and thus need closer monitoring, management of risk factors and early specialist review to delay progression.” (Mathur R, Dreyer G, Yaqoob MM, et al Ethnic differences in the progression of chronic kidney disease and risk of death in a UK diabetic population: an observational cohort study	Thank you for your comment. Subgroup analyses may be reported but this will depend on the availability of data. The appraisal committee will consider the relevance of subgroups (if the data allows this) but will only be able to make recommendations within the licensed marketing authorisation. This may also be considered a potential equality issue and is

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		BMJOpen 2018;8:e020145. doi: 10.1136/bmjopen-2017-020145)	documented in the equalities impact assessment form for this appraisal. No changes have been made.
	Napp Pharmaceuticals Ltd	[redacted]	nk you for your comment. anticipated that a full anation of subgroup yses will be included in company submission. No nges have been made.
		Within this population there are no groups that should be considered separately. Prespecified subgroup analyses examined both the primary composite endpoint and the renal specific composite endpoint across three baseline eGFR ranges (Stages 2, 3a & 3b) and two baseline uACR ranges (≥ 100 mg/mmol vs <100 mg/mmol). However, no heterogeneity was demonstrated for either composite endpoint across all subgroups analysed.	
	Primary Care Diabetes Society	As detailed above, we feel the TA should include those with more advanced CKD and eGFR 30-60mls/min/1.73m2. The subgroup analysis might also suggest some differences in out comes by age and/or ethnic background, although it is not known whether or not these subgroups were sufficiently powered to demonstrate significant difference in outcomes.	Thank you for your comment. Subgroup analyses may be reported but this will depend on the availability of data. The appraisal committee will consider the relevance of subgroups (if the data allows this) but will only be able to make recommendations within the licensed marketing

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			authorisation. No changes have been made.
	Association of British Clinical Diabetologists (ABCD), British Renal Society and The Renal Association UK	Adults with chronic kidney disease and type 2 diabetes – this needs to be more clearly defined in relation to the CKD stage of those individuals who may benefit from this intervention (with or without multiple risk factors or established CVD)	Thank you for your comment. The population has been left broad in line with the clinical trial evidence. The appraisal committee will consider the clinical and cost-effectiveness evidence for canagliflozin but will only be able to make recommendations within the licensed marketing authorisation. No changes have been made.
Comparators	Napp Pharmaceuticals Ltd	Prior to the publication of the CREDENCE trial, no treatment specific to DKD (i.e. indicated for DKD but not for non-diabetic CKD) existed. Therefore, there is no specific pharmacological agent that would constitute an appropriate comparator. Published clinical guidelines and actual clinical practice instead address T2DM and CKD as distinct clinical phenomena, even when co-existing in a single patient. Established clinical practice in the UK for the treatment of T2DM is largely based on NG28, and for CKD is largely based on CG182 "Standard of Care" for disease-modifying DKD therapies in the UK therefore consists only of: • Maximally tolerated dose of a RAAS inhibitor[iii] (due to direct intra-renal haemodynamic effects)	Thank you for your comments. The scope includes 'established clinical management without canagliflozin' to capture all treatments currently used in clinical practice in the NHS in England including those in NG28 and CG182. No changes have been made.

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		• Control of systemic hypertension via standard antihypertensive therapies (if required in addition to RAAS inhibition), to a target blood pressure of 130/80 mmHg.[6] • Control of hyperglycaemia, as measured by HbA1c, to a personalised target. [6] Additional supportive therapies may include the following; however, these are symptomatic treatments and not disease modifying with respect to DKD: • Erythropoietic agents and oral / intravenous iron for CKD/DKD associated anaemia.[iv] • Phosphate binders, cholecalciferol, calcium supplementation or cinacalcet for mineral and bone disorder associated with renal insufficiency.[v] Lipid modifying treatment with statins or PCSK9 inhibitors to mitigate the increased cardiovascular risk associated with renal insufficiency.[vi]	
	Primary Care Diabetes Society	Currently, national guidance recommends the use of ACEi/ARB therapies in people with evidence of diabetic nephropathy. However, in the CREDENCE trial, the use of ACEi/ARB was one of the predetermined inclusion criteria and, therefore, canagliflozin was “add on” therapy.	Thank you for your comments. The scope includes ‘established clinical management without canagliflozin’ to capture all treatments currently used in clinical practice in the NHS in England including those in NG28 and CG182. No changes have been made.
	Association of British Clinical Diabetologists (ABCD), British	Agreed as described in the background comparison with treatment with the appropriate dose of inhibitors of the renin angiotensin system. (This is an additional rather than comparative proposed treatment)	Thank you for your comments. The scope includes ‘established clinical management without

