Single Technology Appraisal

Dapagliflozin for treating chronic heart failure with preserved or mildly reduced ejection fraction [ID1648]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Dapagliflozin for treating chronic heart failure with preserved or mildly reduced ejection fraction [ID1648]

Contents:

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1. **Response to consultee, commentator and public comments on the Draft Guidance**

2. **Comments on the Draft Guidance from** AstraZeneca**:**
   a. Main response
   b. Response to EAG request for data

3. **Consultee and commentator comments on the Draft Guidance Document** from:
   a. Pumping Marvellous Foundation
   b. British Cardiovascular Society (BCS) – *endorsed by Royal College of Physicians*
   c. British Society for Heart Failure (BSHF)
   d. Primary Care Cardiovascular Society (PCCS)
   e. UK Clinical Pharmacy Association (UKCPA)

4. **Comments on the Draft Guidance Document from experts:**
   a. Dr Lisa Anderson, Consultant Cardiologist and Chair Elect British Society for Heart Failure – clinical expert, nominated by British Society for Heart Failure

5. **Comments on the Draft Guidance Document received through the NICE website**

6. **External Academic Group critique of company response to the DG**

7. **External Academic Group updated base case incorporating committee preferences**

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

Dapagliflozin for treating chronic heart failure with preserved or mildly reduced ejection fraction

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	Consultee	British Cardiovascular Society	Section 3.3 - "Symptomatic treatments for comorbidities are also offered to people with heart failure with preserved ejection fraction, including angiotensin converting enzyme inhibitors, angiotensin II receptor blockers, beta blockers or mineralocorticoid receptor antagonists." This statement appears incorrect, in that these medications are used to treat comorbidities which co-exist in patients with HFpEF/HFmrEF (such as hypertension) on an indication by indication basis. Symptoms from these co-morbidities may improve but this is not the main aim. Prognosis or prevention of hospitalisation are some examples depending on the condition/co-morbidity being treated.	Thank you for your comment. The treatments referenced highlight the possible treatments which may be given to people with heart failure with preserved or mildly reduced ejection fraction.
2	Consultee	British Cardiovascular Society	Section 3.7 – "This pooled analysis showed that dapagliflozin significantly reduced cardiovascular mortality compared with placebo (hazard ratio 0.86, 95% confidence interval 0.76 to 0.96; Jhund et al. [2022]). In this pooled analysis there was no evidence that the effect of dapagliflozin differed by level of ejection fraction. The committee noted that evidence from the pooled analysis was not incorporated into the economic model." If there is evidence, independent of ejection fraction, demonstrating reduced cardiovascular mortality, was this used in modelling by the EAG? If not, please could this be explained.	Thank you for your comment. The EAG conducted scenario analysis examining the impact of different treatment effects on cardiovascular and all-cause mortality. See section 3.11 of the FDG for further details.
3	Consultee	British Cardiovascular Society	Section 3.8 - The group of patients with previously reduced ejection fraction that is now >40% were specifically considered in the DELIVER trial and appeared to have significant benefit, over and above the benefit shown in the whole group. A specific recommendation for this group could have been given and would avoid them falling between the two different NICE SGLT2i appraisals (HFrEF & HFpEF). The current statement in the explanatory text does not make the position clear enough. Currently there are patients with HFrEF who have their LVEF re-evaluated following initiation of first line medications and the EF has improved to >40 prior to commencing a SGLT2i. Current guidance would exclude this group from being prescribed a SGLT2i.	Thank you for your comment. Dapagliflozin has been recommended by the committee for people with heart failure with preserved or mildly reduced ejection fraction.
4	Consultee	British Cardiovascular Society	Symptoms and quality of life are valid targets for treatment, particularly in a largely elderly group of patients with multiple co-morbidities. It is not clear to BCS that the economic modelling adequately represents this benefit from a patient perspective, particularly given the lack of other therapies.	Thank you for your comment. Symptoms and quality of life are captured within the economic modelling calculations which use

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				quality-adjusted life years (QALYs). Please see section 3.16 of the FDG for more details.
5	Consultee	British Cardiovascular Society	Section 3.17 – The opinion on disutility attributed to a patient following a heart failure hospitalisation clearly varied across the discussion. BCS would prefer that a full evidence search was completed to inform this input more accurately and then used across both SGLT2i appraisals. Disutility should probably not solely apply after an index hospitalisation. There is also the period of deterioration prior to the hospitalisation which may be of variable length and severity.	Thank you for your comment. The committee considered all the evidence submitted, including from both clinical experts and the literature.
6	Consultee	British Cardiovascular Society	Section 3.21 – "The EAG noted that because of fewer treatments being available for this group (see section 3.3), approximately 6 GP or other primary care visits would be expected per year." BCS does not consider the lack of specific treatments for HFpEF to mean that healthcare contacts will be fewer. The opposite could equally be true. An evidence based approach would be preferable.	Thank you for your comment. The committee considered all the evidence submitted, including from both clinical experts and the literature.
7	Consultee	British Cardiovascular Society	Section 3.26 – "The committee considered that there was uncertainty regarding whether it was appropriate to use non-elective inpatient costs taken from NHS reference costs 2019/2020 and inflated to the 2020/2021 cost year, or from NHS reference costs 2020/21, because of the unknown impact of the COVID-19 pandemic (see section 3.18)." BCS considers it unfortunate that it is difficult to agree the correct NHS reference cost and concerned regarding the subsequent impact this may have had on the decision.	Thank you for your comment. The EAG provided further data after consultation. The committee concluded it was most appropriate to use NHS reference costs 2019/2020 and inflated to the 2020/2021 cost year. Section 3.18 of the FDG has been updated to reflect this.
8	Consultee	British Cardiovascular Society	Section 3.27 – "The lower bound of the threshold (£20,000 to £30,000 per QALY gained) was preferred by the committee given the large impact of the uncertainties relating to survival estimates on the ICER." BCS is concerned that the decision on which willingness-to-pay threshold to use is subjective and not fully explained. It would be preferable, if possible, to aim to resolve some of the uncertainty in the modelling through further evidence appraisal and expert discussion and fully explain why, in this case, a higher threshold is not thought appropriate.	Thank you for your comment. Above a most plausible ICER of £20,000/QALY, judgments about the acceptability of the technology as an effective use of NHS resources are more likely to make reference to explicit factors

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				including the degree of uncertainty
9	Consultee	British Cardiovascular Society	Section 3.30- "the cost-effectiveness estimates for dapagliflozin are likely higher than what NICE considers a cost-effective use of NHS resources" BCS would prefer a more definitive statement that communicates less uncertainty around the decision. Ideally a statement that dapagliflozin is or is not cost effective. If there is inadequate evidence to make a decision then this could also be described.	Thank you for your comment. Dapagliflozin has been recommended by the committee for people with preserved or mildly reduced ejection fraction.
10	Consultee	British Society for Heart Failure	**Section 3.3 Treatment options** - We are concerned that this recommendation may imply that Frusemide and medications used to treat co-morbidities in HFpEF, offer treatment options that can act as comparators to Dapagliflozin for the treatment of HFpEF. Diuretics are used for the treatment of fluid overload in any type of heart failure however they are not indicated in the absence of fluid overload as the are not disease modifying treatments (i.e. Have not been shown to improve outcomes in patients with heart failure). The comorbidities that accompany HFpEF (hypertension, diabetes, chronic kidney disease) do not usually cause heart failure symptoms and hence treatment for comorbidities does not necessarily amerliorate symptoms in HFpEF either. We feel that it is important to acknowledge that there is simply no other disease modifying therapy available for HFpEF and SGLT2i currently represent the 1st treatment option that has become available to alleviate symptoms as well as prevent adverse outcomes, for a condition affecting nearly half a million people in the UK.	Thank you for your comment. Section 3.2 of the FDG notes there are no disease-modifying treatments for this group. Dapagliflozin was compared to established clinical management without dapagliflozin. The company defined standard care in their model as loop diuretics (furosemide and bumetanide). The committee agreed this was appropriate to use as a comparator. Please see section 3.4 of the FDG for further detail.
11	Consultee	British Society for Heart Failure	**Section 3.4 Comparators**– concerns as above that diuretics and treatment of comorbidities are not appropriate comparators for SGLT2i	Thank you for your comment. Section 3.2 of the FDG notes there are no disease-modifying treatments for this group. Dapagliflozin was compared to established clinical management without dapagliflozin. The company defined standard care in their model as loop diuretics (furosemide and bumetanide). The committee agreed this

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				was appropriate to use as a comparator. Please see section 3.4 of the FDG for further detail.
12	Consultee	British Society for Heart Failure	**Section 3.5 Data sources and generalisability** This section seems to imply that the trial population in DELIVER was much younger than that seen in clinical practice. This is inaccurate as >40% of patients in DELIVER were ≥75 years, 77% were ≥65 yrs and the recruited population represented a broad spectrum of age groups (Peikert A, et al. Circ Heart Fail. 2022 Oct;15(10):e010080). Among 6263 randomized patients (aged 40–99 years, mean age 71.7±9.6 years which was older than many of the previous HF trials), 338 (5.4%) were <55 years, 1007 (16.1%) were 55–64 years, 2326 (37.1%) were 65 to 74 years, and 2592 (41.4%) were ≥75 years.Older patients in DELIVER had the highest LVEF with more patients whose LVEF ≥60%. The benefits of Dapgliflozin on reduction of primary composite outcome measure and improvement of symptoms, were irrespective of age. DELIVER not only randomised older patients but also a significant number of patents with HFpEF and frailty (≈63%), according to a pre-specified analysis (Butt JH et al. Ann Intern Med. 2022 Jun;175(6):820-830.) The beneficial outcomes were seen irrespective of degree of frailty but more importantly patients with the greatest frailty experienced the most improvement in symptoms, physical function, and quality of life	Thank you for your comment. The committee concluded that the results from DELIVER were broadly generalisable to NHS clinical practice. Please see section 3.5 of the FDG.
13	Consultee	British Society for Heart Failure	**Section 3.7**. **Impact of treatment on cardiovascular and all-cause mortality** The pooled analysis by Jhund et al (Nature Medicine 2022; volume 28, pages 1956–1964) also showed that Dapagliflozin reduced all-cause mortality by 10% (HR 0.90 (95% CI 0.82–0.99); P = 0.03) irrespective of ejection fraction. Similarly, another pre-specified analysis of the effect of Dapagliflozin on cause-specific mortality showed significant reductions in cardiovascular mortality irrespective of ejection fraction (attributable both due to reductions in HF death and sudden death - Desai AS, et al. JAMA Cardiol. 2022;7(12):1227–1234) A meta-analysis of 12,251 participants from DELIVER and EMPEROR-Preserved (Vaduganathan M, et al. Lancet 2022 Sep 3;400(10354):757-767), demonstrated significant reductions in the composite of cardiovascular death or first hospitalisation for heart failure (hazard ratio 0·80 [95% CI 0·73-0·87]) with consistent reductions in both components: cardiovascular death (0·88 [0·77-1·00]) and first hospitalisation for heart failure (0·74 [0·67-0·83]). As DELIVER was not powered to detect a reduction in cardiovascular or all-cause mortality, findings from the pooled pre-specified analyses as well as meta-analyses provide a more meaningful statistical estimate on cardiovascular and all-cause mortality benefit irrespective of ejection fraction. It is also important to note that in contrast to HFrEF, patients with HFpEF and HFmrEF, experience a greater proportion of non-cardiovascular mortality (mainly due to greater multimorbidity burden -Vaduganathan M et al. J Am Coll Cardiol. 2017;69(5):556-569). For a condition such as HFpEF which is associated with a constellation of comorbidities and which has not had such benefits noted from other therapies, this finding is important and cannot simply be glossed over.	Thank you for your comment. Further evidence provided around the mortality benefit of dapagliflozin was considered in the second committee meeting. Section 3.11 of the FDG has been updated to reflect the committee's preference
14	Consultee	British Society for Heart Failure	**Section 3.8** Amongst the DELIVER population of patients, a minority (18%) had HF with improved EF (HFimpEF). In a pre-specified analysis (Vardeny et al Nature Medicine 2022, volume 28, pages 2504–2511) Dapagliflozin reduced the primary composite end point compared to placebo in participants with HFimpEF (HR = 0.74, 95% CI = 0.56–0.97) to a similar extent as patients with LVEF consistently over 40% (HR = 0.84, 95% CI 0.73–0.95; interaction P = 0.43). The benefits were similar and irrespective of age age ≥75 versus <75 years.. It is also important to note that the event rate (worsening HF, cardiovascular or all-cause death) was similar in the HFimpEF cohort and LVEF consistently>40% cohort indicating comparable risk profiles. There was also similar	Thank you for your comment. The committee considered all evidence that was submitted.

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			symptom benefit in the 2 groups (although those with HFimpEF were less symptomatic at baseline). These benefits are significant as this unique cohort of patients with HFimpEF has not been studied previously, however it is important to emphasise that inclusion of this cohort in DELIVER, does not accentuate the benefits seen in those with LVEF consistently >40%.	
15	Consultee	British Society for Heart Failure	**Quality of life** People with HFpEF suffer from poor quality of life, significant burden of symptoms and physical limitation and improving symptomatic status is an important goal of heart failure guidelines. Results from the DELIVER Trial in its pre-specified sub-study (Kosiborod et al. JACC Volume 81, Issue 5, 7 February 2023, Pages 460-473), through evaluation of KCCQ-TSS, Physical Limitations (PLS), Clinical Summary (CSS), and Overall Summary (OSS) domains, show that Dapagliflozin use in HFpEF leads to an early (within 1 month) and sustained, significant improvement in symptoms and health status. We are concerned about the rationale for questioning KCCQ as a valid questionnaire to assess quality of life, when there is a weath of evidence that it is a robust measure in all types of HF (G-CHF Study. Circulation. 2021;143:2129–2142, Spertus et al. JACC 2020, Joseph S et al. Circ Heart Fail. 2013 Nov;6(6):1139-46, Sepehrvand N, J Am Heart Assoc. 2020;9(17):e017278.) to detect meaningful change in health status and also has a better prognostic value in comparison to NYHA Class which is a more subjective and non-patient-centric score (Greene et al JAMA 2021). Our Pumping Marvellous "Living with Heart Failure" patient survey responses indicate that most important outcome for patients is to improve day-to-day quality of life (78.5% of patients), followed by increasing life expectancy (72.5% of patients), http://pumpingmarvellous.org/wp-content/uploads/2018/02/Pumping-Marvellous-Living-With-Heart-Failure-Infographic.pdf The importance of quality of life for a person living well with heart failure is emphasised by patients, carers and clinicians surveyed in the Pumping Marvellous "Living Well with Heart Failure "report https://pumpingmarvellous.org/wp-content/uploads/2022/04/Living-well-with-heart-failure-report-FINAL.pdf Similarly we are also concerned that the symptomatic benefit of Dapagliflozin in DELIVER is seemingly trivialised again due to the factor that the KCCQ use as a predictor of cause and cardiovascular mortality, has been questioned. SGLT2i are the 1st in class of therapies that have shown symptomatic benefit in people with HFpEF (despite associated multimorbidity, frailty).	Thank you for your comment. The committee considered all evidence that was submitted. Symptoms and quality of life are captured within the economic modelling calculations which use quality-adjusted life years (QALYs). Please see section 3.16 of the FDG for more details.
16	Consultee	British Society for Heart Failure	**Section 3.10 Health state transition** The modelling approach for health state transition is similar to that approved for NICE TA 679. As also described below in Section 3.17, it is our opinion that currently there is no fool-proof modelling approach available to account for the transient and time-bound nature of HRQoL assessment.	Thank you for your comment. Comment noted.
17	Consultee	British Society for Heart Failure	**Section 3.11 Modelling of treatment effect on cardiovascular and all-cause mortality** Points made in Section 3.7 are also relevant here. Based on the totality of evidence outlined above, we are concerned that impact of the significant reduction in cardiovascular mortality in particular due to Dapagliflozin use in people with HF and LVEF>40% (and in particular HFmrEF as opposed to HFpEF), is being excluded by the committee. This is all the more relevant due to the inherent limitations of both sensitivity and scenario analyses being used to compute incremental cost-effectiveness ratios.	Thank you for your comment. Comment noted.
18	Consultee	British Society for Heart Failure	**Section 3.13 Ability of the model to replicate observed all-cause and cardiovascular survival outcomes** We find it confusing that when time-updated model covariate and a treatment effect coefficient were used in NICE TA for Dapagliflozin and Empagliflozin in HFrEF TA679 [TA773], yet the committee did not consider this a	Thank you for your comment. The committee considered

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			standard modelling approach for HFpEF, despite the totality of evidence indicating that heart failure is a condition that represents a continuum and the beneficial effects of SGLT2i are seen across the range of ejection fraction.	the validity of the economic model in its decision making. Please see updates to section 3.13 in the FDG.
19	Consultee	British Society for Heart Failure	**Section 3.14 Modelling of treatment effect on HF events** We are concerned by the EAG statement "DELIVER data did not convincingly support a benefit of dapagliflozin in reducing urgent hospitalisation for heart failure" and on this basis the exclusion of dapagliflozin treatment effect on urgent hospitalisation for heart failure in its base case. DELIVER and other SGLT2i trials have shown a significant reduction in HF hospitalisation.	Thank you for your comment. Urgent hospitalisations for heart failure were considered separately to other hospitalisations for heart failure. Please see section 3.14 of the FDG which has been updated with further information after the second committee meeting.
20	Consultee	British Society for Heart Failure	**Section 3.17 Duration of impact of heart failure events on quality of life** We are concerned that the impact of HF hospitalisation has not been adequately represented both in terms of the impact upon patients nor upon healthcare resources. HF hospitalisation represents a crucial inflection point in the trajectory of a patient as it is associated with 10% in-hospital mortality and 15% 30-day mortality as well as a 25% 30-day readmission rate and 50% readmission rate over 6 months. There are recognised limitations of applying disutlity due to HF hospitalisation to economic models, due to the variation in timing of disutility assessment, time-bound nature of estimation of disutility at a specific time followed by linear extrapolation to longer time periods and impact of recurrent hospitalisations (a frequent event in HFpEF), nature of hospitalisation (HF versus other causes due to multimorbidity and the impact of individual patient characteristics upon disutility (Di Tanna, G.L.,et al. PharmacoEconomics 39, 211–229 (2021). However previous studies have indicated that a HF related hospitalisation reflects a disutility period upto 12 months. We feel this is a more realistic estimate of the impact of HF hospitalisation on HRQoL due to additional effects of falls, delirum, muscle wasting, hospital acquired infections and effect on nutrion. This is particularly relevant for patients with HFpEF who are frequently older than those with HFrEF; HFpEF is also associated withgreater multimorbdity as well as frailty.	Thank you for your comment. The committee considered all the evidence submitted, including from both clinical experts and the literature.
21	Consultee	British Society for Heart Failure	**Section 3.21 GP visits** We are concerned that there appears to be an underestimate of the healthcare resources by people with HFpEF in primary care. Evidence indicates that HFpEF is under diagnosed and less recognised in primary care as symptoms and signs may be mis-attributed to obesity, ageing, frailty etc *Hossain et al https://doi.org/10.1177/1742395320983887). In our opinion 6 annual GP visits is therefore an underestimate, as these patients also frequently contact urgent care centres or community heart failure teams.	Thank you for your comment. The committee considered all the evidence submitted, including from both clinical experts and the literature.

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22	Consultee	British Society for Heart Failure	**Section 3.26 Committee preferred assumptions** We express concerns regarding some of the assumptions as follows: 1. Hospitalisation disutility of 6 months is an underestimate and disutlity of 12 months is more accurate as per explanation above in Section 3.17 2. GP visits of 6/year is a likely underestimate 3. Removal of treatment effect of dapagliflozin on cardiovascular and all-cause deaths (see section 3.11) or on urgent heart failure visit events	Thank you for your comment. Comment noted.
23	Consultee	British Society for Heart Failure	We are concerned that the ICER cut off of £20,000 is being used despite a threshold of £30,000 having been used previously for other therapies and though outcomes of HFpEF comparable/worse than some of the cancers, there does not appear to be the same consistency in application of criteria for recommendations BSH would like to alert the committee to the fact that not recommending empagliflozin for this indication will be a major disadvantage to a large number of patients in the UK with HFmrEF and HFpEF who have a high symptom burden and experience frequent and recurrent hospitalisation and currently have very limited treatment options. The SGLT2 inhibitors dapagliflozin and empagliflozin are the first drugs shown to improve symptoms and reduce heart failure hospitalisation in this population. [redacted]	Thank you for your comment. Above a most plausible ICER of £20,000/QALY, judgments about the acceptability of the technology as an effective use of NHS resources are more likely to make reference to explicit factors including the degree of uncertainty surrounding the ICERs,
24	Company	AstraZeneca	**CVM and ACM extrapolations should consider both the treatment effect of dapagliflozin and the impact of KCCQ-TSS quartile on mortality, incorporating the data from the pivotal DELIVER trial. It is inappropriate to arbitrarily assume equivalence between dapagliflozin and placebo with respect to CVM or ACM.** The extrapolation of the observed CVM and ACM data for dapagliflozin and placebo from the DELIVER trial represents the most robust methodology for the base case economic analysis and is in line with NICE's own methodology. However, upon request from the Committee, the Company has conducted two additional scenario analyses for this response: • Scenario 1: Removal of the dapagliflozin treatment effect as a candidate variable from the regression models used to generate CVM and ACM extrapolations, thereby removing any direct effect of dapagliflozin on CVM and ACM versus placebo; • Scenario 2: Removal of both the dapagliflozin treatment effect, and KCCQ-TSS quartile as candidate variables from the regression models used to generate CVM and ACM extrapolations, thereby removing any direct or indirect effect of dapagliflozin on CVM and ACM versus placebo. Full methodological details of these scenario analyses are provided in Appendix 2. However, the Company does not believe that these scenarios are valid for decision-making, for the reasons detailed below. **The DELIVER trial was not powered to detect statistically significant differences for dapagliflozin versus placebo with respect to CVM or ACM.** As previously detailed in the Company's response to Clarification Questions B14–B16, the published literature extensively highlights the limitations associated with p-values and the importance of interpreting them correctly.[1, 2] In this case, non-significant p-values do not mean that dapagliflozin has no impact on CVM or ACM versus	Thank you for your comment. Further evidence provided around the mortality benefit of dapagliflozin was considered in the second committee meeting. Section 3.11 of the FDG has been updated to reflect the committee's preference.

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			placebo. An alternative conclusion is [redacted]. The statistical analyses of the DELIVER trial were planned to ensure sufficient statistical power for hypothesis testing of the primary endpoint, which was a composite endpoint of CV death, HHF or UHFV.[3] [redacted] in the occurrence of CVM or ACM as standalone endpoints.[3] This conclusion is supported by the forest plot presented in Figure 1 below, which demonstrates that all of the components of the primary composite endpoint [redacted] to the statistically significant treatment effect of dapagliflozin for the primary composite endpoint observed in DELIVER. These data do not support a conclusion that dapagliflozin would not reduce CVM compared to placebo.[4] **Figure 1: Forest plot of the primary composite endpoint (CV mortality and HF events) and the individual components in DELIVER[a]**  [redacted] **Abbreviations**: CI: confidence interval; CV: cardiovascular; Dapa: dapagliflozin; FAS: full analysis set; HF: heart failure; HHF: hospitalisation for heart failure; HR: hazard ratio; N: number of patients in treatment group; T2DM: type 2 diabetes mellitus; UHFV: urgent heart failure visit. **Source:** DELIVER CSR.[4]	

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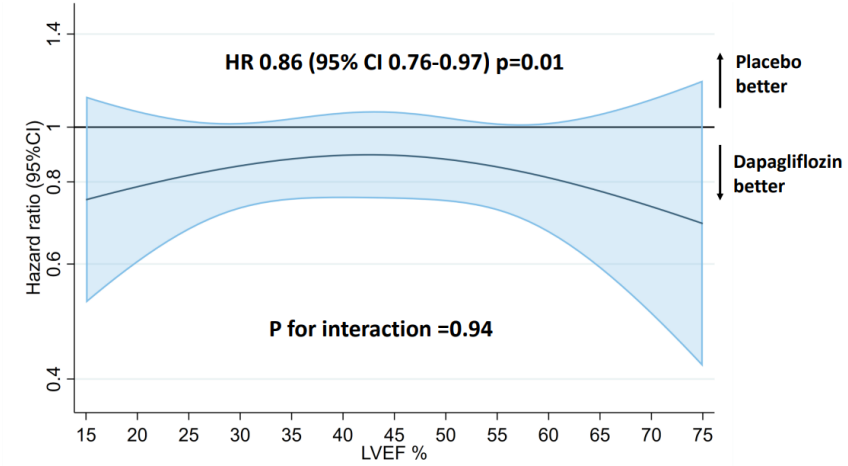
			Pooled analyses demonstrated that dapagliflozin statistically significantly reduced CVM and ACM versus placebo across the spectrum of patients with HF, with no evidence of effect modification by LVEF. A pre-specified pooled analysis of the individual patient-level data from both the DAPA-HF and DELIVER trials, published in *Nature Medicine,* was specifically designed to be powered to detect a difference in the primary endpoint of CVM.[5] Across this pooled cohort, dapagliflozin was associated with statistically significant reductions in both CVM (HR: 0.86, 95% CI: 0.76, 0.97) and ACM (HR: 0.90, 95% CI: 0.82, 0.99) when compared to placebo. In both cases, across this pooled analysis, there was no evidence of effect modification by LVEF when examined as either a categorial or continuous variable (p-value for interaction: 0.63 and 0.94 for CVM and 0.79 and 0.58 for ACM, respectively). This is also aligned with the Summary of Product characteristics (SmPC) for dapagliflozin, where the Medicines and Healthcare products Regulatory Agency (MHRA) noted "In a pre-specified patient level pooled analysis of the DAPA-HF and DELIVER studies, dapagliflozin compared with placebo reduced the risk of cardiovascular death. Both studies contributed to the effect".[6] The consistent effect of dapagliflozin versus placebo, irrespective of LVEF, is highlighted in Figure 2 and Figure 3 below. **Figure 2: Effect of dapagliflozin on CVM across the range of LVEF based on the pooled DAPA-HF and DELIVER dataset**  **Footnotes**: The horizontal blue line shows the continuous HR across the range of LVEF and the shaded area around this line represents the 95% CI from Cox's model. The overall effect of treatment in the pooled population is shown as an HR (95% CI) with the two-sided P value from Cox's model for Wald's test of interaction between treatment and LVEF. No adjustment for multiple comparisons was made. Restricted cubic spline and interaction P value derived from LWYY model for total HF hospitalisation. **Abbreviations**: ACM: all-cause mortality; CI: confidence interval; CV: cardiovascular; CVM: cardiovascular mortality; HF: heart failure; HR: hazard ratio; LVEF: left ventricular ejection fraction; LWYV: Lin-Wei-Yang-Ying model. **Source:** Jhund et al. (2022).[5, 7]	

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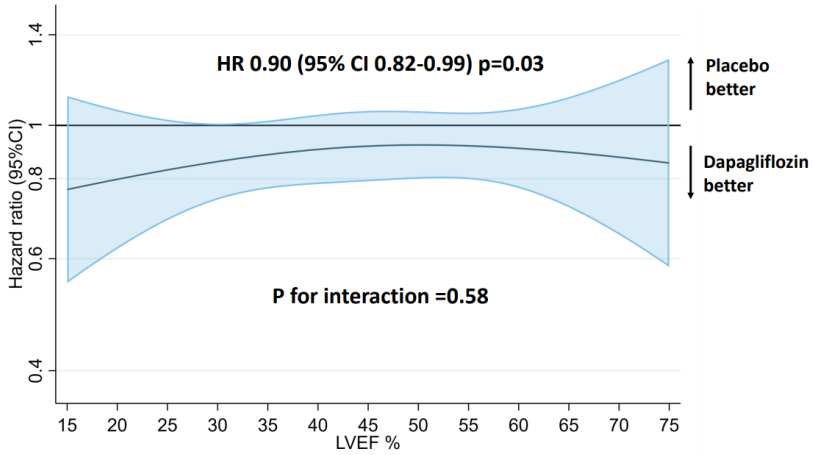
			Figure 3: Effect of dapagliflozin on ACM across the range of LVEF based on the pooled DAPA-HF and DELIVER dataset  **Footnotes**: The horizontal blue line shows the continuous HR across the range of LVEF and the shaded area around this line represents the 95% CI from Cox's model. The overall effect of treatment in the pooled population is shown as an HR (95% CI) with the two-sided P value from Cox's model for Wald's test of interaction between treatment and LVEF. No adjustment for multiple comparisons was made. Restricted cubic spline and interaction P value derived from LWYY model for total HF hospitalisation. **Abbreviations**: ACM: all-cause mortality; CI: confidence interval; CV: cardiovascular; CVM: cardiovascular mortality; HF: heart failure; HR: hazard ratio; LVEF: left ventricular ejection fraction; LWYV: Lin-Wei-Yang-Ying model. **Source:** Jhund et al. (2022).[5, 7] **Statistically significant and clinically meaningful reductions in HHF and improvements in mean KCCQ score for dapagliflozin versus placebo provide a biologically plausible mechanism by which dapagliflozin may reduce CVM and ACM versus placebo.** As part of this appraisal, clinical experts stated that it was plausible that dapagliflozin could reduce CVM in the medium to long-term by reducing HHF in the short to medium term. The experts highlighted that HHF is associated with a substantial quality of life burden and risk of infection and proposed that reducing HHF may be associated with a reduction in the overall decline in heart function and quality of life that people with chronic HF typically experience over time. In addition, the Committee acknowledged that it is plausible that dapagliflozin may directly impact ACM and CVM versus placebo in patients with HF and an LVEF >40%. Furthermore, the DELIVER trial demonstrated that dapagliflozin provided improved KCCQ-TSS, Physical Limitation Score (PLS), Clinical Summary Score (CSS), and Overall Summary Score (OSS) as early as 1 month following treatment initiation, with benefits sustained at 8 months.[8] Significantly fewer patients treated with dapagliflozin experienced clinically meaningful deterioration versus placebo, and more patients receiving dapagliflozin experienced clinically meaningful improvements in symptoms than those receiving placebo. Finally, the benefits of dapagliflozin on symptomatic improvement at 8 months after randomisation were generally	

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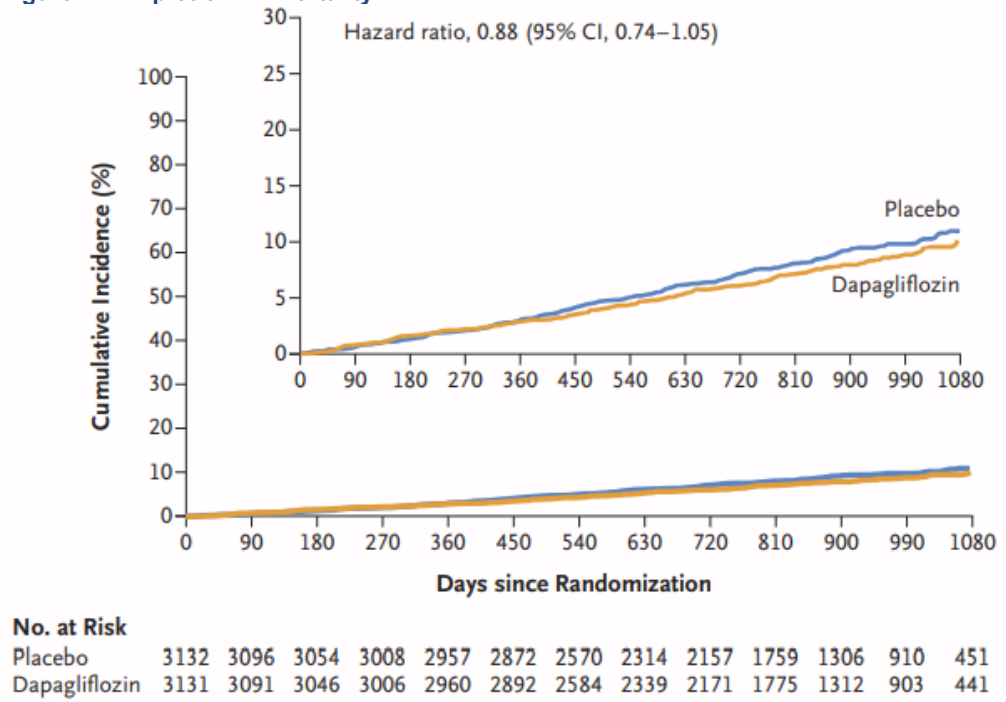
			consistent across key demographic and clinical subgroups, including baseline LVEF.[8] There is extensive evidence in the published literature which highlights the relationship between KCCQ score and mortality; for example in a study of over 23,000 patients, Johansson *et al.* (2021) concluded that health-related quality of life, measured using the KCCQ questionnaire, was a "strong and independent predictor of all-cause death" in HF.[9] In a pre-specified analysis of the DELIVER trial, patients with a lower baseline KCCQ-TSS were found to have a higher likelihood of being previously hospitalised for HF. Further, patients with lower baseline KCCQ-TSS experienced higher rates of CV death or worsening HF (7.8, 5.6, and 4.8 per 100 patient-years in patients across KCCQ-TSS terciles of <63, 63–84 and >84, respectively; p<0.001).[8] There is, therefore, compelling evidence and rationale to conclude that given a sufficient number of events and follow-up, a statistically significant difference would be observed between dapagliflozin and placebo with respect to CVM and ACM in the DELIVER trial. This is based on the delayed separation of Kaplan-Meier (KM) curves for CVM in the DELIVER trial (Figure 4 below), and assuming the observed treatment effect would be maintained beyond the follow-up duration of the DELIVER trial. **Figure 4: KM plot of CV mortality in DELIVER**  **Abbreviations**: CI: confidence interval; CV: cardiovascular; Dapa: dapagliflozin; D: dapa 10mg; HR: hazard ratio; KM: Kaplan-Meier; N: number of patients; P: placebo.	

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			Source: Solomon *et al*. (2022).[10] **The use of the observed DELIVER trial data is more robust than arbitrary assumptions.** In any situation, the use of observed clinical trial data directly should be considered to represent the most appropriate approach for any economic model which is in line with NICE's methods manual, *in lieu* of arbitrary assumptions of clinical equivalence. This approach of using the clinical trial data directly, [redacted], is aligned with the previous NICE appraisals for both dapagliflozin and empagliflozin as treatments for HF and an LVEF ≤40% (TA679[11] and TA773[12]), where the Committee did not state any preference for the removal of a direct or indirect effect on mortality. The Committee's requested scenario analyses of assuming equivalence in terms of CVM and ACM, regardless of the clinical trial results, would directly contradict the approach adopted in these previous appraisals in a very similar indication. Further, assuming clinical equivalence is in direct contrast to NICE's recommendations for their preferred sources of evidence, as the NICE methods manual states that "for relative treatment effects there is a strong preference for high-quality randomised controlled trials (RCTs)", and "the trial should, in principle, provide a minimally biased estimate of the size of any benefits or risks associated with the technology relative to those associated with the comparator. RCTs are, therefore, considered to be most appropriate for measures of relative treatment effect." The use of the observed trial data directly is, therefore, aligned with this guidance and the trial should, in principle, provide a minimally biased estimate of the size of any benefits or risks associated with the technology relative to those associated with the comparator.[13] The Company, therefore, maintains that the use of the observed data from the DELIVER trial to inform the treatment effect of dapagliflozin on CVM and ACM within the base case economic analysis represents the most appropriate methodology. **Any uncertainty relating to the magnitude of treatment effect of dapagliflozin on CVM and ACM has already been captured within the probabilistic sensitivity analysis (PSA), which demonstrates that the base case cost-effectiveness analysis is robust to parameter uncertainty.** It is important to consider that any uncertainty surrounding the magnitude of the treatment effect of dapagliflozin on CVM and ACM has already been robustly explored as part of the PSA. Across each iteration of the PSA, the magnitude of dapagliflozin treatment effect was varied based on probability distributions derived from the uncertainty surrounding the point estimates in the DELIVER trial. Table 1 provides summary statistics for the treatment effects modelled across each iteration of the PSA (based on the revised base case, as detailed in Appendix 1), demonstrating that the average treatment effects modelled for dapagliflozin (in terms of HRs for CVM and ACM versus placebo) are [redacted] for CVM and [redacted] for ACM, directly replicating the observed HRs for dapagliflozin in terms of CVM and ACM from the DELIVER trial. Notably, Table 1 illustrates that the PSA already considers the probability of dapagliflozin being equal or worse than placebo at reducing CVM and ACM, respectively, with only [redacted]% and [redacted]% of iterations modelling an assumption that dapagliflozin is equal or worse than placebo at reducing CVM and ACM. Considering a certain proportion of iterations without a treatment effect on CVM and ACM within the wider PSA is a more robust method of exploring this parameter uncertainty than extreme scenario analyses removing the treatment effect altogether. Table 1 also illustrates that the PSA captures an even more pessimistic worst case scenario compared with an assumption of equal efficacy, with worst case HRs of [redacted] and [redacted] for dapagliflozin versus placebo in terms of CVM and ACM, respectively. Nevertheless, the PSA considers both the lower and upper bounds of uncertainty and so provides a complete picture of parameter uncertainty, rather than the sole consideration of an extremely	

<table>
<tr><th>Comment number</th><th>Type of stakeholder</th><th>Organisation name</th><th>Stakeholder comment
Please insert each new comment in a new row</th><th>NICE Response
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<tr><td></td><td></td><td></td><td>pessimistic assumption of equal efficacy.
Table 1: Summary statistics of the CVM and ACM treatment effects considered in the PSA (revised base case)
<table>
<tr><th>Outcome</th><th>HRs (95% CrI)</th><th>Proportion of iterations in which the HR<1</th><th>Range of HRs considered</th></tr>
<tr><td>CVM</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>ACM</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
</table>
Abbreviations: ACM: all-cause mortality; CrI: credible interval; CVM: cardiovascular mortality; HR: hazard ratio; PSA: probabilistic sensitivity analysis.
A pessimistic scenario analysis, in which direct effects of dapagliflozin on CVM and ACM results are removed, results in an ICER of £19,261 per QALY. This is less than the £20,000 per QALY cost-effectiveness threshold. An extremely pessimistic scenario, in which all direct and indirect effects of dapagliflozin on CVM and ACM are removed, results in an ICER of £26,435 per QALY, less than the £30,000 per QALY cost-effectiveness threshold.
For the reasons detailed above, these scenario analyses removing a direct or indirect effect of dapagliflozin on CVM and ACM are not evidence based and cannot be considered clinically plausible.
Nevertheless, in response to the Committee's requests, these scenario analyses have been conducted as part of this ACD response. In these scenario analyses, the regression models for CVM and ACM have been re-run, excluding the dapagliflozin treatment effect (Scenario 1), and excluding the dapagliflozin treatment effect as well as the indirect effect on mortality via KCCQ-TSS quartile (Scenario 2). Full methodological details of these scenario analyses, which have been run on the revised base case following the ACD response, are provided in Appendix 2, and the results of these scenario analyses are presented in Table 2 below.
It should be noted that in these scenario analyses, the resulting extrapolations for dapagliflozin and SoC are not clinically valid when compared to the observed KM data in the DELIVER trial, as highlighted in Figure 5 to Figure 8 below. The CVM extrapolations in Scenarios 1 and 2 underestimate the risk of CVM for SoC, while the ACM extrapolations overestimate the risk of ACM for dapagliflozin. In contrast, as detailed in Response to Issue #2, the revised base case CVM and ACM extrapolations closely match the observed KM data from the DELIVER trial.
Figure 5: CVM extrapolations for Scenario 1 compared with the KM data from DELIVER</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
			 **Abbreviations**: CVM: cardiovascular mortality; KM: Kaplan-Meier; SoC: standard of care.	

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			Figure 6: ACM extrapolations for Scenario 1 compared with the KM data from DELIVER  **Abbreviations:** ACM: all-cause mortality; KM: Kaplan-Meier; SoC; Standard of care. **Figure 7: CVM extrapolations for Scenario 2 compared with the KM data from DELIVER**	

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			 **Abbreviations**: CVM: cardiovascular mortality; KM: Kaplan-Meier; SoC: standard of care. **Figure 8: ACM extrapolations for Scenario 2 compared with the KM data from DELIVER**  **Abbreviations:** ACM: all-cause mortality; KM: Kaplan-Meier; SoC; Standard of care.	

<table>
<tr><th>Comment number</th><th>Type of stakeholder</th><th>Organisation name</th><th>Stakeholder comment
Please insert each new comment in a new row</th><th>NICE Response
Please respond to each comment</th></tr>
<tr><td></td><td></td><td></td><td>Nevertheless, despite the clinical plausibility concerns and pessimistic nature of these scenario analyses dapagliflozin remains a cost-effective use of NHS resources, with an ICER of less than £20,000 per QALY in Scenario 1 and an ICER of less than £30,000 per QALY in Scenario 2.
As such, the Company believes that sufficient evidence has been provided for any remaining uncertainty in this appraisal to be fully resolved, and given the cost-effective ICERs presented below, dapagliflozin should be recommended as a vital new treatment for patients with HF and an LVEF >40%, who will otherwise continue to face an extremely high burden of disease without any disease-modifying treatments available.
Table 2: Additional scenario analysis results (run based on the Company based case following the ACD response)
<table>
<tr><th rowspan="2">Results</th><th colspan="3">Deterministic results</th></tr>
<tr><th>Inc. costs</th><th>Inc. QALYs</th><th>ICER</th></tr>
<tr><td>Company base case (following clarification questions)</td><td>£1,885</td><td>0.251</td><td>£7,519</td></tr>
<tr><td>Revised base case (following the ACD response)</td><td>£2,117</td><td>0.236</td><td>£8,975</td></tr>
<tr><td>Scenario 1 (removal of dapagliflozin treatment effect from the regression models)</td><td>£1,928</td><td>0.100</td><td>£19,261</td></tr>
<tr><td>Scenario 2 (removal of dapagliflozin treatment effect and indirect effect via KCCQ from the CVM and ACM extrapolations)</td><td>£1,922</td><td>0.073</td><td>£26,435</td></tr>
</table>
Abbreviations: ACD: Appraisal Consultation Document; ACM: all-cause mortality; CVM: cardiovascular mortality; ICER: incremental cost-effectiveness ratio; KCCQ: Kansas City Cardiomyopathy Questionnaire; QALY: quality-adjusted life year.
If NICE still perceive there to be any uncertainty for dapagliflozin in relation to CVM and ACM, Scenario 1 should be considered to represent the most relevant pessimistic scenario analysis, in line with precedent from TA773.[12]
Finally, it should be noted that similarly pessimistic, worst case scenarios were suggested by the EAG as part of the NICE appraisal for empagliflozin as a treatment for patients with HF and an LVEF ≤40% (TA773).[12] Within this appraisal, the submitting Company opted to remove the direct effect of empagliflozin on mortality from their base case analysis, but did not remove the indirect effect, nor did the Committee state any preference for the indirect effect to be removed. This is despite the lack of significant reductions in CVM or ACM being observed in the pivotal trial for empagliflozin versus placebo in this indication (EMPEROR-Reduced).[12]
As such, the Company considers that Scenario 1, with an ICER of £19,261, should be considered the most relevant pessimistic scenario analysis, given the previous precedent of economic modelling approaches in HF. In this scenario analysis, dapagliflozin remains a highly cost-effective treatment option and, taken together with the revised base case ICER of £8,975, should allay any uncertainty as to whether dapagliflozin should be recommended for use in UK clinical practice.</td><td></td></tr>
<tr><td>25</td><td>Company</td><td>AstraZeneca</td><td>The base case economic model structure is appropriate, in line with past precedent for modelling approaches for patients with HF.
The ACD (Section 3.13, Page 15) highlighted that the modelling approach used in this appraisal is ‘not a standard modelling approach and could affect model validity’ and noted that ‘a patient-level multi-state simulation model may have been more appropriate because it generates a patient history and considers competing risk’.
It is important to reiterate that the modelling approach used in this appraisal is directly aligned with the modelling approaches used in previous NICE appraisals for dapagliflozin and empagliflozin in a similar indication (patients</td><td>Thank you for your comment. Evidence around the validity and suitability of the model were considered by the committee. Please see section 3.13 of the FDG</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
			with HF and an LVEF ≤40%). As such, the use of a time-updated model covariate and treatment effect coefficient is considered to represent the most suitable modelling approach in this appraisal, given the past precedent that has already been set in this treatment setting. Furthermore, the Company discussed the proposed modelling approach for this appraisal with the EAG and NICE in advance of this submission. The EAG and NICE confirmed that they did not have any concerns with the Company's proposed approach, and agreed on the general alignment with the modelling approaches used in TA679,[11] with adaptations as needed to reflect the available data for patients with HF and an LVEF >40%. **The economic model is consistent with the observed results in the DELIVER trial.** The ACD (Section 3.13, Page 15) noted that *'a model that does not replicate the trial data to an appropriate level of accuracy would lead to considerable uncertainty around the plausibility of the model results. The Committee concluded that a comparison of the overall survival and cardiovascular survival predictions from the economic model (which includes the impact of changes in KCCQ-TSS state over time) and the observed data from DELIVER is needed to determine whether the modelling approach was reasonable.'* As previously detailed in Section B.3.12.2 of the Company Submission Document B, an extensive model validation process was undertaken during the development of the base case cost-effectiveness analysis, including comparison of the modelled outcomes versus the observed CVM and ACM data from the DELIVER trial. These comparisons were previously presented in Figure 29 of the Company Submission Document B and are re-presented in Figure 9 below for reference. The alignment of the modelled CVM and ACM extrapolations with the KM data from the DELIVER trial suggests that there are no concerns with the validity of the modelled extrapolations within the base case economic analysis. **Figure 9: Internal validation of survival for the DELIVER ITT population**[a]	for further details.