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	Renal Society and The Renal Association UK		canagliflozin' to capture all treatments currently used in clinical practice in the NHS in England including those in NG28 and CG182. No changes have been made.
Outcomes	Kidney Care UK	• Could cardiovascular outcomes be included? • We recommend adding progression to renal replacement therapy (including in the cost effectiveness assessment) • We recommend that due consideration is given to potential side effects and how these are monitored, especially DKA	Thank you for your comments. The outcomes listed are examples and are not intended to be an exhaustive list. The following changes have been made to the outcomes section: • Incidence of kidney disease and renal mortality have been removed • Morbidity has been added and this includes disease progression and cardiovascular outcomes
	Napp Pharmaceuticals Ltd	No, at present several important health-related benefits of this technology in the specified population are not included in the list of outcomes in Appendix B. Specifically, the following two outcomes should be added to the assessment: • Composite outcome of cardiovascular death or hospitalisation for heart failure. (HR 0.69; 95% CI 0.57-0.83; P <0.001; absolute benefit 13.9 fewer events per 1000 patient-yrs. treatment)	Thank you for your comments. The outcomes listed are examples and are not intended to be an exhaustive list. The following changes have been made to the outcomes section:

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		• Composite outcome of cardiovascular death, non-fatal myocardial infarction or non-fatal stroke. (HR 0.80; 95% CI 0.56-0.95; P = 0.001; absolute benefit 10 fewer events per 1000 patient-yrs. treatment) Although these outcomes are not always considered to be directly causally related to CKD/DKD, increased cardiovascular mortality and morbidity have been shown to correlate very strongly with both decreased eGFR and raised albuminuria.[vii,viii] This is reflected in CG182 and other clinical guidelines, where a key component of CKD/DKD clinical practice is management of cardiovascular risk factors.[ix] This is also reflected in the CREDENCE trial outcomes, where absolute event rates for CV outcomes were comparable to, or higher than, event rates for renal outcomes in both intervention and comparator arms. An assessment of any technology for the treatment of DKD would therefore be fundamentally incomplete without consideration of cardiovascular outcomes. **Incidence of kidney disease** It is unclear what is intended by this statement, as the population examined by this TA will all have an established diagnosis of diabetic kidney disease. Napp suggest that the following specific kidney disease related outcomes should be considered: 1. Incidence of End-Stage Kidney Disease (ESKD). Within the CREDENCE trial this was defined as: a. Sustained eGFR < 15 ml/min/1.73m^2 b. Sustained requirement for renal dialysis c. Renal transplant Progression of DKD as measured by progressive loss of eGFR. Napp would suggest considering this outcome on a categorical basis (i.e.	• Incidence of kidney disease and renal mortality have been removed • Morbidity has been added and this includes disease progression and cardiovascular outcomes