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			 [a]Solid lines are the KM from DELIVER; dashed lines are the outcomes from the model. **Abbreviations**: ACD: All-cause death; CV: cardiovascular; ITT: intention-to-treat; KM: Kaplan-Meier; SoC: standard of care. Further model validation has also been conducted as part of this ACD response by visualising the concordance of the observed event rates from DELIVER versus the predicted event rates from the model, and calculating goodness-of-fit statistics. The 45° identity line demonstrates how well predicted event rates compare to reported event rates, with comparisons falling below the line indicative of underprediction and conversely, comparison above the line indicative of overprediction. The comparison of the predicted event rates from the model versus the observed event rates from DELIVER are presented in Figure 10. As the observed event rates from DELIVER are unadjusted for covariate effects, a comparison using the unadjusted risk equations and survival are presented to fairly demonstrate concordance. The regression lines are consistent with the 45° identity line, indicating strong predictive strength in the model outcomes. **Figure 10: Internal validation of predicted versus observed event rates for the ITT DELIVER population**	

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			 **Footnotes:** The solid line is the 45° identity line; dashed line is the regression line; grey shaded area is the 95% CI for the regression line. **Abbreviations**: ACD: all-cause death; CV: cardiovascular; HHF: hospitalisation for heart failure; ITT: intention-to-treat; UHFV: urgent heart failure visit. Validation was also undertaken to compare the modelled proportions of patients in each KCCQ-TSS quartile over time, compared to the observed results in the DELIVER trial. The DELIVER trial data were limited to patients with non-missing KCCQ-TSS data. Health states were based on KCCQ-TSS trial data, using quartile thresholds (Q1: TSS 0–54; Q2: TSS 55–72; Q3: TSS 73–87; Q4: TSS 88–100) and from mortality such that each patient at each timepoint was assigned a mutually exclusive health state (Q1, Q2, Q3, Q4 or death). From Baseline to Month 8, data were assessed at scheduled study visits (Baseline, Month 1, Month 4, Month 8), and the proportion of patients in each KCCQ-TSS quartile were calculated. Data after the Month 8 visit were analysed up to the median trial follow up (28 months) and averaged over that period (mean KCCQ-TSS per patient, which was converted into a KCCQ quartile and plotted at the midpoint of the range at 18 months). Trial results were compared to the base case cost-effectiveness analysis traces, derived from the application of transition probability matrices and adjusted survival equations in the model, as shown in Figure 11. **Figure 11: Comparison of the proportions of patients in each KCCQ-TSS quartile in the DELIVER trial versus the economic model**	

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			 **Footnotes**: Points correspond to trial data, plotted as proportions with 95% confidence intervals while dashed lines correspond to monthly traces estimated by the cost-effectiveness model. Plotted points correspond to scheduled follow-up visits up to 8 months, and thereafter, data were averaged by patient and plotted at the midpoint of the median follow-up period to aggregate results across the variable time of the study closure visit data point. **Abbreviations**: KCCQ-TSS QX: Kansas City Cardiomyopathy Questionnaire – Total Symptom Score Quartile X. The modelled traces show good agreement with the DELIVER trial data. The greatest deviation was seen at Month 1, likely due to the averaging of observed transitions over the period from 0 to 4 months to generate the transition probability matrix used in the economic model. Further, since the single matrix is applied (by arm) over this period, it would not be expected to reproduce finer variations seen in the DELIVER trial observed over this period. Overall, and in the latter phases of the DELIVER trial period up to the median follow up time, closer alignment between observed trial data and the predicted model traces is observed. In conclusion, the extensive model validation conducted as part of this ACD response provides confirmation that the economic model aligns with the observed results in the DELIVER trial and that the modelling approach of a time-updated model covariate and a treatment effect coefficient (as per previous HF NICE appraisals TA679 and TA773[11, 12]) is appropriate for decision making.	
26	Company	AstraZeneca	**The economic model assumes equivalent transition probabilities for dapagliflozin and SoC once patients discontinue treatment with dapagliflozin.**	Thank you for your comment. Evidence

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 (Section 3.15, Page 16) stated that the "*model structure may contribute to a sustained treatment effect for dapagliflozin, which may bias the cost-effectiveness results in favour of dapagliflozin*". It is important to distinguish between the differences in health state distributions in the economic model, versus a sustained or long-term assumption of treatment effect. In the DELIVER trial, dapagliflozin was associated [redacted] in KCCQ score versus placebo. Based on these results, at Month 4, a greater percentage of patients receiving dapagliflozin are modelled to be in higher KCCQ-TSS health states, compared to patients receiving SoC. At the point at which dapagliflozin is discontinued, patients in the dapagliflozin arm of the model are ascribed equivalent health state transition probabilities as patients receiving SoC, and have the same risks of mortality, HHF, UHFV and AEs as patients receiving SoC. Therefore, while the health state occupancy for dapagliflozin versus SoC differs over the time horizon of the analysis, this is due to the modelled on-treatment efficacy of dapagliflozin and not in the post-discontinuation period, where the risk of events for dapagliflozin are assumed equivalent to SoC. This is the most conservative assumption that could plausibly be made and assumes an immediate loss of any treatment effect for dapagliflozin versus placebo upon discontinuation. As such, there is no justification that the current economic modelling approach introduces bias to the cost-effectiveness results in favour of dapagliflozin.	surrounding the model structure was considered by the committee.
27	Company	AstraZeneca	**NHS Reference Costs from 2020/2021 are the most accurate representation of current clinical practice in the UK, and should be included in the base case.** As part of the ACD (Section 3.18, Page 18), the Committee concluded that both sources of NHS reference costs (2020/2021 or 2019/2020 inflated to the current cost year) were plausible, and it was uncertain which NHS reference cost values were most appropriate, given the uncertain impact of the COVID-19 pandemic. However, considering the current economic climate in the UK and the high rate of inflation, there is no evidence that the NHS has returned to operating in line with pre-pandemic conditions. As such, there is a strong risk that the inflation of pre-pandemic reference costs from 2019/2020 does not provide an accurate representation of current NHS clinical practice, which continues to be impacted by the effects of the COVID-19 pandemic. As such, the Company maintains that the most recent 2020/2021 reference costs should be considered in the base case cost-effectiveness analysis as the most recent, and therefore accurate, representation of current NHS clinical practice, and no evidence to suggest otherwise.	Thank you for your comment. The committee concluded that 2019/2020 NHS reference costs inflated to 2020/2021 were the most suitable to use for non-elective care costs. Please see section 3.18 of the FDG for more details.
28	Company	AstraZeneca	**HF and an LVEF >40% is associated with a substantial clinical and economic burden in the UK, and there is a pressing unmet need for the availability of new and effective treatment options. The £30,000 per QALY gained WTP threshold is, therefore, the most appropriate for consideration in this appraisal.** The ACD (Section 3.27, Page 24) highlighted that the Committee preferred the lower bound of the WTP threshold (£20,000–£30,000 per QALY), given the large impact of the uncertainties relating to survival estimates on the ICER. Initially, as detailed extensively in response to Issue 1, the Company believes that sufficient evidence has been provided to justify the most appropriate methodology for modelling survival for dapagliflozin and placebo, and for any remaining uncertainty in this appraisal to be resolved. As such, there is no longer any rationale for the sole consideration of the lower bound of the WTP threshold. Furthermore, it is also important to reiterate the pressing unmet need for new treatment options in this highly underserved patient population. HF and an LVEF >40% represents one of the most significant healthcare challenges in the UK.[14] For these	Thank you for your comment. The committee noted the unmet need in this population. Above a most plausible ICER of £20,000/QALY, judgments about the acceptability of the technology as an effective use of NHS resources are more likely to make reference

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			patients, the 5-year survival rate following a hospitalisation for HF (HHF) is 35%, which is worse than many cancers.[15] HF and an LVEF >40% is also associated with a considerable economic burden, driven by high hospitalisation rates; it is estimated that HF costs the National Health Service (NHS) up to 2% of its annual budget, at a cost of approximately £3 billion per year.[16-20] Further, the prevalence of HF with LVEF >40% is likely to rise in the future due to factors such as the ageing population in the UK, and rising rates of obesity and type 2 diabetes mellitus (T2DM), meaning that the clinical and economic burden associated with HF will only increase without the availability of new treatment options.[21-23] Notably, there are currently no disease-modifying treatments routinely commissioned in UK clinical practice for patients with HF and an LVEF >40%, and until now, there had not been any successful clinical trials in this setting. The distinction between HF and an LVEF >40% and LVEF ≤40% is not based on the aetiology of HF, but is the result of the historical failures of previous trials to demonstrate benefits for patients with HF and an LVEF >40%. The ACD (Section 3.2, Pages 5–6) highlighted that patient experts described that the symptoms, disease severity and impact on daily life of HF and an LVEF >40% are similar to those experienced by people with HF and an LVEF ≤40%. However, while there are a multitude of treatment options for patients with HF and an LVEF ≤40%, the patient experts highlighted the lack of hope experienced by patients with HF and an LVEF >40%, because of the lack of any positive clinical trials and available treatments, and the resulting impact on patients' quality of life and mental health. This is the result of numerous clinical trials conducted over multiple decades in patients with HF and an LVEF >40%, which have failed to identify treatments that are able to provide statistically significant or clinically meaningful benefits for these patients. Consequently, there is an urgent requirement for innovative treatments, such as dapagliflozin, which have been shown to improve disease symptoms and quality of life, and to reduce hospitalisation and mortality for these patients.[10, 24] Furthermore, as part of this appraisal, one of the clinical experts highlighted that "In the UK there are around 100,000 HF admissions annually, with a long length of stay (10 days mean), so a technology with an impact on reduced admissions will have wider benefits for an NHS system currently running at capacity", highlighting the potential impact of introducing dapagliflozin on alleviating current capacity issues within the NHS. With the additional evidence provided as part of this response document, NICE can be confident that dapagliflozin represents a cost-effective treatment for this population of patients who are in significant need of new, disease-modifying treatments. It is inappropriate to anchor decision making to the lower bound of the £20,000–£30,000 per QALY WTP threshold, given the highly innovative nature of dapagliflozin, which would represent a step change in the treatment paradigm for patients with HF and an LVEF >40%, and the significant reduction in uncertainty with respect to the cost-effectiveness estimates for dapagliflozin compared to the analyses previously presented during the first Appraisal Committee meeting.	to explicit factors including the degree of uncertainty surrounding the ICERs.
29	Company	AstraZeneca	**Once a diagnosis of HF and an LVEF >40% is confirmed by a specialist, initiation of treatment with dapagliflozin should be permitted in either primary or secondary care without the need for further specialist advice.** The Company are concerned with the Committee's conclusion that treatment with dapagliflozin in this indication could only be started on the advice of a HF specialist. This would, in the case where NICE recommend dapagliflozin for these patients, likely lead to the majority of dapagliflozin prescriptions taking place in the secondary care setting. This is a particular concern given the current NHS capacity constraints, and the potential for dapagliflozin to alleviate these, as highlighted in Issue #5. The Company proposed that treatment with dapagliflozin in patients with HF and an LVEF >40% could be initiated either in primary or secondary care, contingent on a documented HF diagnosis by a specialist enabling	Thank you for your comment. Comment noted. This is considered in section 3.29 of the FDG.

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			the initiation of dapagliflozin in primary care without the need for further specialist advice. Prior to the publication of any positive recommendation for dapagliflozin by NICE, given the lack of disease-modifying therapies in this setting, there are likely many patients with HF and an LVEF >40% who are unlikely to go back to see a cardiologist until they experience an HF event. In the event that patients have been discharged back to primary care following specialist diagnosis before a care plan is provided or treatment is initiated, it is both appropriate and optimal for the patient that primary care physicians are able to initiate therapy autonomously. This is also critical to ensure that the management of patients already diagnosed with HF and an LVEF >40% who are managed in primary care is optimised, allowing dapagliflozin to be initiated at the earliest opportunity, ideally following proactive invitation for a treatment optimisation review or alternatively, where capacity is a limitation, during their routine check-up appointment without the need for a specific or extended appointment. In the case of both an incident and prevalent population with confirmed HF and an LVEF >40%, the requirement to seek additional specialist advice before treatment initiation would delay access and create additional resource constraints in both primary and secondary care amidst the large post-COVID back-logs and NHS capacity issues still being experienced. As dapagliflozin is currently available across the primary and secondary care treatment settings for patients with T2DM, [25-27] CKD, [28, 29] including those with co-morbid HF and an LVEF >40%, and HFrEF, ,[11] clinicians across care settings have considerable clinical experience with prescribing dapagliflozin. Therefore, the additional advice of a HF specialist seems unnecessary for the initiation of dapagliflozin after HF and an LVEF >40% has already been diagnosed, and delays could be costly in terms of morbidity and mortality. Initiation of dapagliflozin for the treatment of patients with HF and an LVEF >40% in the primary care setting would improve equality of access to dapagliflozin without relying on access to specialist care, which is limited to only a few HF centres commissioning services to support patients with HF and an LVEF >40% after diagnosis, or offering specialised HFpEF clinics alongside their usual HF services.[30] Given that there is substantial clinical experience in the prescribing of SGLT2 inhibitors in primary care, the Company believes that there is no clinical rationale for restricting the initiation of dapagliflozin for patients with HF and an LVEF >40% to the advice from a HF specialist only. This may be particularly suitable for many prevalent patients with HF and an LVEF >40% who are already managed in primary care or for those who are not routinely followed-up within specialist care. For these patients, initiation of dapagliflozin could take place at the earliest opportunity, ideally following proactive invitation for a treatment optimisation review or alternatively, where capacity is a limitation, during their routine check-up appointment without the need for a specific or extended appointment. This should be easily implementable given that most HF services are already organised across primary and secondary care and that dapagliflozin does not require up-titration nor specific monitoring over and above what is recommended for a patient with HF already. There is false equivalence in suggesting that because NICE recommends patients with HF and an LVEF ≤40% (HFrEF) are initiated on specialist advice, the same should hold true for those with HF and an LVEF >40%. It is important to distinguish that people with HFrEF have the opportunity to be considered for other evidence-based therapies, some of which can only be initiated by the specialist. Given that the population of patients with HF and an LVEF >40% have no other treatment options, seeking the advice of a specialist for initiation represents a significant cost and would delay the initiation of dapagliflozin, which in the DELIVER trial produced a statistically significant reduction in the primary endpoint in 13 days after randomisation and KM curves separately immediately following randomisation.[10, 31] Given this, the Company firmly believes that enabling the treatment of patients with dapagliflozin irrespective of care settings without the need for further specialist advice represents the most appropriate approach and ensures	

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			that as many eligible patients as possible are receiving optimal care. This will support the NHS with its COVID-19 recovery plans, reducing wait times to outpatient services,[32] and reducing unwarranted variations in care across England and Wales. Enabling the initiation of dapagliflozin in both primary and secondary care for the treatment of this patient population would, therefore, ensure consistent equality of access without relying on specialist care, which may not exist in some areas for these patients.	
30		AstraZeneca	**Summary of revised base case and scenario analyses.** Following the ACD, the base case cost-effectiveness analysis has been revised in order to align with the following Committee preferred assumptions: • Including age-adjusted and multiplicative population utilities (Section 3.16 of the ACD); • Applying HHF disutility is applied for 6 months (Section 3.17); • Using the HRG cost code (EB03E), associated with less severe HHF, to cost HHF (Section 3.19); • Assuming 6 annual GP visits per year (Section 3.21); • Removing amputation as an adverse event in the economic model (Section 3.22). All other settings are aligned with the previous Company base case, for the reasons detailed throughout this response document. This results in a revised base case deterministic ICER of £8,975 per QALY and a probabilistic ICER of £9,226 per QALY, with 85% and 90.7% probability of being cost-effective at WTP thresholds of £20,000 per QALY and £30,000 per QALY, respectively. Full deterministic and probabilistic results of the revised base case, as well as the scenario analyses conducted as part of this ACD response, are provided in Appendix 1 below. The Company have also presented compelling evidence in order to resolve the uncertainties highlighted in the ACD, demonstrating that dapagliflozin remains cost-effective across all scenarios considered. The Committee should now have full confidence and reassurance that dapagliflozin represents a highly innovative and cost-effective technology, for this underserved patient population, who will otherwise continue to face an extremely high burden of disease without any disease-modifying treatments available.	Thank you for your comment. The committee considered the revised cost effectiveness estimates along with the Evidence Assessment Group's critique.
31	Clinical Expert	N/A	The TA committee was satisfied that dapagliflozin significantly reduced the combined risk of cardiovascular death or first heart failure event in HFpEF and HFmrEF (heart failure with mildly reduced EF) and there are currently no disease-modifying treatments available. Heart failure (HF) is the commonest cause for admission in over 65-year-olds and heart failure admissions increased by one third in the five years before the pandemic.[1] Health education England project a doubling of admissions for cardiology patients in the next 25 years[2] – and this picture will be dominated by HFpEF, as effective medications for HF with reduced EF (HFrEF) has led to reduced admissions for this subgroup.[3] HF is one of the leading causes for readmission – currently 22% in 28 days. HF admissions are long and costly and there is an existing capacity crisis in the NHS. NHS England is investing in experimental alternatives to hospital admission to try and mitigate this crisis (Virtual Ward funding for 22/23, £200m, for 23/24 estimated £250m). Dapagliflozin reduces admission risk in a dominant condition contributing to the NHS bed crisis, but the legacy costing measures used in this TA are unable to take account of this benefit in terms of improved opportunity cost (ability to admit other patients to hospitals which are otherwise at capacity) or the reduced need for NHS investment in untested service models.	Thank you for your comment. The committee noted the unmet need in this population and considered this in its decision making. Please see section 3.2 of the FDG
32	Clinical	N/A	Plausibility for reduced mortality. Dapagliflozin significantly reduced heart failure admissions/worsening HF events	Thank you for your

<table>
<tr><th>Comment number</th><th>Type of stakeholder</th><th>Organisation name</th><th>Stakeholder comment
Please insert each new comment in a new row</th><th>NICE Response
Please respond to each comment</th></tr>
<tr><td></td><td>Expert</td><td></td><td>(hazard ration 0.79). In England, a heart failure admission carries a 10% inpatient mortality and a further 33% post discharge 1 year mortality (total = 43% 12 month mortality).[1] Dapagliflozin's ability to reduce admissions means that it is highly plausible that dapagliflozin will lead to a reduction in mortality.</td><td>comment. Further evidence provided around the mortality benefit of dapagliflozin was considered in the second committee meeting. Section 3.11 of the FDG has been updated to reflect the committee's preference.</td></tr>
<tr><td>33</td><td>Clinical Expert</td><td>N/A</td><td>The resource use estimate for hospitalisation is not correct. The HRG cost is not based on length of stay but on the number of comorbid conditions. The complications and comorbidities for each HRG subchapter are updated annually and for heart failure (EB subchapter) can be taken from a defined list only. The 2020/21 NHS National Cost Collection data shows that heart failure is highly comorbid and the commonest associated HRG is EB03B – with 11-13 comorbidities. A weighted average of the annual admission cost is the most appropriate cost to use and can be considered conservative, as HFpEF patients are generally older than HFrEF patients and have even more comorbidities. The HRG code EB03E was used in only 3.5% of admissions in 2020/21.

<table>
<tr><td>HRG</td><td></td><td>Activity</td><td>Total Cost</td></tr>
<tr><td>EB03A</td><td>Heart Failure or Shock, with CC Score 14+</td><td>46,097</td><td>£187,752,739</td></tr>
<tr><td>EB03B</td><td>Heart Failure or Shock, with CC Score 11-13</td><td>46,620</td><td>£134,096,477</td></tr>
<tr><td>EB03C</td><td>Heart Failure or Shock, with CC Score 8-10</td><td>38,787</td><td>£84,288,556</td></tr>
<tr><td>EB03D</td><td>Heart Failure or Shock, with CC Score 4-7</td><td>29,746</td><td>£49,585,591</td></tr>
<tr><td>EB03E</td><td>Heart Failure or Shock, with CC Score 0-3</td><td>6,017</td><td>£6,899,584</td></tr>
</table>

Use of a weighted average would also be consistent with the method used in TA679.</td><td>Thank you for your comment. The FDG has been amended to reflect this. Please see section 3.19 of the FDG.</td></tr>
<tr><td>34</td><td>Clinical Expert</td><td>N/A</td><td>Severity: the committee should consider employing the severity modifier to give more weight to health benefits in the most severe conditions such as HFpEF. Dapagliflozin reduces HF admissions in HFpEF, a condition with a >40% 12-month mortality following admission and HF is a leading cause for readmission (22% within 28 days). There are no existing treatments available so the introduction of a novel disease modifying therapy would have a wider secondary impact on improved treatment pathways as there is currently no specialist service provision for HFpEF in most ICSs.

1. National HF Audit NICOR NICOR | Heart Failure (Heart Failure audit)
2. Https://eproduct.hee.nhs.uk/
3. Owan, Theophilus E., et al. Trends in prevalence and outcome of heart failure with preserved ejection</td><td>Thank you for your comment. NICE's advice about conditions with a high degree of severity did not apply because the absolute and proportional QALY shortfalls were below the cut-offs required for the severity weighting. Please see section 3.24 of the FDG.</td></tr>
</table>

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			fraction. New England Journal of Medicine 355.3 (2006): 251-259 NHS England » National Cost Collection for the NHS	
35	Consultee	Primary Care Cardiovascular Society (PCCS)	The assumption that all patients with heart failure with improved ejection fraction will be already prescribed dapagliflozin (or empagliflozin) is suspect. Not all patients with a previous diagnosis of heart failure will have been reviewed over the last 2 years and may have missed out on this treatment option. Furthermore, this review may not have considered the previous ejection fraction as a comparator to identify those where the ejection fraction has improved. If this recommendation is made, they will be excluded from consideration of this disease modifying treatment.	Thank you for your comment. The committee noted the unmet need in this population and considered this in its decision making. Please see section 3.2 of the FDG
36	Consultee	Primary Care Cardiovascular Society (PCCS)	The cohort studied in this trial do not have any disease modifying treatments available to them, only treatment of co-morbidities. If dapagliflozin is not recommended as a treatment for heart failure with preserved ejection fraction, patients and clinicians continue to have limited treatment options.	Thank you for your comment. The committee noted the unmet need in this population and considered this in its decision making. Please see section 3.2 of the FDG
37	Consultee	Primary Care Cardiovascular Society (PCCS)	This patient group accounts for a large number of hospital admissions each year. In view of our ageing population and increasing prevalence of heart failure with preserved ejection fraction, the pressure of recurrent hospitalisations on health services will only increase in the future. We are concerned that this recommendation does not allow the use of a treatment that could reduce these hospitalisations.	Thank you for your comment. The committee noted the unmet need in this population and considered this in its decision making. Please see section 3.2 of the FDG
38	Consultee	Primary Care Cardiovascular Society (PCCS)	We are concerned that currently a minority of the HFmrEF and HFpEF populations are routinely seen by HF Specialist services which significantly disadvantages their health care which is not in keeping with the NICE Chronic HF guideline of 2018: people with suspected HF should see a specialist. They therefore do not have the opportunity for HF Specialist teams to assess and make recommendations around managing their symptoms, provide relevant education/support, refer to other services such as Cardiac Rehab etc. For this reason the normally applied ICER threshold of £20k should be reconsidered as too low for a population poorly served at this point in time by health services.	Thank you for your comment. The committee noted the unmet need in this population. Above a most plausible ICER of £20,000/QALY, judgments about the acceptability of the technology as an effective use of NHS resources are more

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				likely to make reference to explicit factors including: the degree of uncertainty surrounding the ICERs.
39	Consultee	Primary Care Cardiovascular Society (PCCS)	We are concerned that an outcome that focusses on mortality is missing the fact that this cohort are elderly with many co-morbidities leading to hospitalisation. In many areas in England heart failure services are only commissioned for the management of the HFrEF leaving primary care to manage the remaining heart failure population. This cohort often have worse QoL than HFrEF patients and more co-morbidities (4.5 at diagnosis and increasing with time: Conrad et al https://doi.org/10.1016/S0140-6736(17)32520-5) and have frequent touch points in primary care and more frequent hospital/rehospitalizations. As the only treatment option for HFpEF these patients often have a high burden of loop diuretics which inconvenience patients, have no outcome benefits and negatively affect renal function (unlike SGLT2i which slow down renal decline and are nephroprotective). By addition of dapagliflozin (alongside a loop diuretic – for which a lower dose may be possible) the trials show, for the first time, a medicine that will improve QoL in HFmrEF and HFpEF.	Thank you for your comment. The committee considered all evidence that was submitted. Quality of life is considered as part of the economic modelling.
40	Consultee	Primary Care Cardiovascular Society (PCCS)	We feel that the NICE modelling for primary care contact at 6/year is likely an underestimate given the number of co-morbidities in this ageing population and is an underestimated cost in the model. A treatment that improves QoL/ symptoms will have a positive impact on the need for primary care resource. The evidence from the relevant trials suggests and improvement in KCCQ which is significant in managing any patient with HF and may have other positive health and social care benefits which are not accounted for.	Thank you for your comment. The committee considered the available evidence and clinical experts' opinion in its decision making. The final draft guidance has been updated to reflect the company's use of 6 annual primary care visits. See section 3.21 of the FDG.
41	Consultee	Primary Care Cardiovascular Society (PCCS)	We are concerned that there is a mismatch in the weighting of outcomes on mortality. Patient preference is for improved quality of life over mortality benefits. This includes avoiding hospital admissions (each admission reduces prognosis; is expensive to overall healthcare system; inconveniences patients, family, and carers; risks hospital acquired infection and will contribute to reduced acute hospital flow and the need for social care). NICE suggest that the impact of hospitalisation for HF will last less than a year before recovery, but that clinician experience suggests that a patient typically never recovers fully post hospitalisation whether this be reflected in their exercise tolerance or general well- being which emphasises the significance of a hospitalisation and the need to avoid if possible.	Thank you for your comment. The committee considered all evidence that was submitted. Quality of life is considered as part of the economic modelling.

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42	Consultee	The Pumping Marvellous Foundation	**Section 3.3 Treatment options** - We are concerned that this recommendation may imply that Frusemide and medications used to treat co-morbidities in HFpEF, offer treatment options that can act as comparators to Dapagliflozin for the treatment of HFpEF. Diuretics are used for the treatment of fluid overload in any type of heart failure however they are not indicated in the absence of fluid overload as they are not disease modifying treatments. The comorbidities that accompany HFpEF (hypertension, diabetes, chronic kidney disease) do not usually cause heart failure symptoms and hence treatment for comorbidities does not necessarily amerliorate symptoms in HFpEF either. We feel that it is important to acknowledge that there is simply no other disease modifying therapy available for HFpEF and SGLT2 inhibitors currently represent the 1st treatment option that has become available to alleviate symptoms as well as adverse outcomes, for a condition affecting nearly half a million people in the UK.	Thank you for your comment. Section 3.2 of the FDG notes there are no disease-modifying treatments for this group. Dapagliflozin was compared to established clinical management without dapagliflozin. The company defined standard care in their model as loop diuretics (furosemide and bumetanide). The committee agreed this was appropriate to use as a comparator. Please see section 3.4 of the FDG for further detail.
43	Consultee	The Pumping Marvellous Foundation	**Section 3.4 Comparators**– concerns similar to above that diuretics and treatment of comorbidities are not appropriate comparators for SGLT2i	Thank you for your comment. Section 3.2 of the FDG notes there are no disease-modifying treatments for this group. Dapagliflozin was compared to established clinical management without dapagliflozin. The company defined standard care in their model as loop diuretics (furosemide and bumetanide). The committee agreed this was appropriate to use as a comparator. Please see section 3.4 of the FDG for further detail.
44	Consultee	The Pumping Marvellous Foundation	**Section 3.5 Data sources and generalisability** This section seems to imply that the trial population in DELIVER was much younger than that seen in clinical practice. This is inaccurate as >40% of patients in DELIVER were ≥75 years,77% were ≥65 yrs and the recruited population represented a broad spectrum of age groups (Peikert A, et al. Circ Heart Fail. 2022 Oct;15(10):e010080). Among 6263 randomized patients (aged 40–99 years, mean age 71.7±9.6 years which was	Thank you for your comment. The committee concluded that the results from DELIVER were broadly

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			older than many of the previous HF trials), 338 (5.4%) were <55 years, 1007 (16.1%) were 55–64 years, 2326 (37.1%) were 65 to 74 years, and 2592 (41.4%) were ≥75 years.Older patients in DELIVER had the highest LVEF with more patients whose LVEF ≥60%. The benefits of Dapgliflozin on reduction of primary composite outcome measure and improvement of symptoms, were seen irrespective of age. DELIVER not only randomised older patients but also a significant number of patents with HFpEF and frailty (≈63%), according to a pre-specified analysis (Butt JH et al. Ann Intern Med. 2022 Jun;175(6):820-830.) The beneficial outcomes were seen irrespective of degree of frailty but more importantly patients with the greatest frailty experienced the most improvement in symptoms, physical function, and quality of life	generalisable to NHS clinical practice. Please see section 3.5 of the FDG.
45	Consultee	The Pumping Marvellous Foundation	**Section 3.7**. **Impact of treatment on cardiovascular and all-cause mortality** The pooled analysis by Jhund et al (Nature Medicine volume 28, pages1956–1964 2022) also showed that Dapagliflozin reduced all-cause mortality by 10% (HR 0.90 (95% CI 0.82–0.99); P = 0.03) irrespective of ejection fraction. Similarly another pre-specified analysis of the effect of Dapagliflozin on cause-specific mortality, showed significant reductions in cardiovascular mortality irrespective of ejection fraction (attributable both due to reductions in HF death and sudden death - Desai AS, et al. JAMA Cardiol. 2022;7(12):1227–1234) A meta-analysis of 12 251 participants from DELIVER and EMPEROR-Preserved (Vaduganathan M, et al. Lancet 2022 Sep 3;400(10354):757-767), demonstrated significant reductions in composite cardiovascular death or first hospitalisation for heart failure (hazard ratio 0·80 [95% CI 0·73-0·87]) with consistent reductions in both components: cardiovascular death (0·88 [0·77-1·00]) and first hospitalisation for heart failure (0·74 [0·67-0·83]). As DELIVER was not powered to detect a reduction in cardiovascular or all-cause mortality, findings from the pooled pre-specified analyses as well as meta-analyses provide a more meaningful statistical estimate on cardiovascular and all-cause mortality benefit irrespective of ejection fraction. It is also important to note that in contrast to HFrEF, patients with HFpEF and HFmrEF, experience a greater proportion of non-cardiovascular mortality (mainly due to greater multimorbidity burden -Vaduganathan M et al. J Am Coll Cardiol. 2017;69(5):556-569). For a condition such as HFpEF which is associated with a constellation of comorbidities and which has not had such benefits noted from other therapies, this finding is important and should not be overlooked.	Thank you for your comment. Further evidence provided around the mortality benefit of dapagliflozin was considered in the second committee meeting. Section 3.11 of the FDG has been updated to reflect the committee's preference
46	Consultee	The Pumping Marvellous Foundation	**Section 3.8** Amongst the DELIVER population of patients, a minority (18%) had HF with improved EF (HFimpEF). In a pre-specified analysis (Vardeny et al Nature Medicine volume 28, pages2504–2511 2022), Dapagliflozin reduced the primary composite end point compared to placebo in participants with HFimpEF (HR = 0.74, 95% CI = 0.56–0.97) to a similar extent as patients with LVEF consistently over 40% (HR = 0.84, 95% CI 0.73–0.95; interaction P = 0.43). The benefits were similar and irrespective of age age ≥75 versus <75 years. It is also important to note that the event rate (worsening HF, cardiovascular or all-cause death) was similar in the HFimpEF cohort and LVEF consistently>40% cohort indicating comparable risk profiles. There was also similar symptom benefit in the two groups (although those with HFimpEF were less symptomatic at baseline). These benefits are significant as this unique cohort of patients with HFimpEF has not been studied previously, however it is important to emphasise that inclusion of this cohort in DELIVER, does not accentuate the benefits seen in those with LVEF consistently >40%.	Thank you for your comment. The committee considered all evidence that was submitted.
47	Consultee	The Pumping Marvellous Foundation	**Section 3.9** People with HFpEF suffer from poor quality of life, significant burden of symptoms and physical limitation and improving symptomatic status is an important goal of heart failure guidelines. Results from the DELIVER Trial Kosiborod et al. (JACC Volume 81, Issue 5, 7 February 2023, Pages 460-473), through evaluation of KCCQ-TSS, Physical Limitations (PLS), Clinical Summary (CSS), and Overall Summary (OSS) domains, show	Thank you for your comment. The committee considered all evidence that was

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			that Dapagliflozin use in HFpEF leads to an early (within 1 month) and sustained, significant improvement in symptoms and health status. We are concerned about the rationale for questioning KCCQ as a valid questionnaire to assess quality of life, when there is a weath of evidence that it is a robust measure in all types of HF (G-CHF Study. Circulation. 2021;143:2129–2142, Spertus et al. JACC 2020, Joseph S et al. Circ Heart Fail. 2013 Nov;6(6):1139-46, Sepehrvand N, J Am Heart Assoc. 2020;9(17):e017278.) to detect meaningful change in health status and also has a better prognostic value in comparison to NYHA Class which is a more subjective and non-patient-centric score (Greene et al JAMA 2021). Our Pumping Marvellous "Living with Heart Failure" patient survey responses indicate that the most important outcome for patients is to improve day-to-day quality of life (78.5% of patients), followed by increasing life expectancy (72.5% of patients), http://pumpingmarvellous.org/wp-content/uploads/2018/02/Pumping-Marvellous-Living-With-Heart-Failure-Infographic.pdf The importance of quality of life for a person living well with heart failure is emphasised by patients, carers and clinicians surveyed in the Pumping Marvellous "Living Well with Heart Failure "report https://pumpingmarvellous.org/wp-content/uploads/2022/04/Living-well-with-heart-failure-report-FINAL.pdf Similarly we are also concerned that the symptomatic benefit of Dapagliflozin in DELIVER is seemingly trivialised again due to the factor that the KCCQ use as a predictor of cause and cardiovascular mortality has been questioned. SGLT2i are the 1st class of therapies that have shown symptomatic benefit in people with HFpEF (despite associated multimorbidity, frailty).	submitted. Symptoms and quality of life are captured within the economic modelling calculations which use quality-adjusted life years (QALYs). Please see section 3.16 of the FDG for more details.
48	Consultee	The Pumping Marvellous Foundation	**Section 3.10 Health state transition** The modelling approach for health state transition is similar to that approved for NICE TA 679. As also described below in Section 3.17, it is our opinion that currently there is no fool-proof modelling approach available to account for the transient and time-bound nature of HRQoL assessment.	Thank you for your comment. Comment noted. The committee was made aware of these points when issuing the final draft guidance. Section 3.10 of the FDG has been updated following the consultation.
49	Consultee	The Pumping Marvellous Foundation	**Section 3.11 Modelling of treatment effect on cardiovascular and all-cause mortality** Points made in Section 3.7 are also relevant here. Based on the totality of evidence outlined above, we are concerned that impact of the significant reduction in cardiovascular mortality, in particular due to Dapagliflozin use in people with HF and LVEF>40%, is being excluded by the committee. This is all the more relevant due to the inherent limitations of both sensitivity and scenario analyses being used to compute incremental cost-effectiveness ratios.	Thank you for your comment. The committee was made aware of these points when issuing the final draft guidance. Section 3.11 of the FDG has been updated following the consultation.
50	Consultee	The Pumping Marvellous Foundation	**Section 3.13 Ability of the model to replicate observed all-cause and cardiovascular survival outcomes** We find it confusing that when time-updated model covariate and a treatment effect coefficient were used in NICE TA for Dapagliflozin and Empagliflozin in HFrEF TA679 [TA773], yet the committee did not consider this a standard modelling approach for HFpEF, despite the totality of evidence indicating that heart failure is a condition that represents a continuum and the beneficial effects of SGLT2i are seen across the range of ejection fraction.	Thank you for your comment. The committee considered the validity of the economic model in its decision making. Please

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				see updates to section 3.13 in the FDG.
51	Consultee	The Pumping Marvellous Foundation	**Section 3.14 Modelling of treatment effect on HF events** We are concerned by the EAG statement "DELIVER data did not convincingly support a benefit of dapagliflozin in reducing urgent hospitalisation for heart failure" and on this basis the exclusion of dapagliflozin treatment effect on urgent hospitalisation for heart failure in its base case. DELIVER and other SGLT2i trials have shown a significant reduction in HF hospitalisations.	Thank you for your comment. Urgent hospitalisations for heart failure were considered separately to other hospitalisations for heart failure. Please see section 3.14 of the FDG which has been updated with further information after the second committee meeting.
52	Consultee	The Pumping Marvellous Foundation	**Section 3.17 Duration of impact of heart failure events on quality of life** We are concerned that the impact of HF hospitalisation has not been adequately represented both in terms of the impact upon patients nor upon healthcare resources. HF hospitalisation represents a crucial inflection point in the trajectory of a patient as it is associated with 10% inhospital mortality and 15% 30 day mortality as well as a 25% 30 day readmission rate and 50% readmission rate over 6 months. There a recognised limitations of applying disutlity due to HF hospitalisation to economic models, due to the variation in timing of disutility assessment, time-bound nature of estimation of disutility at a specific time followed by linear extrapolation to longer time periods and impact of recurrent hospitalisations (a frequent event in HFpEF), nature of hospitalisation (HF versus other causes due to multimorbidity and the impact of individual patient characteristics upon disutility (Di Tanna, G.L.,et al. PharmacoEconomics 39, 211–229 (2021).However previous studies have indicated that a HF related hospitalisation reflects a disutility period up to 12 months. We feel this is a more realistic estimate of the impact of HF hospitalisation on HRQoL due to additional effects of falls, delirum, muscle wasting, hospital acquired infections and effect on nutrion. This is particularly relevant for patients with HFpEF who are frequently older than those with HFrEF; HFpEF is also associated with greater multimorbidity as well as frailty.	Thank you for your comment. The committee considered all the evidence submitted, including from both clinical experts and the literature.
53	Consultee	The Pumping Marvellous Foundation	**Section 3.21 GP visits** We are concerned that there appears to be an underestimate of the healthcare resources by people with HFpEF in primary care. Evidence indicates that HFpEF is under diagnosed and less recognised in primary care as symptoms and signs may be mis-attributed to obesity, ageing, frailty etc *Hossain et al https://doi.org/10.1177/174239532098387). In our opinion 6 annual GP visits is therefore an underestimate, as these patients also frequently contact urgent care centres or community heart failure teams.	Thank you for your comment. The committee considered all the evidence submitted, including from both clinical experts and the literature.
54	Consultee	The Pumping Marvellous Foundation	**Section 3.26 Committee preferred assumptions** We express concerns regarding some of the assumptions as follows 1.hospitalisation disutility of 6 months is an underestimate and disutlity of 12 months is more accurate as per explanation above in Section 3.17 2. GP visits of 6/year is a likely underestimate	Thank you for your comment. The committee was made aware of these points when issuing the final

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			3. removal of treatment effect of dapagliflozin on cardiovascular and all-cause deaths (see section 3.11) or on urgent heart failure visit events	draft guidance. Sections 3.25 to 3.27 of the FDG has been updated following the consultation.
55	Consultee	The Pumping Marvellous Foundation	Statement by Pumping Marvellous Foundation UK HFpEF Patient Advisory Board The decision has led to a feeling of great disappointment. To HFpEF patients, SGLT2 inhibitors represented not just another treatment but a beacon of hope that, at last, a medicine had arrived that could make a real difference to our lot. It is easy for a HFpEF patient to feel left behind as we are often denied the educational and support services of a complete heart failure medical team because NICE has now not recommended any treatments for our population. Commissioners of services use NICE published guidance to create services and due to this decision, they will not create services. The impact of this decision is far reaching outside just the prescribing of an innovative medication. This is another reason for reconsideration of changing the recommendation. Quality of Life is an essential consideration and reduction in hospitalisation, a significant element in that, however, achieved. Unfortunately, a whole class of drugs that promise to improve our QoL has been rejected with no apparent justification other than subjective economic assumption. We ask that the current decision is reversed and that SGLT2i are reimbursed. There are members in our HFpEF advisory committee that have benefited from this treatment. Pumping Marvellous UK HFpEF Advisory Board [redacted]	Thank you for your comment. The views of patient experts were considered by the committee when formulating its recommendations. Dapagliflozin has been recommended by the committee for people with preserved or mildly reduced ejection fraction.
56	Consultee	The Pumping Marvellous Foundation	**Pumping Marvellous Foundation, Patient Educators (43 Expert Patients) Response** This response comes from the Pumping Marvellous Foundation of Patient Educators (Expert Patients) in our community who have heart failure, a mixture of HFrEF, HFpEF and HFmrEF. Heart failure afflicts us all irrespective of the type. We total 43 patients across the UK and 4 Nations. We stand together as a community of humans with the same debilitating issues; those of us with HFrEF are fortunate enough to have medications that make a difference to us daily. We have hope for a better future & the decision from this appraisal has essentially removed that from people who have HFpEF. Below is a mixture of quotes from some of our Patient Educators – **[redacted] summarises [redacted] thoughts here.** "I feel that blocking these meds is playing with people's lives. These meds could potentially be someone's lifeline, but by blocking them, in my opinion, it feels like a kick in the teeth to those patients that could benefit from them". **[redacted] summarises [redacted] thoughts.** "In turning your backs on the use of these drugs for HFPEF patients, despite their benefits identified in large	Thank you for your comment. The views of patient experts were considered by the committee when formulating its recommendations. Dapagliflozin has been recommended by the committee for people with preserved or mildly reduced ejection fraction..

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			RCT's, primarily on the grounds of cost, will NICE be issuing guidance to clinicians on how to assist patients in amortising/depreciate their quality of life? Will the cost of mental health support for those patients who feel they have no hope for an improved QOL outweigh the cost of allowing these patients to access these medications?" **The feeling from our community is confusion & a colossal disappointment.** [redacted] **summarises** [redacted] **thoughts.** "I'm incredibly disappointed that NICE has decided not to approve SGLT2i's for heart failure patients that have preserved ejection fraction when they have already approved it for those of us that have HF with reduced ejection fraction. The chance to finally prescribe medication that can help improve the quality of life for a group of patients with so few treatment options feels like a missed opportunity." **A missed opportunity is precisely how this feels. We worry that it could also impact future research for treatments for patients with HFpEF, why invest? Research that is desperately needed & that would also have long-term cost benefits to the NHS. These patients deserve every opportunity to live better with their condition, and this decision goes against that fundamentally.** [redacted] **summarises** [redacted] **thoughts.** "Whilst NICE's recommendation to withdraw SGLT2i's from patients with HFpEF doesn't affect me personally, I kindly request that the decision is reviewed with a reversal in mind as I'm aware of many fellow heart failure patients whose quality of life will be affected by this decision. Heart failure is tough enough to live with, and the prospect of increased symptoms due to the non-prescribing of the drugs mentioned above is both unnerving and irresponsible". **It is unnerving to think that NICE would make this decision despite clinicians, patients & the heart failure community, in general, knowing that these treatments would be a positive and necessary addition to our arsenal of tools in the fight to live with heart failure. As patients, we want to live, not just exist. Although we often hear that with a diagnosis of heart failure, patients feel that their lives are diminished, this decision is another blow to people who are often already living a physically & mentally difficult life. This decision impacts that difficulty massively for many of us & we are saddened to think of the far-reaching implications it will have.** [redacted] **summarises** [redacted] **thoughts, on behalf of us all.** "I am astonished to hear about the recent decision by NICE to not recommend SGLT2i's for those Heart Failure Patients with Preserved Ejection Fraction or mildly reduced ejection fraction. I believe, the reason for this is that this treatment is not deemed to be cost-effective. I cannot see why cost would be an issue when clinical trials have shown benefits such as improved Quality of Life, reduced hospital admissions and improved outcomes regarding life expectancy. I urge NICE to reconsider their decision and give this group of patients the opportunity they deserve".	

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			We appreciate your consideration on this matter; we hope this response will go some way to a reconsideration of this decision.	
57	Consultee	The Pumping Marvellous Foundation	**Section 3.27 Committee cost-effectiveness estimates** We would also like to note that Patients with heart failure and an ejection fraction more than 40% should not be held to the lower end of the willingness to pay threshold of £20000 per QALY but instead should have access up to the £30,000 per QALY. NICE would not deny patients with cancer, who have a comparable prognosis as patients with heart failure with an ejection fraction of more than 40%, access to innovations up to and sometimes exceeding the £30000 per QALY threshold. It is clear thst the decision is inappropriate, for a population of patients that does not have any other form of treatment.	Thank you for your comment. The committee noted the unmet need in this population. Above a most plausible ICER of £20,000/QALY, judgments about the acceptability of the technology as an effective use of NHS resources are more likely to make reference to explicit factors including: the degree of uncertainty surrounding the ICERs.
58	Consultee	UK Clinical Pharmacy Association	The assumption that all patients with Heart failure with improved ejection fraction will be already prescribed dapagliflozin (or empagliflozin) is suspect. Not all patients with a previous diagnosis of heart failure with reduced ejection fraction will have been reviewed over the last 2 years and may have missed out on this treatment. If this recommendation is made they will be excluded from consideration of this disease modifying treatment.	Thank you for your comment. The committee noted the unmet need in this population and considered this in its decision making. Please see section 3.2 of the FDG
59	Consultee	UK Clinical Pharmacy Association	The cohort studied in this trial do not have any disease modifying treatments available to them, only treatment of co-morbidities. If dapagliflozin is not recommended as a treatment for Heart failure with preserved ejection fraction, patients and clinicians continue to have limited treatment options.	Thank you for your comment. The committee noted the unmet need in this population and considered this in its decision making. Please see section 3.2 of the FDG
60	Consultee	UK Clinical Pharmacy Association	This patient group accounts for a large proportion of hospital admissions. In view of our ageing population and increasing prevalence of heart failure with preserved ejection fraction, the pressure of recurrent hospitalisations on health services will only increase in the future. This recommendation does not allow the use of a treatment that could reduce these hospitalisations.	Thank you for your comment. The committee noted the unmet need in this population and

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				considered this in its decision making. Please see section 3.2 of the FDG
61	Consultee	UK Clinical Pharmacy Association	It is estimated that patients with mildly and preserved ejection fraction have between 6-12 GP visits per year. Dapagliflozin has been shown to improve the QOL with significant improvement in KCCQ scores. This could reduce the number of GP visits this patient group might need. There was a numerical reduction in cardiovascular mortality (not powered to show a significance) and an improvement in KCCQ scores is indirectly linked to reducing the risk of death.	Thank you for your comment. The committee considered all the evidence submitted, including from both clinical experts and the literature.
62	Public	[redacted]	To those it may concern, Regarding NICE GID-TA10942 (Dapagliflozin for treating chronic heart failure with preserved or mildly reduced ejection fraction). I am writing on behalf of the South Coast Heart Failure departments (Trust and community). Our hospitals and community services (University Hospitals Southampton, Isle of Wight and Portsmouth Hospitals University NHS Trust) serve a combined population of approximately 2.7 million patients. Heart failure is a condition that necessitates a relatively long length of stay, at double the average LOS for all conditions. The changing population demographics and co-morbidity burden mean that heart failure with mildly reduced and preserved ejection fraction is set to become the dominant subtype. Following an admission with decompensated heart failure there are high rates of mortality and readmission and markedly impaired quality of life. At present the only treatment option available is to manage symptoms by decongestion with loop diuretics. As heart failure Cardiologists and Physicians working with the wider MDT, we are acutely aware of the growing pressure on the emergency and acute medical departments at our respective hospitals. Any treatment which has the capability to reduce rates of heart failure hospitalisation should be considered within the wider pressures on the NHS. Deliver-HF has demonstrated an early risk reduction in heart failure hospitalisation, with separation of the treatment and placebo curves seen within the 0-3 month period. Patients with heart failure with preserved ejection fraction are more likely to be elderly and co-morbid. The consequence of an inpatient episode in this cohort is often functional decline. Frail patients are likely to develop sarcopenia, suffer complications of inpatient management such as falls and infection and lose mobility. In our experience many patients never regain the quality of life they enjoyed before being hospitalised with heart failure. Often a heart failure admission is followed by a readmission at a point before quality of life has recovered to baseline, beginning a ‘step-wise’ decline in overall health. For this reason, we contest that the impact of a heart failure hospitalisation is limited to 6 months post discharge. We would like to highlight that heart failure with mildly reduced and preserved ejection fraction is a spectrum of disease severity. Some patients will be higher risk and this can be determined by NYHA class, magnitude of NT-	Thank you for your comments. The committee concluded that there is an unmet need for people with heart failure with preserved or mildly reduced ejection fraction and a new treatment option for this group would be welcome (see section 3.2 of the FDG). The committee considered clinical experts’ opinion and the company’s additional data on the duration of impact of heart failure events on quality of life in its decision making. It concluded that its preferred HHF disutility period is 6 months (see section 3.17 of the FDG). The committee considered all the

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			proBNP (or BNP) elevation, requirement for inpatient management, and presence of co-morbidities. We would like to ensure that our high-risk patients do not miss out on a treatment which may improve quality of life and reduce readmissions because it has been determined not be cost effective in the population as a whole. It is important to reiterate that for patients with HFPEF, still a high risk group, there is no other life changing therapy. The trial point estimate of benefit is in a position that would normally be considered and approved by NICE. In addition, published meta-analysis demonstrates no modification of effect according to ejection fraction. It is vital that patients do not have inequitable access to heart failure care solely based on their ejection fraction. As heart failure specialists we have positive experience of using SGLT2 inhibitors widely in heart failure with reduced ejection fraction. From this basis we would like to be able to recommend the use of SGLT2 inhibitors in heart failure with mildly reduced and preserved ejection fraction to improve quality of life and reduce risk of heart failure hospitalisation. On behalf of the Trust base and community heart failure teams at University Hospitals Southampton, Isle of Wight and Portsmouth Hospitals University NHS Trust. [redacted]	evidence submitted, including evidence from clinical trials, patient and clinical experts, the Assessment Group's economic analysis and the companies' submissions in its decision making. Its recommendation was based on the available evidence.
63	Public	[redacted]	**Question: Has all of the relevant evidence been taken into account?** Response: No, it doesn't appear to have been. The pre-specified individual patient level data pooled analysis demonstrating a clear, consistent, and meaningful cv mortality benefit, for the first time in this population of patients, who to date have had no evidence-based therapies does not appear to have been fully appreciated. **Question: Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?** Response: The cost-effectiveness interpretations appear to assume no cv benefit (see above) nor recognise the prognostic importance of symptomatic deterioration nor heart failure hospitalisation in this cohort of patients. From the national heart failure audit, in-patient mortality from heart failure is 9%. Heart failure represents the condition with single biggest cost to the NHS, predominantly via hospitalisations. Patients with heart failure often have very prolonged and complicated hospital admissions and to date there has been nothing to prevent these prior to these data. Hospitalisations in DELIVER were reduced within two weeks, which if translated to a decrease in NHS hospitalisations would be welcomed by all given the current stresses on services. **Question: Are the recommendations sound and a suitable basis for guidance to the NHS?** Response: No, prior to the DELIVER trial, other than loop diuretics, patients with HF with an EF>40%, who represent a broad range of cardiomyopathy patients, had no other treatment options, and had a prognosis that is	Thank you for your comments. The committee considered all the evidence submitted, including evidence from clinical trials, patient and clinical experts, the Assessment Group's economic analysis and the companies' submissions in its decision making. Its recommendation was based on the available evidence. Dapagliflozin has been recommended by the committee for people with heart failure with preserved or mildly reduced ejection fraction.