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		transition between the defined stages) rather than on the basis of a continuous spectrum of eGFR values. This is because data exists to quantify healthcare costs associated with each categorical stage of eGFR reduction.[x] **Doubling of Serum Creatinine (DSCr)** DSCr was a component of the primary composite outcome in the CREDENCE trial and showed a large benefit of treatment to a high degree of statistical certainty. DSCr is a commonly used and well-accepted outcome measure and is thought to correlate closely with structural renal function decline (as it approximates a halving of the eGFR) as well as increased likelihood of progression to ESKD.[xi] DSCr has been used as a component of the primary renal composite endpoint in numerous significant nephrology trials. However, DSCr may also be influenced by several other factors not necessarily reflective of true GFR, is an arbitrary threshold, and cannot be quantified clinically or economically. Therefore, this outcome may be less suitable for inclusion in a health-economic analysis, and Napp instead suggest a categorical analysis of eGFR decline (as detailed above) would be the most appropriate method of analysing changes in serum creatinine. Progression of albuminuria Similarly to DSCr, uACR was examined in the CREDENCE trial and showed a large and statistically significant benefit in favour of the intervention.2 Severity of albuminuria is a well-established and powerful prognostic marker for the rate of future decline in eGFR, likelihood of ESKD, and major adverse cardiovascular events. Consideration of albuminuria may therefore be most relevant to consider as a biomarker for predicting future risk.	

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		Renal mortality Napp suggest that renal mortality would not be a useful outcome measure to examine, as there were very low rates of mortality due to renal causes in both the intervention and comparator arms in the CREDENCE trial, with no statistical difference observed.**Error! Bookmark not defined.** The majority of mortality events in patients with moderate-severe renal impairment typically are assigned as deaths due to cardiovascular causes, even though the proximate cause is likely of renal origin – see first outcomes section above. **HbA1c control** This is not a relevant outcome measure for this STA and should not be included. HbA1c is a surrogate marker for mean blood glucose, and as such has utility only when considering efficacy of technologies intended for glycaemic control. Canagliflozin was originally licensed for glycaemic control in T2DM, however when used for treating DKD the effect of canagliflozin is not mediated via glycaemic control, but rather by an independent mechanism acting directly on renal haemodynamics and/or other renal physiology.[xii] It is also well-established that SGLT2 inhibitors have significantly reduced or absent glycaemic effects in patients with moderate-severe renal impairment. The CREDENCE trial design also specifically allowed for glycaemic control interventions (other than SGLT2i) to be made at the sole discretion of the responsible physician.[xiii] This resulted in a closely matched mean HbA1c between the intervention and comparator groups, with a LS mean difference of only -0.25% over the course of the trial.**Error! Bookmark not defined.** Furthermore, a recent mediation analysis has provided some insight into the putative non-glycaemic mechanisms of renal benefit in this trial.[xiv]	

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		Diabetic ketoacidosis risk See **Adverse effects of treatment** below **Mortality** See separate responses above regarding renal mortality and cardiovascular mortality. Any-cause mortality was analysed in the CREDENCE trial, with a strong numerical trend in favour of the intervention.6 However this outcome did not reach statistical significance due to early termination of the trial. **Adverse effects of treatment** Yes, adverse events should be considered as relevant outcome measures in this analysis. Though not a prespecified analysis, overall AEs, renal-related AEs and serious AE rate were statistically significantly lower in the intervention arm (canagliflozin 100 mg + SoC) than the comparator arm (placebo + SoC) in the CREDENCE trial. Two adverse events of special interest would be particularly suitable for inclusion in the analysis. Both of these occurred with significantly increased frequency in the intervention group, have plausible biological mechanisms, and have been observed in a number of other studies:[xv,xvi] • Male genital mycotic infections: 28 events *vs* 3 events (HR 9.30; 95% CI 2.83-30.60) Diabetic ketoacidosis: 11 events *vs* 1 event. (HR 10.80; 95% CI 1.39-83.65) **Health-related quality of life.**	