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			worse than most cancers. The DELIVER trial represents a paradigm shift in the management of this patient group, with evidence of both symptomatic relief and CV mortality benefit. Dapagliflozin should be recommended in patients with HF>40% and given the familiarity in primary care of the drug and the number of such patients within primary care, patients should not have to wait for specialist advice before being prescribed Dapa for this condition. Hospital specialist MDTs do not currently have capacity and re-referral of already diagnosed patients who should be initiated in primary care. **Question: Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?** Response: HF with preserved ejection fraction tends to affect the elderly (although the young too in those with inherited cardiac conditions) and therefore, given the same relative risk reduction in mortality is seen in the younger patients with reduced ejection fraction in Dapa-HF as in older cohort of preserved ejection fraction in DELIVER, HFpEF should be approved in the same way as HFrEF is approved. Were the current recommendations to persist, those patients with diabetes or CKD and HFpEF would have access to this disease-modifying agent and those without would not.	
64	Public	[redacted]	**Question: Has all of the relevant evidence been taken into account?** Response: Yes I have looked at all the evidence. **Question: Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?** Response: I agree with the cost effectiveness evidence. They are reasonable. **Question: Are the recommendations sound and a suitable basis for guidance to the NHS?** Response: I am in disagreement with the guidance. I am the first HCP in the UK to set up a Cardio Metabolic Clinic in the NHS. I have had persoanl experience in managing HfpEf patients , hundreds of them. I can vouch that SGLT2i as per evidence and reseach have played very important role in managing these complex patients. All range of heart failure patients should get SGLT2i as part of their four pillars." The recommendations should be to use in Hfpef patients as per research globally. When the whole world is using it for hfpef and it is in the best interest of the patient. I have personally used this in many Hfpef patients & they have shown several advantages which will lead to improvement in morbidity & mortality of these group of patients.	Thank you for your comments. Dapagliflozin has been recommended by the committee for people with heart failure with preserved or mildly reduced ejection fraction.

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			Question: Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity? Response: There is no discrimination in the document. No all good in this section.	
65	Public	[redacted]	**Question: Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?** Response: The data is hard to use to persuade us it has a Quality of Life (QoL)/symptomatic improvement. The outcome is mainly driven by reduced hospitalisation for heart failure or worsening heart failure episode - both of these could be argued to improve QoL for patients. There is a significant numerical change between KCCQ score but it is not possible to see if the KCCQ change from baseline in the Dapagliflozin arm is >5 points (which is deemed a significant change in QoL). We feel the assumption of 6 GP visits per year is not evidenced based and, therefore, not a reliable marker of cost. The meta-analysis of Dapagliflozin across all HF syndrome shows a significant CV death reduction RRR 14% and we feel also that dapagliflozin does reduce hospitalisations, improve QoL and symptoms for patients with HFmEF and HFpEF. **Question: Are the recommendations sound and a suitable basis for guidance to the NHS?** Response: We feel NICE should focus on the QoL benefits to patients as QoL matters. Achieving prognostic benefit in this heterogeneous group is difficult. We think that the effect of a long (> 1 week) hospitalisation for a probably elderly, co morbid patient is very difficult to assess and we suspect has a very long impact on the QoL. Furthermore, we know that longer hospitalisations are likely to have an impact on consumption of social care resource when patients decondition so we think that reduction in HF hospitalisation for these patients is long, and the economic impact almost certainly underestimated. We believe very strongly that a focus on analysis of effect on QoL is actually the most important metric to a patient and, that given the number of other medical complaints that these patients have, any beneficial effect on QoL is of high importance. We feel that dapagliflozin does reduce hospitalisations. improve QoL and symptoms for patients with HFmEF and HFpEF.	Thank you for your comment. Symptoms and quality of life are captured within the economic modelling calculations which use quality-adjusted life years (QALYs). Please see section 3.16 of the FDG for more details.
66	Public	[redacted]	**Question: Has all of the relevant evidence been taken into account?** Response: There is significant unmet need, with trials of all other classes of agent e.g. ARB/ ARNI/ Digoxin/ MRA failing to demonstrate any benefit in patients with HF and EF>40% • Jund et al. demonstrate consistent RRR in mortality across the range of ejection fraction with no attenuation at higher EFs • Vaduganathan et al. demonstrated that dapagliflozin can add up to 2.4 years of event-free survival in this highly morbid, currently untreated group of patients.	Thank you for your comments. The committee considered all the evidence submitted, including evidence from clinical trials, patient and clinical experts, the Assessment Group's economic analysis and the

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			• Kosiborod et al. and Ostrominski demonstrated significant improvement in quality of life as measured by KCCQ and NYHA respectively with comparable magnitude of effect as seen in Dapa-HF and Paradigm studies. • Butt et al. demonstrated that even frailest of patients derive benefit from Dapagliflozin and that it was as well tolerated as placebo even in the frailest of patients **Question: Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?** Response: There is a clear and established causative link between heart failure hospitalisations and mortality in heart failure. • Heart failure symptoms are highly predictive of overall prognosis • Patients with HF and ejection fraction>40% do not currently have access to any evidence-based therapies and therefore Dapagliflozin represents true innovation • Patients with HF and ejection fraction>40% should not be held to the lower end of the willingness to pay threshold ie £20000 per QALY but instead should have access up to the £30000 per QALY threshold • Patients with cancer have a comparable prognosis as patients with HF and ejection fraction>40% and have access to innovations up to and sometimes exceeding the £30000 per QALY threshold **Question: Are the recommendations sound and a suitable basis for guidance to the NHS?** Response: Dapagliflozin is widely prescribed in primary care for diabetes and CKD at the same dose and frequency and with the same counselling as for HF>40% • People with HF>40% have been discharged to primary care due to the lack of evidence-based therapies and lack of commissioning of secondary care services • Secondary care are overwhelmed managing patients that require specialist input and expertise e.g., HF with EF<40% where other treatment options are available • Dapagliflozin should be available to any patient diagnosed with HF >40% and initiation should not depend on specialist advice which is time-consuming and represents significant opportunity costs for the specialist **Question: Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?** Response: HFpEF tends to be a disease of elderly women and therefore this group of patients should have equitable access to Dapagliflozin as the younger more gender-balanced diabetes and CKD cohorts are routinely initiated in primary care	companies' submissions in its decision making. Its recommendation was based on the available evidence. Dapagliflozin has been recommended by the committee for people with heart failure with preserved or mildly reduced ejection fraction.

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67	Public	[redacted]	I am writing this purely to provide what I hope is useful information. I will be [redacted] years of age on [redacted] and attend a local heart care clinic plus a local physical play group, both, generally on a weekly basis,in an effort to keep me fit for as long as possible. (I played tennis until nearly [redacted]) My EF is around 20% and was first evident about [redacted], and since the first echogram I have been taking [redacted]. My Cardiologists have recently advised me to take Dapagliflozin which I have now commenced. My query , to be answered is, am I now taking too many tablets, and duplicating. NICE recommendations are that Dap can be taken with the other drugs. Ignoring my own status, it would seem to me that physical fitness may have a significant effect on HF	Thank you for your comment. Unfortunately this guidance cannot address your individual circumstance directly. Please seek advice from your GP or specialist doctor

NICE National Institute for Health and Care Excellence

Dapagliflozin for treating chronic heart failure with preserved or mildly reduced ejection fraction [ID1648]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on 1 March 2023. 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

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Dapagliflozin for treating chronic heart failure with preserved or mildly reduced ejection fraction [ID1648]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on 1 March 2023. Please submit via NICE Docs.

Name of commentator person completing form:	[redacted] Market Access Team Lead
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.
Summary	**Executive Summary** The Company would like to thank the External Assessment Group (EAG) and the National Institute for Health and Care Excellence (NICE) Appraisal Committee for their review of the submission for dapagliflozin in patients with heart failure (HF) and a left ventricular ejection fraction (LVEF) >40% (hereafter referred to as "patients with HF and an LVEF >40%" for ease of reading), and the comments that have been provided as part of the Appraisal Consultation Document (ACD). Following the ACD, the Company has accepted the following Committee's preferred base case settings: • Including age-adjusted and multiplicative population utilities (Section 3.16 of the ACD); • The hospitalisation for heart failure (HHF) disutility is applied for 6 months (Section 3.17); • The Healthcare Resource Group (HRG) cost code (EB03E), associated with less severe HHF, is used to cost HHF (Section 3.19); • The economic model assumes 6 annual general practitioner (GP) visits per year (Section 3.21); • Removal of amputation as an adverse event in the economic model (Section 3.22). This results in a revised base case deterministic incremental cost-effectiveness ratio (ICER) for dapagliflozin in addition to standard of care (SoC), compared with SoC alone, of £8,975 per quality-adjusted life year (QALY), and a probabilistic ICER of £9,226 per QALY, with 85% and 90.7% probability of being cost-effective at the NICE willingness-to-pay (WTP) threshold of £20,000 per QALY and £30,000 per QALY, respectively. Full results of the revised base case and additional scenario analyses are provided in Appendix 1 below. As part of the draft guidance (Section 3.26), the Committee highlighted some residual uncertainty relating to the modelling of survival, which could be resolved through consultation, by the Company submitting the following:

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	• Scenario analyses exploring the exclusion of a direct and/or indirect treatment benefit for dapagliflozin on cardiovascular (CV) and all-cause deaths, with refitting of the survival models whenever parameters are excluded (issue #1); • Evidence that the economic model can reproduce the outcomes observed in DELIVER (issue #2). The company believe that the scenario analyses requested are overly pessimistic, however in response to the ACD, the Company has provided the additional information requested in Section 3.26 of the ACD which serves to resolve the uncertainties relating to the modelling of survival. We trust that the outputs of these will enable the Committee to make a positive recommendation for dapagliflozin. The Committee requested scenario analyses exploring the exclusion of a direct and/or indirect treatment benefit for dapagliflozin on cardiovascular mortality (CVM) and all-cause mortality (ACM). In both scenarios, the ICERs (£19,261 per QALY and £26,435 per QALY respectively) are below the willingness to pay threshold demonstrating that dapagliflozin represents a cost-effective use of NHS resources even in the most overly pessimistic scenarios. The data presented for the scenario analyses (issue #1) and validation that the economic model reproduces DELIVER trial data (issue #2) provides compelling evidence to resolve the initial uncertainties highlighted in the ACD. The Committee should now have full confidence and reassurance that dapagliflozin represents a highly innovative and cost-effective technology, for this underserved patient population, who will otherwise, continue to face an extremely high burden of disease without any disease-modifying treatments available.
Issue 1	**CVM and ACM extrapolations should consider both the treatment effect of dapagliflozin and the impact of KCCQ-TSS quartile on mortality, incorporating the data from the pivotal DELIVER trial. It is inappropriate to arbitrarily assume equivalence between dapagliflozin and placebo with respect to CVM or ACM.** The extrapolation of the observed CVM and ACM data for dapagliflozin and placebo from the DELIVER trial represents the most robust methodology for the base case economic analysis and is in line with NICE's own methodology. However, upon request from the Committee, the Company has conducted two additional scenario analyses for this response: • Scenario 1: Removal of the dapagliflozin treatment effect as a candidate variable from the regression models used to generate CVM and ACM extrapolations, thereby removing any direct effect of dapagliflozin on CVM and ACM versus placebo; • Scenario 2: Removal of both the dapagliflozin treatment effect, and KCCQ-TSS quartile as candidate variables from the regression models used to generate CVM and ACM extrapolations, thereby removing any direct or indirect effect of dapagliflozin on CVM and ACM versus placebo.

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	Full methodological details of these scenario analyses are provided in Appendix 2. However, the Company does not believe that these scenarios are valid for decision-making, for the reasons detailed below. **The DELIVER trial was not powered to detect statistically significant differences for dapagliflozin versus placebo with respect to CVM or ACM.** As previously detailed in the Company's response to Clarification Questions B14–B16, the published literature extensively highlights the limitations associated with p-values and the importance of interpreting them correctly.[1, 2] In this case, non-significant p-values do not mean that dapagliflozin has no impact on CVM or ACM versus placebo. An alternative conclusion is [redacted]. The statistical analyses of the DELIVER trial were planned to ensure sufficient statistical power for hypothesis testing of the primary endpoint, which was a composite endpoint of CV death, HHF or UHFV.[3] [redacted] in the occurrence of CVM or ACM as standalone endpoints.[3] This conclusion is supported by the forest plot presented in Figure 1 below, which demonstrates that all of the components of the primary composite endpoint [redacted] to the statistically significant treatment effect of dapagliflozin for the primary composite endpoint observed in DELIVER. These data do not support a conclusion that dapagliflozin would not reduce CVM compared to placebo.[4]

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Figure 1: Forest plot of the primary composite endpoint (CV mortality and HF events) and the individual components in DELIVER[a]

Abbreviations: CI: confidence interval; CV: cardiovascular; Dapa: dapagliflozin; FAS: full analysis set; HF: heart failure; HHF: hospitalisation for heart failure; HR: hazard ratio; N: number of patients in treatment group; T2DM: type 2 diabetes mellitus; UHFV: urgent heart failure visit.
Source: DELIVER CSR.[4]

Pooled analyses demonstrated that dapagliflozin statistically significantly reduced CVM and ACM versus placebo across the spectrum of patients with HF, with no evidence of effect modification by LVEF.

A pre-specified pooled analysis of the individual patient-level data from both the DAPA-HF and DELIVER trials, published in *Nature Medicine,* was specifically designed to be powered to detect a difference in the primary endpoint of CVM.[5] Across this pooled cohort, dapagliflozin was associated with statistically significant reductions in both CVM (HR: 0.86, 95% CI: 0.76, 0.97) and ACM (HR: 0.90, 95% CI: 0.82, 0.99) when compared to placebo. In both cases, across this pooled analysis, there was no evidence of effect modification by LVEF when examined as either a categorial or continuous variable (p-value for interaction: 0.63 and 0.94 for CVM and 0.79 and 0.58 for ACM, respectively).

This is also aligned with the Summary of Product characteristics (SmPC) for dapagliflozin, where the Medicines and Healthcare products Regulatory Agency (MHRA) noted "In a pre-specified patient level pooled analysis of the DAPA-HF and DELIVER studies, dapagliflozin

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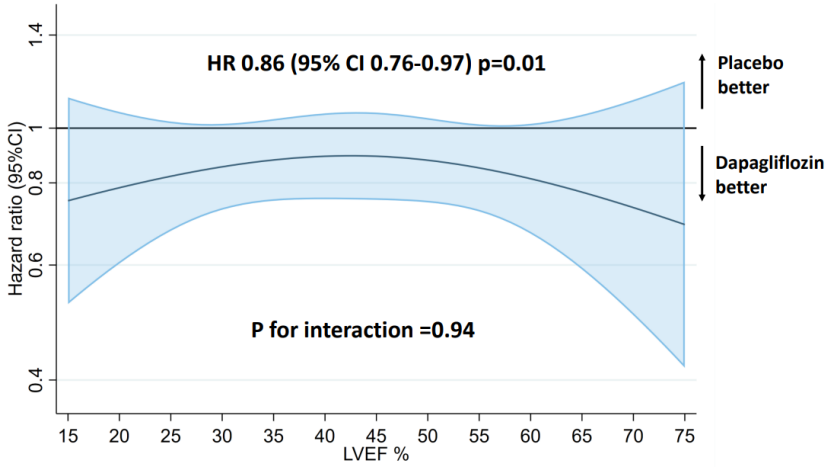
compared with placebo reduced the risk of cardiovascular death. Both studies contributed to the effect".[6]

The consistent effect of dapagliflozin versus placebo, irrespective of LVEF, is highlighted in Figure 2 and Figure 3 below.

Figure 2: Effect of dapagliflozin on CVM across the range of LVEF based on the pooled DAPA-HF and DELIVER dataset



Footnotes: The horizontal blue line shows the continuous HR across the range of LVEF and the shaded area around this line represents the 95% CI from Cox's model. The overall effect of treatment in the pooled population is shown as an HR (95% CI) with the two-sided P value from Cox's model for Wald's test of interaction between treatment and LVEF. No adjustment for multiple comparisons was made. Restricted cubic spline and interaction P value derived from LWYY model for total HF hospitalisation.
Abbreviations: ACM: all-cause mortality; CI: confidence interval; CV: cardiovascular; CVM: cardiovascular mortality; HF: heart failure; HR: hazard ratio; LVEF: left ventricular ejection fraction; LWYV: Lin-Wei-Yang-Ying model.
Source: Jhund et al. (2022).[5, 7]

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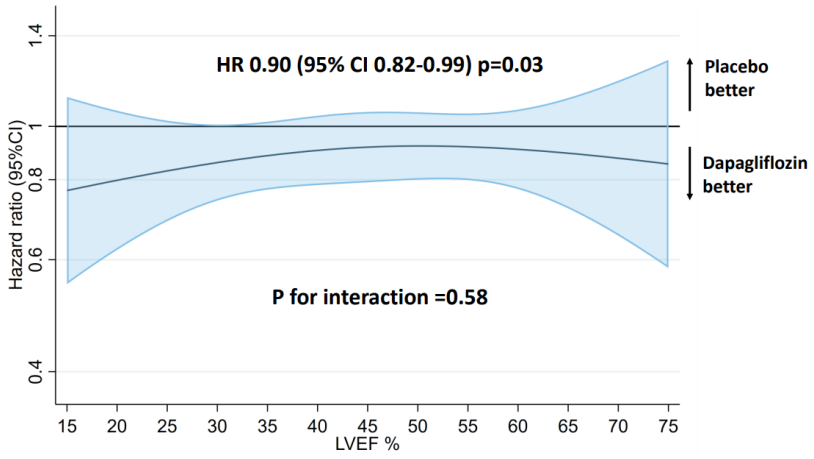
Figure 3: Effect of dapagliflozin on ACM across the range of LVEF based on the pooled DAPA-HF and DELIVER dataset



Footnotes: The horizontal blue line shows the continuous HR across the range of LVEF and the shaded area around this line represents the 95% CI from Cox's model. The overall effect of treatment in the pooled population is shown as an HR (95% CI) with the two-sided P value from Cox's model for Wald's test of interaction between treatment and LVEF. No adjustment for multiple comparisons was made. Restricted cubic spline and interaction P value derived from LWYY model for total HF hospitalisation.
Abbreviations: ACM: all-cause mortality; CI: confidence interval; CV: cardiovascular; CVM: cardiovascular mortality; HF: heart failure; HR: hazard ratio; LVEF: left ventricular ejection fraction; LWYV: Lin-Wei-Yang-Ying model.
Source: Jhund et al. (2022).[5, 7]

Statistically significant and clinically meaningful reductions in HHF and improvements in mean KCCQ score for dapagliflozin versus placebo provide a biologically plausible mechanism by which dapagliflozin may reduce CVM and ACM versus placebo.

As part of this appraisal, clinical experts stated that it was plausible that dapagliflozin could reduce CVM in the medium to long-term by reducing HHF in the short to medium term. The experts highlighted that HHF is associated with a substantial quality of life burden and risk of infection and proposed that reducing HHF may be associated with a reduction in the overall decline in heart function and quality of life that people with chronic HF typically experience over time. In addition, the Committee acknowledged that it is plausible that dapagliflozin may directly impact ACM and CVM versus placebo in patients with HF and an LVEF >40%.