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		Yes, HRQoL should be included as large and well-validated reductions in HRQoL are known to be associated with several of the outcomes discussed above.[9,10,11,12]	
	Primary Care Diabetes Society	The proposed outcomes measured for this TA are appropriate.	Thank you for your comments. The following changes have been made to the outcomes section: • Incidence of kidney disease and renal mortality have been removed • Morbidity has been added and this includes disease progression and cardiovascular outcomes
	Association of British Clinical Diabetologists (ABCD), British Renal Society and The Renal Association UK	There is also a need to include progression to and treatment for end-stage renal disease. Furthermore these drugs have significant benefit in relation to cardiovascular outcomes and proteinuric people with type 2 diabetes are at extremely high risk of adverse cardiovascular outcomes. It would be perverse not to include the assessment of the cardiovascular outcomes in those patients who would now be eligible for canagliflozin if the licence and guidance is changed.	Thank you for your comments. The following changes have been made to the outcomes section: • Incidence of kidney disease and renal mortality have been removed • Morbidity has been added and this includes disease progression and cardiovascular outcomes

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Economic analysis	Kidney Care UK	• The time horizon should include progression to renal replacement therapy as this is a significant cost • The economic analysis should consider the increased risk of depression amongst people with CKD – the impact on HRQoL and cost of treatment (Palmer S., Vecchio M., Craig J.C. Prevalence of depression in chronic kidney disease: systematic review and meta-analysis of observational studies. Kidney Int. 2013;84:179–191.)	Your comments have been noted. It is anticipated that the time horizon is sufficiently long to reflect all important differences in costs or outcomes between the technologies being compared (see section 5.15 to 5.17 of the NICE methods guide for more details). No changes have been made.
	Napp Pharmaceuticals Ltd	**The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year.** Napp support this approach. **The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared.** NICE's current reference case in the UK is a lifetime time horizon. Given the shorter life expectancy of the DKD population and increasing modelling uncertainty with increasing duration, [redacted] **Costs will be considered from an NHS and Personal Social Services perspective.** Napp support this approach, however given the multitude of potential social care cost implications of some of the proposed outcome	Your comments have been noted. No changes have been made.

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		measures (e.g. ESKD,[9,11] Stroke,[10] myocardial infarction[12]) any specific guidance NICE can provide on which costs should or should not be included in the economic model would be appreciated.	
	Primary Care Diabetes Society	The definition of the time horizon is sufficiently broad to give the reviewing committee scope to consider what it considers an appropriate time frame.	Comment noted. No changes have been made.
	Association of British Clinical Diabetologists (ABCD), British Renal Society and The Renal Association UK	The costs of end-stage renal failure management and cardiovascular intervention must be included here	Comment noted. It is anticipated that relevant costs are included in the economic model in line with the NICE methods guide. No changes have been made.
Equality and Diversity	Kidney Care UK	The scope should consider the difference in risk of rapid progression of CKD in different groups with protected characteristics, and consider sub-analysis of these groups. • Ethnicity: (see above) Some ethnic groups, particularly Bangladeshi, appear to be more sensitive to the combined effects of proteinuria and hypertension than other ethnic groups. • Age: Clinicians need to be aware that younger people with diabetes (<55 years) with CKD are at twice the risk of rapid progression of CKD compared with those >65 years and thus need closer monitoring, management of risk factors and early specialist review to delay progression.	Thank you for your comment. Potential equality issues have been included in the equalities impact assessment form for this appraisal. No changes have been made.

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	Napp Pharmaceuticals Ltd	Napp are not able to identify any specific issues relating to equality of access for this TA. It may be relevant to note that a subgroup analysis presented at the American Society of Nephrology Congress in November 2019 showed no heterogeneity of efficacy or safety across several racial and ethnic groups.[xvii]	Thank you for your comment. Potential equality issues have been included in the equalities impact assessment form for this appraisal. No changes have been made.
	Primary Care Diabetes Society	As detailed above, although the current marketing authorisation for canagliflozin specifies eGFR > 60mls/min/1.73m2, it seems possible that this may change in the future and, given the inclusion criteria of the CREDENCE trial and the published data suggesting potential benefits in those with eGFR 30-60mls/min/1.73m2, we would welcome a broader review of the evidence, including use of canagliflozin in those with eGFR in this range.	Thank you for your comment. Subgroup analyses may be reported but this will depend on the availability of data. The appraisal committee will consider the relevance of subgroups (if the data allows this) but will only be able to make recommendations within the licensed marketing authorisation. No changes have been made.
	Association of British Clinical Diabetologists (ABCD), British Renal Society and The Renal Association UK	CKD and type 2 diabetes are both more common in people with lower socio-economic status and in ethnic minorities. Efforts would therefore have to be made to ensure that treatment is made available to these groups.	Thank you for your comment. Potential equality issues have been included in the equalities impact assessment form for this appraisal. No changes have been made.
Other considerations	Napp Pharmaceuticals Ltd	Napp have no additional suggestions.	Noted. No changes have been made.