Furthermore, the DELIVER trial demonstrated that dapagliflozin provided improved KCCQ-TSS, Physical Limitation Score (PLS), Clinical Summary Score (CSS), and Overall Summary Score (OSS) as early as 1 month following treatment initiation, with benefits sustained at 8 months.[8] Significantly fewer patients treated with dapagliflozin experienced clinically meaningful deterioration versus placebo, and more patients receiving dapagliflozin experienced clinically meaningful improvements in symptoms than those receiving placebo. Finally, the benefits of dapagliflozin on symptomatic improvement at 8 months after

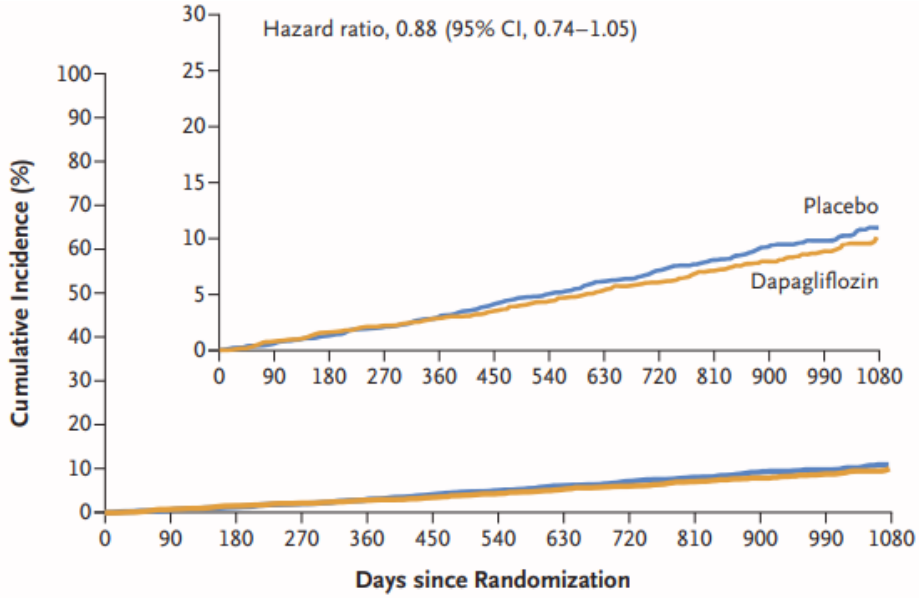
randomisation were generally consistent across key demographic and clinical subgroups, including baseline LVEF.[8]

There is extensive evidence in the published literature which highlights the relationship between KCCQ score and mortality; for example in a study of over 23,000 patients, Johansson *et al.* (2021) concluded that health-related quality of life, measured using the KCCQ questionnaire, was a "strong and independent predictor of all-cause death" in HF.[9]

In a pre-specified analysis of the DELIVER trial, patients with a lower baseline KCCQ-TSS were found to have a higher likelihood of being previously hospitalised for HF. Further, patients with lower baseline KCCQ-TSS experienced higher rates of CV death or worsening HF (7.8, 5.6, and 4.8 per 100 patient-years in patients across KCCQ-TSS terciles of <63, 63–84 and >84, respectively; p<0.001).[8]

There is, therefore, compelling evidence and rationale to conclude that given a sufficient number of events and follow-up, a statistically significant difference would be observed between dapagliflozin and placebo with respect to CVM and ACM in the DELIVER trial. This is based on the delayed separation of Kaplan-Meier (KM) curves for CVM in the DELIVER trial (Figure 4 below), and assuming the observed treatment effect would be maintained beyond the follow-up duration of the DELIVER trial.

Figure 4: KM plot of CV mortality in DELIVER



Abbreviations: CI: confidence interval; CV: cardiovascular; Dapa: dapagliflozin; D: dapa 10mg; HR: hazard ratio; KM: Kaplan-Meier; N: number of patients; P: placebo.
Source: Solomon *et al*. (2022).[10]

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	The use of the observed DELIVER trial data is more robust than arbitrary assumptions. In any situation, the use of observed clinical trial data directly should be considered to represent the most appropriate approach for any economic model which is in line with NICE's methods manual, *in lieu* of arbitrary assumptions of clinical equivalence. This approach of using the clinical trial data directly, [redacted], is aligned with the previous NICE appraisals for both dapagliflozin and empagliflozin as treatments for HF and an LVEF ≤40% (TA679[11] and TA773[12]), where the Committee did not state any preference for the removal of a direct or indirect effect on mortality. The Committee's requested scenario analyses of assuming equivalence in terms of CVM and ACM, regardless of the clinical trial results, would directly contradict the approach adopted in these previous appraisals in a very similar indication. Further, assuming clinical equivalence is in direct contrast to NICE's recommendations for their preferred sources of evidence, as the NICE methods manual states that "for relative treatment effects there is a strong preference for high-quality randomised controlled trials (RCTs)", and "the trial should, in principle, provide a minimally biased estimate of the size of any benefits or risks associated with the technology relative to those associated with the comparator. RCTs are, therefore, considered to be most appropriate for measures of relative treatment effect." The use of the observed trial data directly is, therefore, aligned with this guidance and the trial should, in principle, provide a minimally biased estimate of the size of any benefits or risks associated with the technology relative to those associated with the comparator.[13] The Company, therefore, maintains that the use of the observed data from the DELIVER trial to inform the treatment effect of dapagliflozin on CVM and ACM within the base case economic analysis represents the most appropriate methodology. **Any uncertainty relating to the magnitude of treatment effect of dapagliflozin on CVM and ACM has already been captured within the probabilistic sensitivity analysis (PSA), which demonstrates that the base case cost-effectiveness analysis is robust to parameter uncertainty.** It is important to consider that any uncertainty surrounding the magnitude of the treatment effect of dapagliflozin on CVM and ACM has already been robustly explored as part of the PSA. Across each iteration of the PSA, the magnitude of dapagliflozin treatment effect was varied based on probability distributions derived from the uncertainty surrounding the point estimates in the DELIVER trial. Table 1 provides summary statistics for the treatment effects modelled across each iteration of the PSA (based on the revised base case, as detailed in Appendix 1), demonstrating that the average treatment effects modelled for dapagliflozin (in terms of HRs for CVM and ACM versus placebo) are [redacted] for CVM and [redacted] for ACM, directly replicating the observed HRs for

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dapagliflozin in terms of CVM and ACM from the DELIVER trial. Notably, Table 1 illustrates that the PSA already considers the probability of dapagliflozin being equal or worse than placebo at reducing CVM and ACM, respectively, with only [redacted]% and [redacted]% of iterations modelling an assumption that dapagliflozin is equal or worse than placebo at reducing CVM and ACM. Considering a certain proportion of iterations without a treatment effect on CVM and ACM within the wider PSA is a more robust method of exploring this parameter uncertainty than extreme scenario analyses removing the treatment effect altogether.

Table 1 also illustrates that the PSA captures an even more pessimistic worst case scenario compared with an assumption of equal efficacy, with worst case HRs of [redacted] and [redacted] for dapagliflozin versus placebo in terms of CVM and ACM, respectively. Nevertheless, the PSA considers both the lower and upper bounds of uncertainty and so provides a complete picture of parameter uncertainty, rather than the sole consideration of an extremely pessimistic assumption of equal efficacy.

Table 1: Summary statistics of the CVM and ACM treatment effects considered in the PSA (revised base case)

Outcome	HRs (95% CrI)	Proportion of iterations in which the HR<1	Range of HRs considered
CVM	[redacted]	[redacted]	[redacted]
ACM	[redacted]	[redacted]	[redacted]

Abbreviations: ACM: all-cause mortality; CrI: credible interval; CVM: cardiovascular mortality; HR: hazard ratio; PSA: probabilistic sensitivity analysis.

A pessimistic scenario analysis, in which direct effects of dapagliflozin on CVM and ACM results are removed, results in an ICER of £19,261 per QALY. This is less than the £20,000 per QALY cost-effectiveness threshold. An extremely pessimistic scenario, in which all direct and indirect effects of dapagliflozin on CVM and ACM are removed, results in an ICER of £26,435 per QALY, less than the £30,000 per QALY cost-effectiveness threshold.

For the reasons detailed above, these scenario analyses removing a direct or indirect effect of dapagliflozin on CVM and ACM are not evidence based and cannot be considered clinically plausible.

Nevertheless, in response to the Committee's requests, these scenario analyses have been conducted as part of this ACD response. In these scenario analyses, the regression models for CVM and ACM have been re-run, excluding the dapagliflozin treatment effect (Scenario 1), and excluding the dapagliflozin treatment effect as well as the indirect effect on mortality via KCCQ-TSS quartile (Scenario 2). Full methodological details of these scenario analyses, which have been run on the revised base case following the ACD response, are provided in Appendix 2, and the results of these scenario analyses are presented in Table 2 below.

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It should be noted that in these scenario analyses, the resulting extrapolations for dapagliflozin and SoC are not clinically valid when compared to the observed KM data in the DELIVER trial, as highlighted in Figure 5 to Figure 8 below. The CVM extrapolations in Scenarios 1 and 2 underestimate the risk of CVM for SoC, while the ACM extrapolations overestimate the risk of ACM for dapagliflozin. In contrast, as detailed in Response to Issue #2, the revised base case CVM and ACM extrapolations closely match the observed KM data from the DELIVER trial.

Figure 5: CVM extrapolations for Scenario 1 compared with the KM data from DELIVER

Abbreviations: CVM: cardiovascular mortality; KM: Kaplan-Meier; SoC: standard of care.

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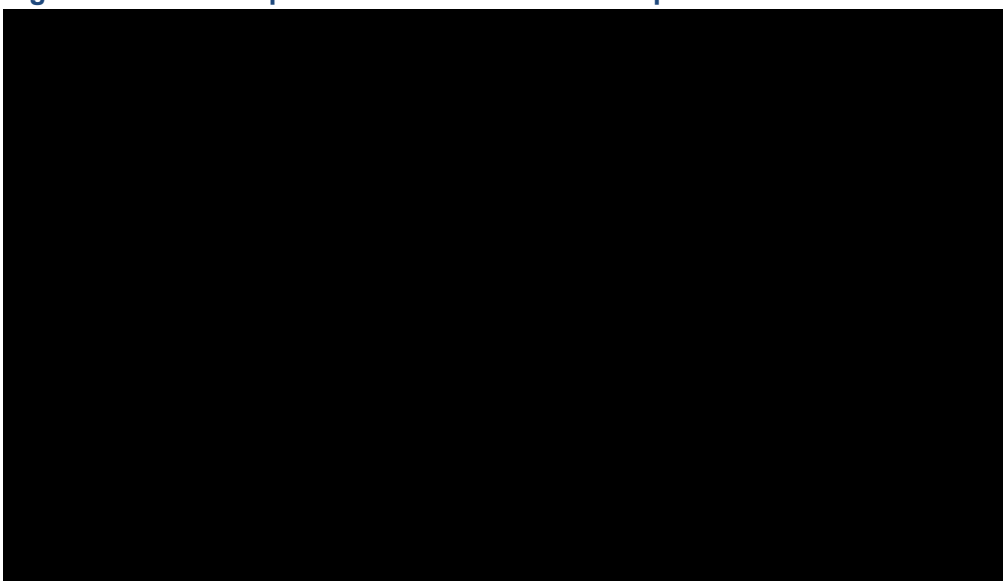
Figure 6: ACM extrapolations for Scenario 1 compared with the KM data from DELIVER



Abbreviations: ACM: all-cause mortality; KM: Kaplan-Meier; SoC; Standard of care.

Figure 7: CVM extrapolations for Scenario 2 compared with the KM data from DELIVER

Abbreviations: CVM: cardiovascular mortality; KM: Kaplan-Meier; SoC: standard of care.

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Figure 8: ACM extrapolations for Scenario 2 compared with the KM data from DELIVER

Abbreviations: ACM: all-cause mortality; KM: Kaplan-Meier; SoC; Standard of care.

Nevertheless, despite the clinical plausibility concerns and pessimistic nature of these scenario analyses dapagliflozin remains a cost-effective use of NHS resources, with an ICER of less than £20,000 per QALY in Scenario 1 and an ICER of less than £30,000 per QALY in Scenario 2.

As such, the Company believes that sufficient evidence has been provided for any remaining uncertainty in this appraisal to be fully resolved, and given the cost-effective ICERs presented below, dapagliflozin should be recommended as a vital new treatment for patients with HF and an LVEF >40%, who will otherwise continue to face an extremely high burden of disease without any disease-modifying treatments available.

Table 2: Additional scenario analysis results (run based on the Company based case following the ACD response)

Results	Deterministic results		
	Inc. costs	Inc. QALYs	ICER
Company base case (following clarification questions)	£1,885	0.251	£7,519
Revised base case (following the ACD response)	£2,117	0.236	£8,975
Scenario 1 (removal of dapagliflozin treatment effect from the regression models)	£1,928	0.100	£19,261
Scenario 2 (removal of dapagliflozin treatment effect and indirect effect via KCCQ from the CVM and ACM extrapolations)	£1,922	0.073	£26,435

Abbreviations: ACD: Appraisal Consultation Document; ACM: all-cause mortality; CVM: cardiovascular mortality; ICER: incremental cost-effectiveness ratio; KCCQ: Kansas City Cardiomyopathy Questionnaire; QALY: quality-adjusted life year.

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	If NICE still perceive there to be any uncertainty for dapagliflozin in relation to CVM and ACM, Scenario 1 should be considered to represent the most relevant pessimistic scenario analysis, in line with precedent from TA773.[12] Finally, it should be noted that similarly pessimistic, worst case scenarios were suggested by the EAG as part of the NICE appraisal for empagliflozin as a treatment for patients with HF and an LVEF ≤40% (TA773).[12] Within this appraisal, the submitting Company opted to remove the direct effect of empagliflozin on mortality from their base case analysis, but did not remove the indirect effect, nor did the Committee state any preference for the indirect effect to be removed. This is despite the lack of significant reductions in CVM or ACM being observed in the pivotal trial for empagliflozin versus placebo in this indication (EMPEROR-Reduced).[12] As such, the Company considers that Scenario 1, with an ICER of £19,261, should be considered the most relevant pessimistic scenario analysis, given the previous precedent of economic modelling approaches in HF. In this scenario analysis, dapagliflozin remains a highly cost-effective treatment option and, taken together with the revised base case ICER of £8,975, should allay any uncertainty as to whether dapagliflozin should be recommended for use in UK clinical practice.
Issue 2	**The base case economic model structure is appropriate, in line with past precedent for modelling approaches for patients with HF.** The ACD (Section 3.13, Page 15) highlighted that the modelling approach used in this appraisal is *'not a standard modelling approach and could affect model validity'* and noted that *'a patient-level multi-state simulation model may have been more appropriate because it generates a patient history and considers competing risk'.* It is important to reiterate that the modelling approach used in this appraisal is directly aligned with the modelling approaches used in previous NICE appraisals for dapagliflozin and empagliflozin in a similar indication (patients with HF and an LVEF ≤40%). As such, the use of a time-updated model covariate and treatment effect coefficient is considered to represent the most suitable modelling approach in this appraisal, given the past precedent that has already been set in this treatment setting. Furthermore, the Company discussed the proposed modelling approach for this appraisal with the EAG and NICE in advance of this submission. The EAG and NICE confirmed that they did not have any concerns with the Company's proposed approach, and agreed on the general alignment with the modelling approaches used in TA679,[11] with adaptations as needed to reflect the available data for patients with HF and an LVEF >40%.

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The economic model is consistent with the observed results in the DELIVER trial.

The ACD (Section 3.13, Page 15) noted that *'a model that does not replicate the trial data to an appropriate level of accuracy would lead to considerable uncertainty around the plausibility of the model results. The Committee concluded that a comparison of the overall survival and cardiovascular survival predictions from the economic model (which includes the impact of changes in KCCQ-TSS state over time) and the observed data from DELIVER is needed to determine whether the modelling approach was reasonable.'*

As previously detailed in Section B.3.12.2 of the Company Submission Document B, an extensive model validation process was undertaken during the development of the base case cost-effectiveness analysis, including comparison of the modelled outcomes versus the observed CVM and ACM data from the DELIVER trial. These comparisons were previously presented in Figure 29 of the Company Submission Document B and are re-presented in Figure 9 below for reference.

The alignment of the modelled CVM and ACM extrapolations with the KM data from the DELIVER trial suggests that there are no concerns with the validity of the modelled extrapolations within the base case economic analysis.

Figure 9: Internal validation of survival for the DELIVER ITT population[a]

[a]Solid lines are the KM from DELIVER; dashed lines are the outcomes from the model.
Abbreviations: ACD: All-cause death; CV: cardiovascular; ITT: intention-to-treat; KM: Kaplan-Meier; SoC: standard of care.

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Further model validation has also been conducted as part of this ACD response by visualising the concordance of the observed event rates from DELIVER versus the predicted event rates from the model, and calculating goodness-of-fit statistics. The 45° identity line demonstrates how well predicted event rates compare to reported event rates, with comparisons falling below the line indicative of underprediction and conversely, comparison above the line indicative of overprediction.

The comparison of the predicted event rates from the model versus the observed event rates from DELIVER are presented in Figure 10. As the observed event rates from DELIVER are unadjusted for covariate effects, a comparison using the unadjusted risk equations and survival are presented to fairly demonstrate concordance. The regression lines are consistent with the 45° identity line, indicating strong predictive strength in the model outcomes.

Figure 10: Internal validation of predicted versus observed event rates for the ITT DELIVER population

Footnotes: The solid line is the 45° identity line; dashed line is the regression line; grey shaded area is the 95% CI for the regression line.
Abbreviations: ACD: all-cause death; CV: cardiovascular; HHF: hospitalisation for heart failure; ITT: intention-to-treat; UHFV: urgent heart failure visit.

Validation was also undertaken to compare the modelled proportions of patients in each KCCQ-TSS quartile over time, compared to the observed results in the DELIVER trial. The DELIVER trial data were limited to patients with non-missing KCCQ-TSS data. Health states were based on KCCQ-TSS trial data, using quartile thresholds (Q1: TSS 0–54; Q2: TSS 55–72; Q3: TSS 73–87; Q4: TSS 88–100) and from mortality such that each patient at each timepoint was assigned a mutually exclusive health state (Q1, Q2, Q3, Q4 or death).

From Baseline to Month 8, data were assessed at scheduled study visits (Baseline, Month 1, Month 4, Month 8), and the proportion of patients in each KCCQ-TSS quartile were

calculated. Data after the Month 8 visit were analysed up to the median trial follow up (28 months) and averaged over that period (mean KCCQ-TSS per patient, which was converted into a KCCQ quartile and plotted at the midpoint of the range at 18 months). Trial results were compared to the base case cost-effectiveness analysis traces, derived from the application of transition probability matrices and adjusted survival equations in the model, as shown in Figure 11.

Figure 11: Comparison of the proportions of patients in each KCCQ-TSS quartile in the DELIVER trial versus the economic model

Footnotes: Points correspond to trial data, plotted as proportions with 95% confidence intervals while dashed lines correspond to monthly traces estimated by the cost-effectiveness model. Plotted points correspond to scheduled follow-up visits up to 8 months, and thereafter, data were averaged by patient and plotted at the midpoint of the median follow-up period to aggregate results across the variable time of the study closure visit data point.
Abbreviations: KCCQ-TSS QX: Kansas City Cardiomyopathy Questionnaire – Total Symptom Score Quartile X.

The modelled traces show good agreement with the DELIVER trial data. The greatest deviation was seen at Month 1, likely due to the averaging of observed transitions over the period from 0 to 4 months to generate the transition probability matrix used in the economic model. Further, since the single matrix is applied (by arm) over this period, it would not be expected to reproduce finer variations seen in the DELIVER trial observed over this period. Overall, and in the latter phases of the DELIVER trial period up to the median follow up time, closer alignment between observed trial data and the predicted model traces is observed.

In conclusion, the extensive model validation conducted as part of this ACD response provides confirmation that the economic model aligns with the observed results in the

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	DELIVER trial and that the modelling approach of a time-updated model covariate and a treatment effect coefficient (as per previous HF NICE appraisals TA679 and TA773[11, 12]) is appropriate for decision making.
Issue 3	**The economic model assumes equivalent transition probabilities for dapagliflozin and SoC once patients discontinue treatment with dapagliflozin.** The ACD (Section 3.15, Page 16) stated that the "*model structure may contribute to a sustained treatment effect for dapagliflozin, which may bias the cost-effectiveness results in favour of dapagliflozin*". It is important to distinguish between the differences in health state distributions in the economic model, versus a sustained or long-term assumption of treatment effect. In the DELIVER trial, dapagliflozin was associated [redacted] in KCCQ score versus placebo. Based on these results, at Month 4, a greater percentage of patients receiving dapagliflozin are modelled to be in higher KCCQ-TSS health states, compared to patients receiving SoC. At the point at which dapagliflozin is discontinued, patients in the dapagliflozin arm of the model are ascribed equivalent health state transition probabilities as patients receiving SoC, and have the same risks of mortality, HHF, UHFV and AEs as patients receiving SoC. Therefore, while the health state occupancy for dapagliflozin versus SoC differs over the time horizon of the analysis, this is due to the modelled on-treatment efficacy of dapagliflozin and not in the post-discontinuation period, where the risk of events for dapagliflozin are assumed equivalent to SoC. This is the most conservative assumption that could plausibly be made and assumes an immediate loss of any treatment effect for dapagliflozin versus placebo upon discontinuation. As such, there is no justification that the current economic modelling approach introduces bias to the cost-effectiveness results in favour of dapagliflozin.
Issue 4	**NHS Reference Costs from 2020/2021 are the most accurate representation of current clinical practice in the UK, and should be included in the base case.** As part of the ACD (Section 3.18, Page 18), the Committee concluded that both sources of NHS reference costs (2020/2021 or 2019/2020 inflated to the current cost year) were plausible, and it was uncertain which NHS reference cost values were most appropriate, given the uncertain impact of the COVID-19 pandemic. However, considering the current economic climate in the UK and the high rate of inflation, there is no evidence that the NHS has returned to operating in line with pre-pandemic conditions. As such, there is a strong risk that the inflation of pre-pandemic reference costs from 2019/2020 does not provide an accurate representation of current NHS clinical practice, which continues to be impacted by the effects of the COVID-19 pandemic.

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	As such, the Company maintains that the most recent 2020/2021 reference costs should be considered in the base case cost-effectiveness analysis as the most recent, and therefore accurate, representation of current NHS clinical practice, and no evidence to suggest otherwise.
Issue 5	**HF and an LVEF >40% is associated with a substantial clinical and economic burden in the UK, and there is a pressing unmet need for the availability of new and effective treatment options. The £30,000 per QALY gained WTP threshold is, therefore, the most appropriate for consideration in this appraisal.** The ACD (Section 3.27, Page 24) highlighted that the Committee preferred the lower bound of the WTP threshold (£20,000–£30,000 per QALY), given the large impact of the uncertainties relating to survival estimates on the ICER. Initially, as detailed extensively in response to Issue 1, the Company believes that sufficient evidence has been provided to justify the most appropriate methodology for modelling survival for dapagliflozin and placebo, and for any remaining uncertainty in this appraisal to be resolved. As such, there is no longer any rationale for the sole consideration of the lower bound of the WTP threshold. Furthermore, it is also important to reiterate the pressing unmet need for new treatment options in this highly underserved patient population. HF and an LVEF >40% represents one of the most significant healthcare challenges in the UK.[14] For these patients, the 5-year survival rate following a hospitalisation for HF (HHF) is 35%, which is worse than many cancers.[15] HF and an LVEF >40% is also associated with a considerable economic burden, driven by high hospitalisation rates; it is estimated that HF costs the National Health Service (NHS) up to 2% of its annual budget, at a cost of approximately £3 billion per year.[16-20] Further, the prevalence of HF with LVEF >40% is likely to rise in the future due to factors such as the ageing population in the UK, and rising rates of obesity and type 2 diabetes mellitus (T2DM), meaning that the clinical and economic burden associated with HF will only increase without the availability of new treatment options.[21-23] Notably, there are currently no disease-modifying treatments routinely commissioned in UK clinical practice for patients with HF and an LVEF >40%, and until now, there had not been any successful clinical trials in this setting. The distinction between HF and an LVEF >40% and LVEF ≤40% is not based on the aetiology of HF, but is the result of the historical failures of previous trials to demonstrate benefits for patients with HF and an LVEF >40%. The ACD (Section 3.2, Pages 5–6) highlighted that patient experts described that the symptoms, disease severity and impact on daily life of HF and an LVEF >40% are similar to those experienced by people with HF and an LVEF ≤40%. However, while there are a multitude of treatment options for patients with HF and an LVEF ≤40%, the patient experts highlighted the lack of hope experienced by patients with HF and an LVEF >40%, because of

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	the lack of any positive clinical trials and available treatments, and the resulting impact on patients' quality of life and mental health. This is the result of numerous clinical trials conducted over multiple decades in patients with HF and an LVEF >40%, which have failed to identify treatments that are able to provide statistically significant or clinically meaningful benefits for these patients. Consequently, there is an urgent requirement for innovative treatments, such as dapagliflozin, which have been shown to improve disease symptoms and quality of life, and to reduce hospitalisation and mortality for these patients.[10, 24] Furthermore, as part of this appraisal, one of the clinical experts highlighted that "In the UK there are around 100,000 HF admissions annually, with a long length of stay (10 days mean), so a technology with an impact on reduced admissions will have wider benefits for an NHS system currently running at capacity", highlighting the potential impact of introducing dapagliflozin on alleviating current capacity issues within the NHS. With the additional evidence provided as part of this response document, NICE can be confident that dapagliflozin represents a cost-effective treatment for this population of patients who are in significant need of new, disease-modifying treatments. It is inappropriate to anchor decision making to the lower bound of the £20,000–£30,000 per QALY WTP threshold, given the highly innovative nature of dapagliflozin, which would represent a step change in the treatment paradigm for patients with HF and an LVEF >40%, and the significant reduction in uncertainty with respect to the cost-effectiveness estimates for dapagliflozin compared to the analyses previously presented during the first Appraisal Committee meeting.
Issue 6	**Once a diagnosis of HF and an LVEF >40% is confirmed by a specialist, initiation of treatment with dapagliflozin should be permitted in either primary or secondary care without the need for further specialist advice.** The Company are concerned with the Committee's conclusion that treatment with dapagliflozin in this indication could only be started on the advice of a HF specialist. This would, in the case where NICE recommend dapagliflozin for these patients, likely lead to the majority of dapagliflozin prescriptions taking place in the secondary care setting. This is a particular concern given the current NHS capacity constraints, and the potential for dapagliflozin to alleviate these, as highlighted in Issue #5. The Company proposed that treatment with dapagliflozin in patients with HF and an LVEF >40% could be initiated either in primary or secondary care, contingent on a documented HF diagnosis by a specialist enabling the initiation of dapagliflozin in primary care without the need for further specialist advice. Prior to the publication of any positive recommendation for dapagliflozin by NICE, given the lack of disease-modifying therapies in this setting, there are likely many patients with HF and an LVEF >40% who are unlikely to go back to see a cardiologist until they experience an HF event.

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	In the event that patients have been discharged back to primary care following specialist diagnosis before a care plan is provided or treatment is initiated, it is both appropriate and optimal for the patient that primary care physicians are able to initiate therapy autonomously. This is also critical to ensure that the management of patients already diagnosed with HF and an LVEF >40% who are managed in primary care is optimised, allowing dapagliflozin to be initiated at the earliest opportunity, ideally following proactive invitation for a treatment optimisation review or alternatively, where capacity is a limitation, during their routine check-up appointment without the need for a specific or extended appointment. In the case of both an incident and prevalent population with confirmed HF and an LVEF >40%, the requirement to seek additional specialist advice before treatment initiation would delay access and create additional resource constraints in both primary and secondary care amidst the large post-COVID back-logs and NHS capacity issues still being experienced. As dapagliflozin is currently available across the primary and secondary care treatment settings for patients with T2DM, [25-27] CKD, [28, 29] including those with co-morbid HF and an LVEF >40%, and HFrEF, ,[11] clinicians across care settings have considerable clinical experience with prescribing dapagliflozin. Therefore, the additional advice of a HF specialist seems unnecessary for the initiation of dapagliflozin after HF and an LVEF >40% has already been diagnosed, and delays could be costly in terms of morbidity and mortality. Initiation of dapagliflozin for the treatment of patients with HF and an LVEF >40% in the primary care setting would improve equality of access to dapagliflozin without relying on access to specialist care, which is limited to only a few HF centres commissioning services to support patients with HF and an LVEF >40% after diagnosis, or offering specialised HFpEF clinics alongside their usual HF services.[30] Given that there is substantial clinical experience in the prescribing of SGLT2 inhibitors in primary care, the Company believes that there is no clinical rationale for restricting the initiation of dapagliflozin for patients with HF and an LVEF >40% to the advice from a HF specialist only. This may be particularly suitable for many prevalent patients with HF and an LVEF >40% who are already managed in primary care or for those who are not routinely followed-up within specialist care. For these patients, initiation of dapagliflozin could take place at the earliest opportunity, ideally following proactive invitation for a treatment optimisation review or alternatively, where capacity is a limitation, during their routine check-up appointment without the need for a specific or extended appointment. This should be easily implementable given that most HF services are already organised across primary and secondary care and that dapagliflozin does not require up-titration nor specific monitoring over and above what is recommended for a patient with HF already. There is false equivalence in suggesting that because NICE recommends patients with HF and an LVEF ≤40% (HFrEF) are initiated on specialist advice, the same should hold true for those with HF and an LVEF >40%. It is important to distinguish that people with HFrEF have the opportunity to be considered for other evidence-based therapies, some of which can only be initiated by the specialist. Given that the population of patients with HF and an LVEF >40%

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	have no other treatment options, seeking the advice of a specialist for initiation represents a significant cost and would delay the initiation of dapagliflozin, which in the DELIVER trial produced a statistically significant reduction in the primary endpoint in 13 days after randomisation and KM curves separately immediately following randomisation.[10, 31] Given this, the Company firmly believes that enabling the treatment of patients with dapagliflozin irrespective of care settings without the need for further specialist advice represents the most appropriate approach and ensures that as many eligible patients as possible are receiving optimal care. This will support the NHS with its COVID-19 recovery plans, reducing wait times to outpatient services,[32] and reducing unwarranted variations in care across England and Wales. Enabling the initiation of dapagliflozin in both primary and secondary care for the treatment of this patient population would, therefore, ensure consistent equality of access without relying on specialist care, which may not exist in some areas for these patients.
Conclusion	**Summary of revised base case and scenario analyses.** Following the ACD, the base case cost-effectiveness analysis has been revised in order to align with the following Committee preferred assumptions: • Including age-adjusted and multiplicative population utilities (Section 3.16 of the ACD); • Applying HHF disutility is applied for 6 months (Section 3.17); • Using the HRG cost code (EB03E), associated with less severe HHF, to cost HHF (Section 3.19); • Assuming 6 annual GP visits per year (Section 3.21); • Removing amputation as an adverse event in the economic model (Section 3.22). All other settings are aligned with the previous Company base case, for the reasons detailed throughout this response document. This results in a revised base case deterministic ICER of £8,975 per QALY and a probabilistic ICER of £9,226 per QALY, with 85% and 90.7% probability of being cost-effective at WTP thresholds of £20,000 per QALY and £30,000 per QALY, respectively. Full deterministic and probabilistic results of the revised base case, as well as the scenario analyses conducted as part of this ACD response, are provided in Appendix 1 below. The Company have also presented compelling evidence in order to resolve the uncertainties highlighted in the ACD, demonstrating that dapagliflozin remains cost-effective across all scenarios considered. The Committee should now have full confidence and reassurance that dapagliflozin represents a highly innovative and cost-effective technology, for this underserved patient population, who will otherwise continue to face an extremely high burden of disease without any disease-modifying treatments available.

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Insert extra rows as needed

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Appendix 1: Revised cost-effectiveness results

The revised base case economic analysis results expressed in terms of ICERs and net health benefit (NHB) are presented in Table 3 and Table 4, respectively.

Over a lifetime horizon, treatment with dapagliflozin in addition to SoC, compared with SoC alone, was highly cost-effective compared with SoC, with an ICER of £8,975 per QALY gained. The NHB associated with dapagliflozin in addition to SoC was 4.064 and 4.206 at WTP thresholds of £20,000 per QALY and £30,000 per QALY gained, respectively.

Table 3: Base case economic analysis results – ICERs (revised base case)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Dapagliflozin plus SoC	£8,527	8.295	4.490	£2,117	0.370	0.236	£8,975
SoC	£6,410	7.926	4.255	-	-	-	-

Abbreviations: ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years.

Table 4: Base case economic analysis results – NHB (revised base case)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	NHB at £20,000/QALY	NHB at £30,000/QALY
Dapagliflozin plus SoC	£8,527	4.490	£2,117	0.236	4.064	4.206
SoC	£6,410	4.255	-	-	3.934	4.041

Abbreviations: ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years; NHB: net health benefit.

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Probabilistic sensitivity analysis results

The results of the revised base case PSA are presented in Table 5 below, with the scatterplot and cost-effectiveness acceptability curves presented Figure 12 and Figure 13, respectively. Figure 14 shows the ICER convergence plot from PSA of the revised base case. The results show that dapagliflozin in addition to SoC had 85% and 90.7% probability of being cost-effective at WTP thresholds of £20,000 per QALY and £30,000 per QALY gained, respectively.

Table 5: Base case PSA results (revised base case)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Dapagliflozin plus SoC	£8,496	4.497	£2,137	0.232	£9,226
SoC	£6,359	4.265	-	-	-

Abbreviations: ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years.

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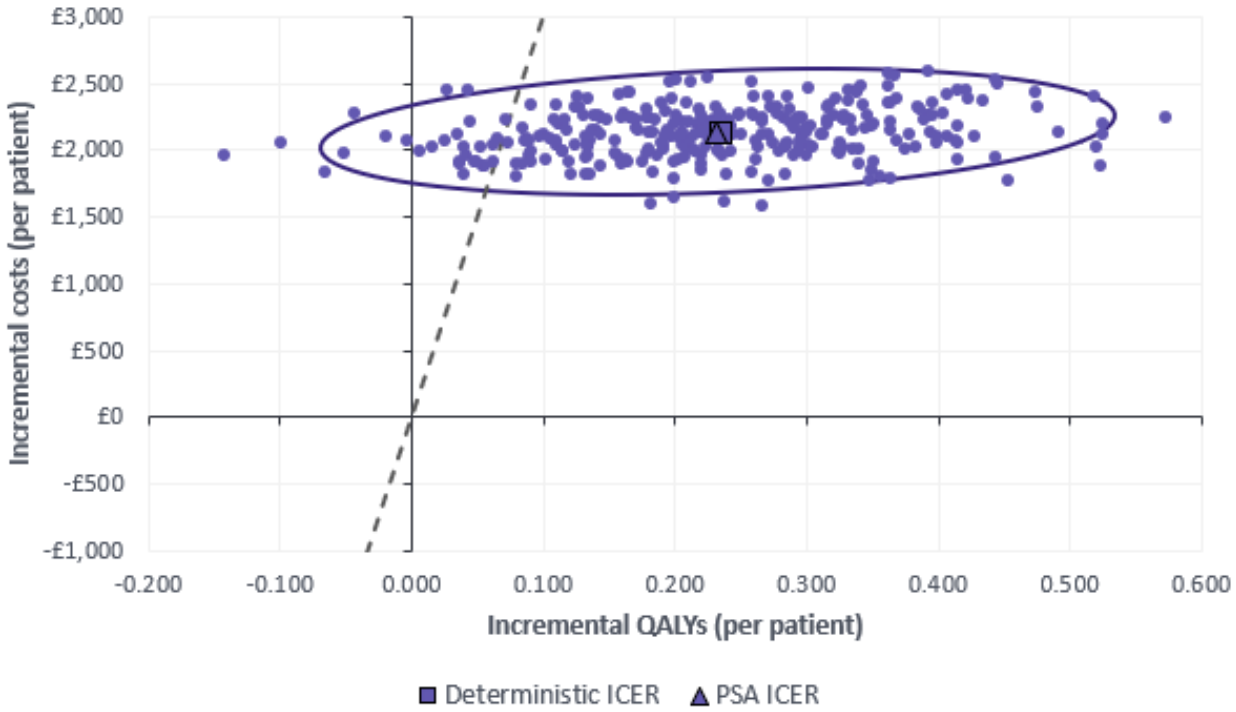
Figure 12: Cost-effectiveness scatter plot from PSA (revised base case)



Abbreviations: ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year; PSA: probabilistic sensitivity analysis.

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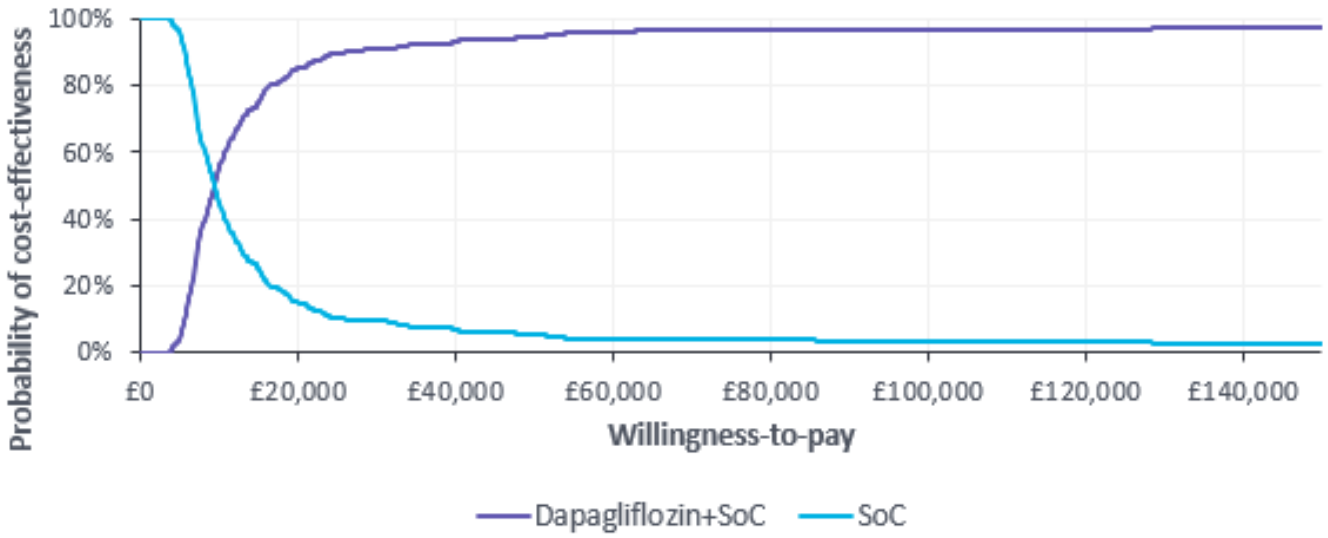
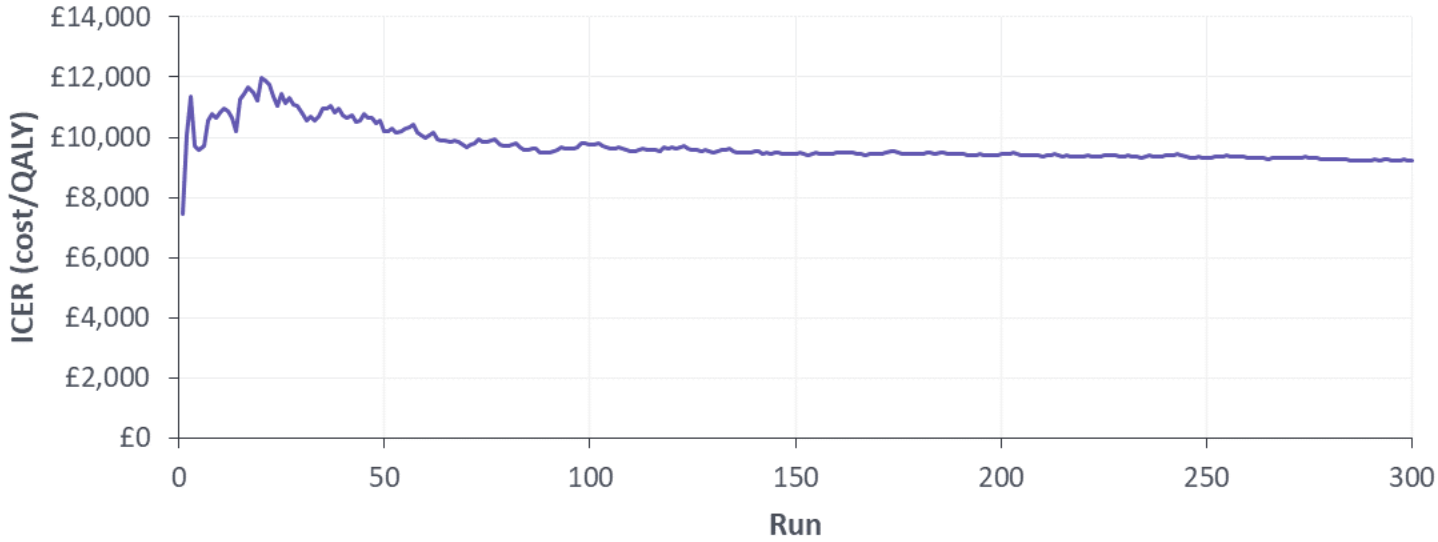
Figure 13: Cost-effectiveness acceptability curve from PSA (revised base case)



Abbreviations: PSA: probabilistic sensitivity analysis; SoC: standard of care.

Figure 14: ICER convergence plot from PSA (revised base case)



Abbreviations: ICER: incremental cost-effectiveness ratio; PSA: probabilistic sensitivity analysis.

Deterministic sensitivity analysis results

The results of the DSA are summarised in Figure 15 below; the most influential factors on the DSA were utility decrement and cost associated with HHF. However, the DSA showed that none of the included parameters had a substantial impact on the ICER, with all ICERs remaining below £10,000 per QALY gained across the DSA scenarios.

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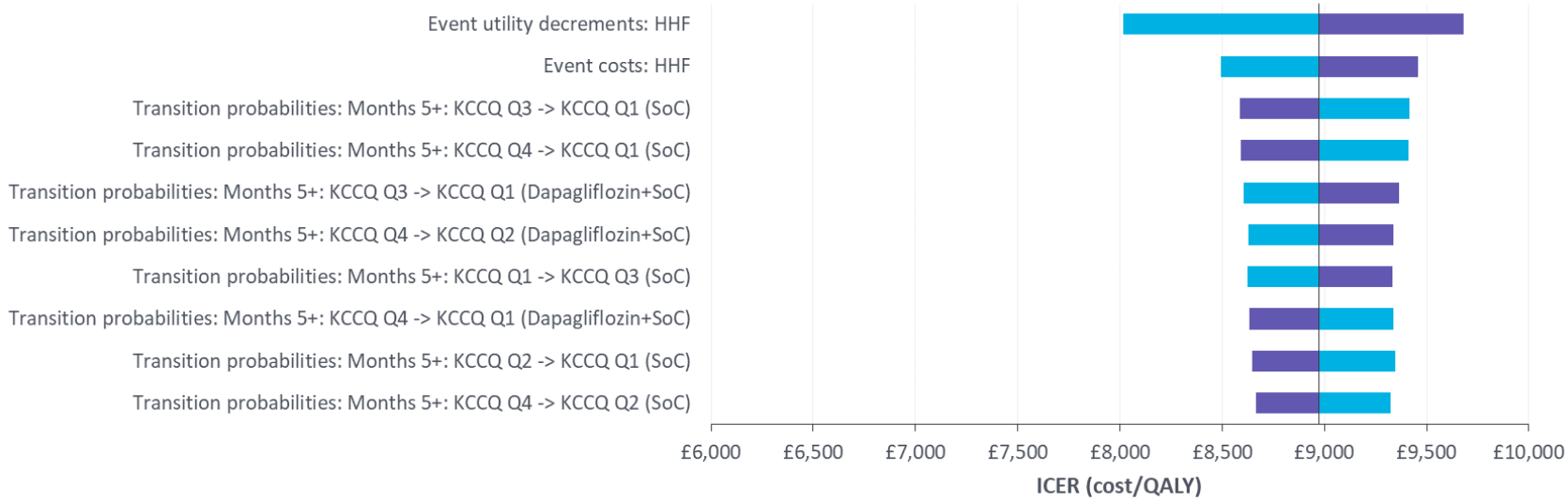
Figure 15: Tornado plot of DSA results (revised base case)



Footnotes: [a]Blue: upper ICER; purple: lower ICER.
Abbreviations: DSA: deterministic sensitivity analysis; HHF: hospitalisation for heart failure; ICER: incremental cost-effectiveness ratio; KCCQ-TSS: Kansas City Cardiomyopathy Questionnaire Total Symptom Score; SoC: standard of care; QALY: quality-adjusted life year.

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Appendix 2: Alternative risk equation coefficients for modelling CVM and ACM

Scenario 1: Removal of the dapagliflozin treatment effect for CVM/ACM

The regression models were re-fitted to the CVM and ACM data from the DELIVER trial, and dapagliflozin was excluded as a potential candidate variable, meaning that the final models did not include any direct treatment effect for dapagliflozin versus placebo on CVM or ACM. With the exception of removing dapagliflozin as a candidate variable, the regression models for CVM and ACM were fitted using the same process as previously detailed in Section B.3.3.5 of the Company Submission Document B, and all other variables previously included in Document B were included in the final regression models in this scenario.

A summary of the CVM and ACM extrapolations for each of the six curve choices are provided in Figure 16 to Figure 18 below. As the resulting extrapolations were very closely aligned with the CVM and ACM extrapolations used in the Company base case, then the Weibull extrapolation was considered to represent the most appropriate extrapolation for both CVM and ACM in this scenario analysis.

Figure 16: Summary of CVM and ACM extrapolations for dapagliflozin + SoC[a] for Scenario 1

Footnotes: CVM and ACM extrapolations for SoC only varied by more than 3 decimal places compared to the extrapolations for dapagliflozin + SoC; these are not presented above for simplicity, but can be found on the plots tab of the CEM.
Abbreviations: ACM: all-cause mortality; CEM: cost-effectiveness; CVM: cardiovascular mortality; SoC: standard of care.

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Figure 17: Summary of CVM extrapolations for dapagliflozin + SoC for Scenario 1

Footnotes: CVM extrapolations for SoC only varied by more than 3 decimal places compared to the extrapolations for dapagliflozin + SoC; these are not presented above for simplicity, but can be found on the plots tab of the CEM.
Abbreviations: CEM: cost-effectiveness; CVM: cardiovascular mortality; SoC: standard of care.

Figure 18: Summary of ACM extrapolations for dapagliflozin + SoC for Scenario 1

Footnotes: ACM extrapolations for SoC only varied by more than 3 decimal places compared to the extrapolations for dapagliflozin + SoC; these are not presented above for simplicity, but can be found on the plots tab of the CEM.
Abbreviations: ACM: all-cause mortality; CEM: cost-effectiveness; CVM: cardiovascular mortality; SoC: standard of care.

Notably, the CVM and ACM extrapolations used in Scenario 1 are closely aligned with those previously presented in Document B, Section B.3.3.5 resulting in similar predictions of CVM and ACM at each time point.

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As such, based on validation versus the published literature, and as previously acknowledged by the EAG's clinical experts, the Weibull curve should still be considered to represent the most, and only, plausible extrapolation in these new scenario analyses.

For example, as part of the original submission (Section B.3.3.5 and Clarification Question B17), the original survival extrapolations were validated via comparison with Shahim *et al.* (2021), a prospective, observational, multi-centre study which investigated long-term mortality outcomes in 397 patients with complete follow-up in the community setting in Sweden and France.[33] In this study, patients were enrolled after an acute HF event and had a mean baseline age of 78.[33]

In order to inform the selection of the most appropriate extrapolation, the DELIVER individual patient trial data were re-weighted to align with the reported patient characteristics in Shahim *et al.* (2021), meaning that the two populations could be compared directly.[33] The re-weighted all-cause mortality KM curves and resulting extrapolations for the placebo arm in the DELIVER trial are presented in Figure 19 below, and compared with the reported survival predictions from Shahim *et al.* (2021).[33]

As can be observed in Figure 19, the predicted survival using the Gompertz curve was very pessimistic compared with the 10-year estimate of survival from Shahim *et al.* (2021); whereas, the Weibull curve was aligned with the 10-year estimate of survival from Shahim *et al.* (2021).

Figure 19: Adjusted all-cause mortality predictions for patients receiving placebo in the DELIVER trial compared with long-term survival reported in Shahim *et al.* (2021)[33a]

[a]The black dots relate to 1-, 3-, 5- and 10-year survival reported in Shahim *et al.* (2021). Survival model extrapolations are presented only for the placebo arm.