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	Association of British Clinical Diabetologists (ABCD), British Renal Society and The Renal Association UK	• As described above it would be wrong to separate the cardiovascular from the renal benefits • Most patients with CKD and type 2 diabetes are cared for in primary care and referred to secondary according criteria set out in the NICE guidance on the management of CKD. Referral criteria include a rapid decline in GFR (>15ml/min/year) and severe proteinuria, diagnosed by urine albumin to creatinine ratio >70mg/mmol). There is substantial variation in annual monitoring of these patients in primary care despite guidelines being in place https://www.nice.org.uk/guidance/ng28 • Annual urine testing was achieved in only 30% of people with type 2 diabetes in the National CKD audit. (2015/16) https://www.lshtm.ac.uk/research/centres-projects-groups/ckdaudit • The removal of ACR testing from QOF in 2014 is likely to have contributed to the lower number of patients having an annual screen for ACR. It is important that NICE address issues around the recording of albumin:creatinine measurements in primary care for people with diabetes. The removal of this measurement from the Quality Outcomes Framework means that there is a significant risk that these measurements will no longer be undertaken (or be undertaken at a reduced frequency) across the population of patients with diabetes. This could significantly reduce the identification of people who will benefit from the use of canagliflozin.	Thank you for your comments. These have been noted. Although NICE understand the importance of recording of albumin:creatinine measurements, technology appraisal committee recommendations will be limited to whether canagliflozin should be used in the NHS. No changes have been made
Innovation	Kidney Care UK	We do consider the treatment to be innovative and it has potential to make a significant and substantial impact on health-related benefits. It is the first treatment in 18 years with positive results for the treatment of CKD in people with diabetes (and observed benefits were obtained on a	Comment noted. During the development of the appraisal, the committee will consider the degree to which

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		background of renin–angiotensin system blockade, the only approved renoprotective medications in type 2 diabetes, a factor that highlights the clinical significance of the findings)	canagliflozin is an innovative technology when making its recommendations. No changes have been made.
	Napp Pharmaceuticals Ltd	Yes. As detailed above in various sections above: • There is significant and increasing unmet clinical need in DKD. • At present there are no specific pharmacotherapies available for the treatment of DKD. • There have not been any significant developments in approaches to preventing CKD progression since demonstration of RAAS blockade benefit in 2001. • Canagliflozin, when used in this indication, does not represent an alternative to any established treatment option – the outcomes demonstrated in the CREDENCE trial intervention arm were on top of those achievable with best current SoC, therefore canagliflozin does truly represent a significant development in the treatment of this condition. The anticipated licensed indication for canagliflozin for the treatment of DKD (in addition to current standard of care) provides an unprecedented opportunity to improve the treatment of DKD in the UK; with meaningful improvements in patient survival and QoL expected, alongside long-term cost savings from prevented dialysis and transplantation.	Comment noted. During the development of the appraisal, the committee will consider the degree to which canagliflozin is an innovative technology when making its recommendations. No changes have been made.
	Primary Care Diabetes Society	Yes, potentially so. Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy. Perkovic et al. N Engl J Med 2019; 380:2295-2306 DOI: 10.1056/NEJMoa1811744	Comment noted. During the development of the appraisal, the committee will consider the degree to which canagliflozin is an innovative

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			technology when making its recommendations. No changes have been made.
	Association of British Clinical Diabetologists (ABCD), British Renal Society and The Renal Association UK	• The data supporting the use of SGLT2 inhibitors in reducing poor renal outcomes in people with diabetes and kidney disease has been identified through large cardiovascular outcome trials undertaken on these class of agents. (EMPA-REG CANVAS and DECLARE TIMI 58) Whilst these trials were primarily directed at assessment of cardiovascular safety, these trials assessed renal variables. • In contrast, the Canagliflozin and Renal Endpoints in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) trial was designed as a primary renal outcome trial and showed the renoprotective effects of canagliflozin on 'hard' renal outcomes when used in addition to standard of care. • Furthermore, the hazard ratio reductions in CREDENCE was significantly greater than seen in the key trials with inhibitors of the renin angiotensin system and on a background of optimal standard of care.	Comment noted. During the development of the appraisal, the committee will consider the degree to which canagliflozin is an innovative technology when making its recommendations. No changes have been made.
Questions for consultation	Kidney Care UK	• We consider that canagliflozin would fit in the NICE CKD pathway after 'establishing cause'. If diabetes is considered to be the cause then treatment with canagliflozin should be considered. • Barriers to treatment: the major barrier to treatment is the current low rate of implementation of the NICE recommended kidney function tests (HQIP (2017) National Chronic Kidney Disease Audit, London.) • Can the population already have treatment with canagliflozin under TA315 and TA390? Both of those TAs have restrictions in	Thank you for your comments. These have been noted. No changes have been made

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		terms of eGFR, which would mean people with impaired kidney function are unlikely to be eligible for treatment with canagliflozin under those TAs. This technology appraisal would address access to canagliflozin for people with CKD and type 2 diabetes.	
	Napp Pharmaceuticals Ltd	**To help NICE prioritise topics for additional adoption support, do you consider that there will be any barriers to adoption of this technology into practice? If yes, please describe briefly.** Yes, the major barrier to adoption of this technology in clinical practice will be inconsistently measured / recorded urinary albumin: creatine ratio (uACR) testing. [redacted] Numerous clinical guidelines and standards recommend at least annual testing of both eGFR and uACR in all T2DM patients.[xviii,xix] However the UK National Diabetes Audit 2017-2018[xx] identifies that only 65.6% of T2DM patients received a uACR test in that audit year. Furthermore, this proportion has remained static or declined compared to all previous audit years, and is more than 20% less frequently achieved than the next lowest recommended care process (Foot surveillance; 86.1% achievement) At present uACR testing rates, approximately 1 in 3 patients that could potentially benefit from this technology will therefore remain unidentified and untreated. Whether or not the outcome of this proposed STA is positive, Napp would strongly encourage NICE to consider methods to increase the achievement of this recommended care process. – e.g.	Thank you for your comments. These have been noted. No changes have been made

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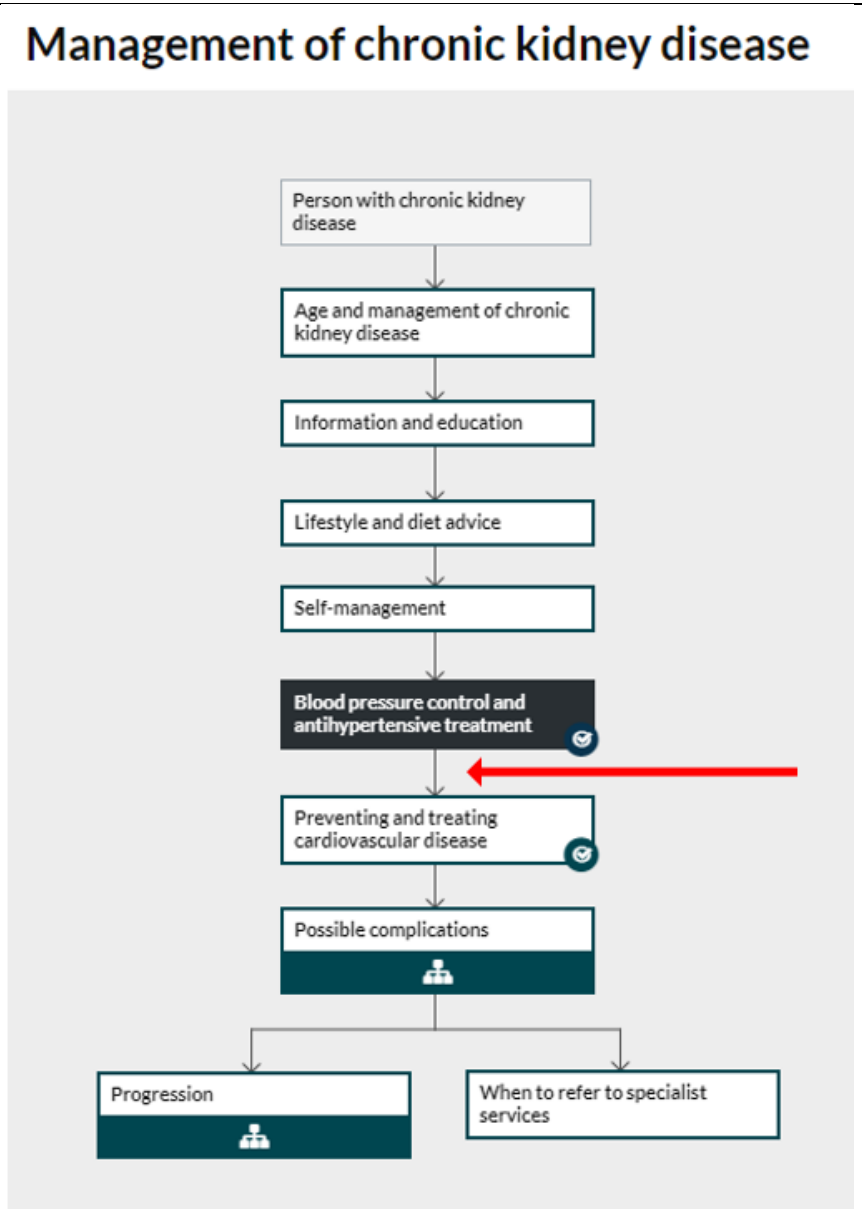
		reinstatement of uACR measurement rates as a Quality and Outcomes Framework indicator for primary care. Another potential barrier may be the current restrictions on use of canagliflozin in patients with reduced eGFR that are specified in STAs 315 and 390. If the current proposed TA is positive, NICE should consider amendment of these existing TAs to make it clear that patients with reduced eGFR should be considered in the context of the new TA. **Can the population defined in this scope already have treatment with canagliflozin based on recommendations in TA315 and TA390? If there are patients in this scope population who cannot currently have treatment with canagliflozin, please outline this population and how they can be identified in clinical practice.** Please see Napp's previous response to this question pasted as an appendix to this document. (Not reported here) **Where do you consider canagliflozin will fit into the existing NICE pathway, Chronic kidney disease?** Napp suggests that canagliflozin will fit into the existing pathway after the step currently titled *"Blood pressure control and antihypertensive treatment"*. This positioning aligns with the proposed new indication for canagliflozin in DKD as: "adjunct to standard of care". Napp are therefore of the opinion that the marketing authorisation provides a clear position for canagliflozin within the established pathway. However, it will also be important to make it clear within the guidance that any recommendation regarding canagliflozin only applies to people with both DKD and T2DM. Suggested pathway position is marked with red arrow below.	


Management of chronic kidney disease
Person with chronic kidney disease
Age and management of chronic kidney disease
Information and education
Lifestyle and diet advice
Self-management
Blood pressure control and antihypertensive treatment
Preventing and treating cardiovascular disease
Possible complications
Progression
When to refer to specialist services

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		Napp would also like to suggest NICE considers the potential position of canagliflozin within NG28 if a positive recommendation results from this STA, as well as the possibility of producing a standalone clinical guideline specifically for DKD.	
	Primary Care Diabetes Society	Different ethnic groups such as south Asians have worse outcomes in particular renal outcomes and cardiovascular disease. We would recommend consideration of ethnicity when making recommendations.	Thank you for your comment. Potential equality issues have been included in the equalities impact assessment form for this appraisal. No changes have been made.
	Association of British Clinical Diabetologists (ABCD), British Renal Society and The Renal Association UK	No comment	Noted. No changes have been made.
Additional comments on the draft scope	Kidney Care UK	Kidney Care UK believes it's vital that people are provided with lifestyle and diet advice so they can take action to reduce their risk of further kidney damage, and it is important that any NICE guidance resulting from this review recommends the provision of suitable advice.	Comment noted. The appraisal committee will consider the clinical and cost-effectiveness evidence when making its recommendations. No changes have been made.
	Napp Pharmaceuticals Ltd	No further comments	Noted. No changes have been made.

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	Association of British Clinical Diabetologists (ABCD), British Renal Society and The Renal Association UK	There is evidence of benefit in CREDENCE even when HbA1c levels are 6.5-7.5% suggesting even well controlled patients benefit. A practical consideration is the addition to or modification of other diabetes medication when the therapy is initiated. This would be particularly a consideration to avoid risk of hypoglycaemia without dose reduction of insulin and or sulphonylureas	Comment noted. The appraisal committee will consider the clinical and cost-effectiveness evidence when making its recommendations. No changes have been made.
Provisional stakeholder list of consultees and commentators	Napp Pharmaceuticals Ltd	The list appears comprehensive and broadly appropriate, however Napp suggests the following three amendments: 1. Addition of the Welsh Endocrine and Diabetes Society as a Commentator: http://www.weds-wales.co.uk/contact-us.htm 2. Addition of the "At the 4-Front" Diabetes Nursing leadership organisation as a Consultee.	Thank you for your comment. The Welsh Endocrine and Diabetes Society & At the 4-Front Diabetes Nursing leadership have been added to the stakeholder matrix.

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

[i] https://www.nice.org.uk/guidance/ng28
[ii] https://kdigo.org/wp-content/uploads/2017/02/KDIGO_2012_CKD_GL.pdf
[iii] https://www.kidney.org/sites/default/files/docs/diabetes-ckd-update-2012.pdf
[iv] https://kdigo.org/wp-content/uploads/2016/10/KDIGO-2012-Anemia-Guideline-English.pdf
[v] https://kdigo.org/wp-content/uploads/2017/02/2017-KDIGO-CKD-MBD-GL-Update.pdf
[vi] https://kdigo.org/wp-content/uploads/2017/02/KDIGO-2013-Lipids-Guideline-English.pdf
[vii] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3559486/
[viii] https://www.sciencedirect.com/science/article/abs/pii/S0085253817300959?via%3Dihub
[ix] https://care.diabetesjournals.org/content/39/Supplement_1/S60.long
[x] https://www.lshtm.ac.uk/media/9941
[xi] https://www.karger.com/Article/Fulltext/327614
[xii] https://www.asn-online.org/education/kidneyweek/2019/program-abstract.aspx?controlId=3237497

[xiii] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5804835/
[xiv] https://www.asn-online.org/education/kidneyweek/2019/program-abstract.aspx?controlId=3235578
[xv] https://bpspubs.onlinelibrary.wiley.com/doi/pdf/10.1111/bcp.13782
[xvi] https://www.gov.uk/drug-safety-update/sglt2-inhibitors-updated-advice-on-the-risk-of-diabetic-ketoacidosis
[xvii] https://www.asn-online.org/education/kidneyweek/2019/program-abstract.aspx?controlId=3235411
[xviii] https://www.nhs.uk/conditions/acr-test/
[xix] http://www.pulsetoday.co.uk/gps-urged-to-do-acr-testing-for-patients-at-risk-of-kidney-disease/20033661.article
[xx] https://files.digital.nhs.uk/88/F1E544/National%20Diabetes%20Audit%202017-18%20Full%20Report%201%2C%20Care%20Processes%20and%20Treatment%20Targets.pdf