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While Figure 19 relates to the original extrapolations (prior to the removal of the dapagliflozin treatment effect), Figure 18 above shows that the revised ACM extrapolations are closely aligned with the original extrapolations. The new Gompertz extrapolation for Scenario 1 is very similar to the Gompertz ACM extrapolation presented in Document B, and still shows that almost all patients would have died after approximately 12 years (representing a modelled age of [redacted] years), which is extremely pessimistic. The Committee's conclusions in the ACD (Section 3.12, Page 14), where it is noted that the Gompertz model was likely overly pessimistic, should therefore continue to hold in this scenario analysis.

Additionally, the fit statistics provided in Table 6 and Table 7 below highlight that the Weibull generally represents one of the three best fitting extrapolations for both CVM and ACM. The log-logistic and generalised gamma extrapolations provided better statistic fit, but they are associated with implausibly high survival predictions, and cannot be considered clinically valid.

Table 6: AIC and BIC values of the parametric survival model distributions for CVM for Scenario 1

Curve	AIC	AIC rank	BIC	BIC rank
Exponential	[redacted]	6	[redacted]	4
Generalised gamma	[redacted]	2	[redacted]	6
Gompertz	[redacted]	4	[redacted]	3
Log-logistic	[redacted]	1	[redacted]	1
Log-normal	[redacted]	5	[redacted]	5
Weibull	[redacted]	3	[redacted]	2

Abbreviations: AIC: Akaike Information Criterion; BIC: Bayesian Information Criterion; CVM: cardiovascular mortality; ITT: intention-to-treat.

Table 7: AIC and BIC values of the parametric survival model distributions for ACM for Scenario 1

Curve	AIC	AIC rank	BIC	BIC rank
Exponential	[redacted]	6	[redacted]	6
Generalised gamma	[redacted]	2	[redacted]	3
Gompertz	[redacted]	4	[redacted]	4
Log-logistic	[redacted]	1	[redacted]	1
Log-normal	[redacted]	5	[redacted]	5
Weibull	[redacted]	3	[redacted]	2

Abbreviations: ACM: all-cause mortality; AIC: Akaike Information Criterion; BIC: Bayesian Information Criterion; ITT: intention-to-treat.

As such, the Weibull extrapolation represents the most, and only, plausible extrapolation to model CVM and ACM in Scenario 1.

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Scenario 2: Removal of the dapagliflozin treatment effect and KCCQ effect on CVM/ACM

A second scenario analysis was conducted where new regression models were fitted to the CVM and ACM data from the DELIVER trial, excluding both dapagliflozin and KCCQ stage as potential candidate variables, meaning that the final models did not include any direct or indirect treatment effects for dapagliflozin versus placebo on CVM or ACM.

Given the removal of both dapagliflozin and KCCQ stage, the stepwise fitting process resulted in a new variable, New York Heart Association (NYHA) Class, being included as a variable in the final regression models, when compared to the regression models used in the Company base case. With this exception, the regression models for CVM and ACM were fitted using the same process as previously detailed in Section B.3.3.5 of the Company Submission Document B, and all other variables previously included in Document B were included in the final regression models in this scenario.

A summary of the CVM and ACM extrapolations for each of the six curve choices are provided in Figure 20 to Figure 22 below.

As previously detailed for Scenario 1, the new CVM and ACM extrapolations for Scenario 2 are very closely aligned to the CVM and ACM extrapolations previously presented in the Company submission Document B, as well as Scenario 1 above. As such, for the same reasons as detailed previously, the Committee's conclusion in the ACD (Section 3.12, Page 14) that the Gompertz curve is likely overly pessimistic should also be considered to hold true in Scenario 2. Therefore, the Weibull curve represents the most, and only clinically plausible extrapolation, and was used to model both CVM and ACM in this scenario analysis.

Figure 20: Summary of CVM and ACM extrapolations for dapagliflozin + SoC and SoC alone for Scenario 2

Abbreviations: ACM: all-cause mortality; CVM: cardiovascular mortality; SoC: standard of care.

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Figure 21: Summary of CVM extrapolations for dapagliflozin + SoC and SoC alone for Scenario 2

Abbreviations: CVM: cardiovascular mortality; SoC: standard of care.

Figure 22: Summary of ACM extrapolations for dapagliflozin + SoC and SoC alone for Scenario 2

Abbreviations: ACM: all-cause mortality; SoC: standard of care.

In line with Scenario 1, the fit statistics provided in Table 8 and Table 9 below show that the Weibull generally represents one of the three best fitting extrapolations for both CVM and ACM. While the log-logistic and generalised gamma extrapolations provided better statistic fit, they cannot be considered clinically plausible for the reasons detailed above.

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Table 8: AIC and BIC values of the parametric survival model distributions for CVM for Scenario 2

Curve	AIC	AIC rank	BIC	BIC rank
Exponential	[redacted]	6	[redacted]	4
Generalised gamma	[redacted]	2	[redacted]	5
Gompertz	[redacted]	4	[redacted]	3
Log-logistic	[redacted]	1	[redacted]	1
Log-normal	[redacted]	5	[redacted]	6
Weibull	[redacted]	3	[redacted]	2

Abbreviations: AIC: Akaike Information Criterion; BIC: Bayesian Information Criterion; CVM: cardiovascular mortality; ITT: intention-to-treat.

Table 9: AIC and BIC values of the parametric survival model distributions for ACM for Scenario 1

Curve	AIC	AIC rank	BIC	BIC rank
Exponential	[redacted]	6	[redacted]	6
Generalised gamma	[redacted]	2	[redacted]	3
Gompertz	[redacted]	4	[redacted]	4
Log-logistic	[redacted]	1	[redacted]	1
Log-normal	[redacted]	5	[redacted]	5
Weibull	[redacted]	3	[redacted]	2

Abbreviations: ACM: all-cause mortality; AIC: Akaike Information Criterion; BIC: Bayesian Information Criterion; ITT: intention-to-treat.

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Single Technology Appraisal

Dapagliflozin for treating chronic heart failure with preserved or mildly reduced ejection fraction [ID1648]

EAG request for company post draft guidance response

Please could the company provide the data that was used to inform Figure 10 in the company response to the draft guidance and fill out the table below with the number of events from the DELIVER trial. Additionally, could they provide an updated model which refits the event risk equations to allow for dapagliflozin to not have a treatment effect on UHFV events.

Response:

Event rates of HHF, UHFV, CVM and ACM from the DELIVER trial

The data used to inform Figure 10 in the company response to the draft guidance are presented in Table 1, and the requested event counts are presented in Table 2 below. It should be noted that the values in the tables below are cumulative occurrences up to and including the indicated month (26 or 36), or until the primary analysis censoring day ("End of Trial").

Further, the first column counts (highlighted) were reported as hospitalisation for heart failure (HHF) as opposed to HF events, the latter of which would represent a composite of HHF and urgent heart failure visits (UHFV).

Table 1: Data used for validation Figure 10 in ACD response (event rates reported as per 100 patient-years)

Source	HHF event rate		UHFV event rate		CVM event rate		ACM event rate	
	Dapagliflozin + SoC	SoC	Dapagliflozin + SoC	SoC	Dapagliflozin + SoC	SoC	Dapagliflozin + SoC	SoC
Trial	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Model	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ACM: all-cause mortality; CV: cardiovascular mortality; HHF: hospitalisation for heart failure; SoC: standard of care; UHFV: urgent heart failure visit

Table 2. Cumulative event counts from the DELIVER trial

Time	[redacted] events		UHFV events		CV deaths		ACM deaths	
	Dapagliflozin + SoC	SoC	Dapagliflozin + SoC	SoC	Dapagliflozin + SoC	SoC	Dapagliflozin + SoC	SoC
Up to Month 26	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Up to Month 36	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
End of trial	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ACM: all-cause mortality; CV: cardiovascular mortality; HHF: hospitalisation for heart failure; SoC: standard of care; UHFV: urgent heart failure visit

Updated regression model assuming no dapagliflozin treatment effect on urgent heart failure visit (UHFV)

Initially, it should be noted that, for the reasons previously detailed in response to Clarification Question B14, and Issue 1 of the Company's response to the draft guidance, it is inappropriate to assume that the absence of a statistically significant difference for UHFV in the DELIVER trial means that dapagliflozin should be considered clinically equivalent to standard of care (SoC) with respect to UHFV events. The DELIVER trial was not powered to detect statistically significant differences with respect to UHFV, and the forest plot presented in below does not support a conclusion that dapagliflozin would not reduce UHFV compared to SoC.[1]

Figure 1: Forest plot of the primary composite endpoint (CV mortality and HF events) and the individual components in DELIVER[a]

Abbreviations: CI: confidence interval; CV: cardiovascular; Dapa: dapagliflozin; FAS: full analysis set; HF: heart failure; HHF: hospitalisation for heart failure; HR: hazard ratio; N: number of patients in treatment group; T2DM: type 2 diabetes mellitus; UHFV: urgent heart failure visit.
Source: DELIVER CSR.[1]

However, as requested, an updated regression model was refitted to UHFV, using the same methodology as previously outlined in the Company Submission Document B (Section B.3.3.7). The revised null model was defined to include only the health state (defined using baseline quartiles of the Kansas City Cardiomyopathy Questionnaire – Total Symptom Score [KCCQ-TSS]. Treatment arm was excluded as a variable for assessment from the entire analysis. All other candidate variables (including age, sex, race, etc) were included in line with the base case.

From the defined null model, the same forward variable selection approach was applied (minimisation of the quasi-likelihood information criterion (QIC). In the present analysis, the same set of variables (not in the null model) were identified after the variable selection process. These were sex, body mass index, race, N-terminal prohormone of brain natriuretic peptide, type 2 diabetes, and atrial fibrillation/flutter status at baseline. The coefficients and statistics of the adjusted GEE from the requested analysis of UHFV are presented in Table 3.

Table 3: Adjusted GEE coefficients derived from the ITT DELIVER population

Parameter	Coefficient	SE	p-value
UHFV			
Intercept	[redacted]	[redacted]	[redacted]
Male	[redacted]	[redacted]	[redacted]
BMI (kg/m²)	[redacted]	[redacted]	[redacted]
Race: white	[redacted]	[redacted]	[redacted]
Race: black/African	[redacted]	[redacted]	[redacted]
Race: Other	[redacted]	[redacted]	[redacted]
KCCQ-TSS Q2	[redacted]	[redacted]	[redacted]
KCCQ-TSS Q3	[redacted]	[redacted]	[redacted]
KCCQ-TSS Q4	[redacted]	[redacted]	[redacted]
Log(NT-proBNP) (pg/ml)	[redacted]	[redacted]	[redacted]
T2DM	[redacted]	[redacted]	[redacted]
AFF	[redacted]	[redacted]	[redacted]

Abbreviations: AFF: atrial fibrillation/flutter; BMI: body mass index; eGFR: estimated glomerular filtration rate; GEE: generalised estimating equation; ITT: intention-to-treat; KCCQ: Kansas City Cardiomyopathy Questionnaire; NT-proBNP: N-terminal pro-B-type natriuretic peptide; SE: standard error; T2DM: type-2 diabetes mellitus; TSS: total symptom score; UHFV: urgent heart failure visit.

When this revised approach to modelling UHFV is applied to the Company base case cost-effectiveness analysis, the impact on the ICER is negligible, increasing from £8,975 to £9,011, as demonstrated in Table 4 below. Even in a scenario where the dapagliflozin treatment effect is removed from UHFV, CVM and ACM, the ICER remains below the lower £20,000 cost-effectiveness threshold.

Table 4: Additional scenario analysis results (run based on the Company based case following the ACD response)

Results	Deterministic results		
	Inc. costs	Inc. QALYs	ICER
Company base case (following the ACD response)	£2,117	0.236	£8,975
Scenario (removal of dapagliflozin treatment effect from the UHFV regression model)	£2,123	0.236	£9,011
Scenario (removal of dapagliflozin treatment effect from CVM, ACM and UHFV)	£1,934	0.100	£19,384

Abbreviations: ACD: Appraisal Consultation Document; ACM: all-cause mortality; CVM: cardiovascular mortality; ICER: incremental cost-effectiveness ratio; KCCQ: Kansas City Cardiomyopathy Questionnaire; QALY: quality-adjusted life year.

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	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):	[**The Pumping Marvellous Foundation**]
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**No links**

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Name of commentator person completing form:	Pumping Marvellous Foundation – [redacted] of the Pumping Marvellous Foundation representing the patient community and [redacted] – [redacted] representing the combined opinions of the Pumping Marvellous Foundation Clinical Advisory Board including [redacted], [redacted], [redacted], [redacted], [redacted], [redacted] and [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.
Example 1	We are concerned that this recommendation may imply that ……..
1	**Section 3.3 Treatment options** - We are concerned that this recommendation may imply that Frusemide and medications used to treat co-morbidities in HFpEF, offer treatment options that can act as comparators to Dapagliflozin for the treatment of HFpEF. Diuretics are used for the treatment of fluid overload in any type of heart failure however they are not indicated in the absence of fluid overload as they are not disease modifying treatments. The comorbidities that accompany HFpEF (hypertension, diabetes, chronic kidney disease) do not usually cause heart failure symptoms and hence treatment for comorbidities does not necessarily amerliorate symptoms in HFpEF either. We feel that it is important to acknowledge that there is simply no other disease modifying therapy available for HFpEF and SGLT2 inhibitors currently represent the 1st treatment option that has become available to alleviate symptoms as well as adverse outcomes, for a condition affecting nearly half a million people in the UK.
2	**Section 3.4 Comparators**– concerns similar to above that diuretics and treatment of comorbidities are not appropriate comparators for SGLT2i
3	**Section 3.5 Data sources and generalisability** This section seems to imply that the trial population in DELIVER was much younger than that seen in clinical practice. This is inaccurate as >40% of patients in DELIVER were ≥75 years,77% were ≥65 yrs and the recruited population represented a broad spectrum of age groups (Peikert A, et al. Circ Heart Fail. 2022 Oct;15(10):e010080). Among 6263 randomized patients (aged 40–99 years, mean age 71.7±9.6 years which was older than many of the previous HF trials), 338 (5.4%) were <55 years, 1007 (16.1%) were 55–64 years, 2326 (37.1%) were 65 to 74 years, and 2592 (41.4%) were ≥75 years.Older patients in DELIVER had the highest LVEF with more patients whose LVEF ≥60%. The benefits of Dapgliflozin on reduction of primary composite outcome measure and improvement of symptoms, were seen irrespective of age. DELIVER not only randomised older patients but also a significant number of patents with HFpEF and frailty (≈63%), according to a pre-specified analysis (Butt JH et al. Ann Intern Med. 2022

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	Jun;175(6):820-830.) The beneficial outcomes were seen irrespective of degree of frailty but more importantly patients with the greatest frailty experienced the most improvement in symptoms, physical function, and quality of life
4	**Section 3.7**. **Impact of treatment on cardiovascular and all-cause mortality** The pooled analysis by Jhund et al (Nature Medicine volume 28, pages1956–1964 2022) also showed that Dapagliflozin reduced all-cause mortality by 10% (HR 0.90 (95% CI 0.82–0.99); P = 0.03) irrespective of ejection fraction. Similarly another pre-specified analysis of the effect of Dapagliflozin on cause-specific mortality, showed significant reductions in cardiovascular mortality irrespective of ejection fraction (attributable both due to reductions in HF death and sudden death - Desai AS, et al. JAMA Cardiol. 2022;7(12):1227–1234) A meta-analysis of 12 251 participants from DELIVER and EMPEROR-Preserved (Vaduganathan M, et al. Lancet 2022 Sep 3;400(10354):757-767), demonstrated significant reductions in composite cardiovascular death or first hospitalisation for heart failure (hazard ratio 0·80 [95% CI 0·73-0·87]) with consistent reductions in both components: cardiovascular death (0·88 [0·77-1·00]) and first hospitalisation for heart failure (0·74 [0·67-0·83]). As DELIVER was not powered to detect a reduction in cardiovascular or all-cause mortality, findings from the pooled pre-specified analyses as well as meta-analyses provide a more meaningful statistical estimate on cardiovascular and all-cause mortality benefit irrespective of ejection fraction. It is also important to note that in contrast to HFrEF, patients with HFpEF and HFmrEF, experience a greater proportion of non-cardiovascular mortality (mainly due to greater multimorbidity burden -Vaduganathan M et al. J Am Coll Cardiol. 2017;69(5):556-569). For a condition such as HFpEF which is associated with a constellation of comorbidities and which has not had such benefits noted from other therapies, this finding is important and should not be overlooked.
5	**Section 3.8** Amongst the DELIVER population of patients, a minority (18%) had HF with improved EF (HFimpEF). In a pre-specified analysis (Vardeny et al Nature Medicine volume 28, pages2504–2511 2022), Dapagliflozin reduced the primary composite end point compared to placebo in participants with HFimpEF (HR = 0.74, 95% CI = 0.56–0.97) to a similar extent as patients with LVEF consistently over 40% (HR = 0.84, 95% CI 0.73–0.95; interaction P = 0.43). The benefits were similar and irrespective of age age ≥75 versus <75 years. It is also important to note that the event rate (worsening HF, cardiovascular or all-cause death) was similar in the HFimpEF cohort and LVEF consistently>40% cohort indicating comparable risk profiles. There was also similar symptom benefit in the two groups (although those with HFimpEF were less symptomatic at baseline). These benefits are significant as this unique cohort of patients with HFimpEF has not been studied previously, however it is important to emphasise that inclusion of this cohort in DELIVER, does not accentuate the benefits seen in those with LVEF consistently >40%.
6	**Section 3.9** People with HFpEF suffer from poor quality of life, significant burden of symptoms and physical limitation and improving symptomatic status is an important goal of heart failure guidelines. Results from the DELIVER Trial Kosiborod et al. (JACC Volume 81, Issue 5, 7 February 2023, Pages 460-473), through evaluation of KCCQ-TSS, Physical Limitations (PLS), Clinical Summary (CSS), and Overall Summary (OSS) domains, show that Dapagliflozin use in HFpEF leads to an early (within 1 month) and sustained, significant improvement in symptoms and health status. We are concerned about the rationale for questioning KCCQ as a valid questionnaire to assess quality of life, when there is a weath of evidence that it is a robust measure in all types of HF (G-CHF Study. Circulation. 2021;143:2129–2142, Spertus et al. JACC 2020, Joseph S et al. Circ Heart Fail. 2013 Nov;6(6):1139-46, Sepehrvand N, J Am Heart Assoc. 2020;9(17):e017278.) to detect meaningful change in health status and also has a better prognostic value in comparison to NYHA Class which is a more subjective and non-patient-centric score (Greene et al JAMA 2021). Our Pumping Marvellous “Living with Heart Failure” patient

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	survey responses indicate that the most important outcome for patients is to improve day-to-day quality of life (78.5% of patients), followed by increasing life expectancy (72.5% of patients), http://pumpingmarvellous.org/wp-content/uploads/2018/02/Pumping-Marvellous-Living-With-Heart-Failure-Infographic.pdf The importance of quality of life for a person living well with heart failure is emphasised by patients, carers and clinicians surveyed in the Pumping Marvellous "Living Well with Heart Failure "report https://pumpingmarvellous.org/wp-content/uploads/2022/04/Living-well-with-heart-failure-report-FINAL.pdf Similarly we are also concerned that the symptomatic benefit of Dapagliflozin in DELIVER is seemingly trivialised again due to the factor that the KCCQ use as a predictor of cause and cardiovascular mortality has been questioned. SGLT2i are the 1st class of therapies that have shown symptomatic benefit in people with HFpEF (despite associated multimorbidity, frailty).
	Section 3.10 Health state transition The modelling approach for health state transition is similar to that approved for NICE TA 679. As also described below in Section 3.17, it is our opinion that currently there is no fool-proof modelling approach available to account for the transient and time-bound nature of HRQoL assessment.
	Section 3.11 Modelling of treatment effect on cardiovascular and all-cause mortality Points made in Section 3.7 are also relevant here. Based on the totality of evidence outlined above, we are concerned that impact of the significant reduction in cardiovascular mortality, in particular due to Dapagliflozin use in people with HF and LVEF>40%, is being excluded by the committee. This is all the more relevant due to the inherent limitations of both sensitivity and scenario analyses being used to compute incremental cost-effectiveness ratios.
	Section 3.13 Ability of the model to replicate observed all-cause and cardiovascular survival outcomes We find it confusing that when time-updated model covariate and a treatment effect coefficient were used in NICE TA for Dapagliflozin and Empagliflozin in HFrEF TA679 [TA773], yet the committee did not consider this a standard modelling approach for HFpEF, despite the totality of evidence indicating that heart failure is a condition that represents a continuum and the beneficial effects of SGLT2i are seen across the range of ejection fraction.
	Section 3.14 Modelling of treatment effect on HF events We are concerned by the EAG statement "DELIVER data did not convincingly support a benefit of dapagliflozin in reducing urgent hospitalisation for heart failure" and on this basis the exclusion of dapagliflozin treatment effect on urgent hospitalisation for heart failure in its base case. DELIVER and other SGLT2i trials have shown a significant reduction in HF hospitalisations.
	Section 3.17 Duration of impact of heart failure events on quality of life We are concerned that the impact of HF hospitalisation has not been adequately represented both in terms of the impact upon patients nor upon healthcare resources. HF hospitalisation represents a crucial inflection point in the trajectory of a patient as it is associated with 10% inhospital mortality and 15% 30 day mortality as well as a 25% 30 day readmission rate and 50% readmission rate over 6 months. There a recognised limitations of applying disutlity due to HF hospitalisation to economic models, due to the variation in timing of disutility assessment, time-bound nature of estimation of disutility at a specific time followed by linear extrapolation to longer time periods and impact of recurrent hospitalisations (a frequent event in HFpEF), nature of hospitalisation (HF versus other causes due to multimorbidity and the impact of individual patient characteristics upon disutility (Di Tanna, G.L.,et al. PharmacoEconomics 39, 211–229 (2021).However previous studies have indicated that a HF related hospitalisation reflects a disutility period up to 12 months. We feel this is a more

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	realistic estimate of the impact of HF hospitalisation on HRQoL due to additional effects of falls, delirum, muscle wasting, hospital acquired infections and effect on nutrion. This is particularly relevant for patients with HFpEF who are frequently older than those with HFrEF; HFpEF is also associated with greater multimorbidity as well as frailty.
	Section 3.21 GP visits We are concerned that there appears to be an underestimate of the healthcare resources by people with HFpEF in primary care. Evidence indicates that HFpEF is under diagnosed and less recognised in primary care as symptoms and signs may be mis-attributed to obesity, ageing, frailty etc *Hossain et al https://doi.org/10.1177/174239532098387). In our opinion 6 annual GP visits is therefore an underestimate, as these patients also frequently contact urgent care centres or community heart failure teams.
	Section 3.26 Committee preferred assumptions We express concerns regarding some of the assumptions as follows 1.hospitalisation disutility of 6 months is an underestimate and disutlity of 12 months is more accurate as per explanation above in Section 3.17 2. GP visits of 6/year is a likely underestimate 3. removal of treatment effect of dapagliflozin on cardiovascular and all-cause deaths (see section 3.11) or on urgent heart failure visit events
	Statement by Pumping Marvellous Foundation UK HFpEF Patient Advisory Board The decision has led to a feeling of great disappointment. To HFpEF patients, SGLT2 inhibitors represented not just another treatment but a beacon of hope that, at last, a medicine had arrived that could make a real difference to our lot. It is easy for a HFpEF patient to feel left behind as we are often denied the educational and support services of a complete heart failure medical team because NICE has now not recommended any treatments for our population. Commissioners of services use NICE published guidance to create services and due to this decision, they will not create services. The impact of this decision is far reaching outside just the prescribing of an innovative medication. This is another reason for reconsideration of changing the recommendation. Quality of Life is an essential consideration and reduction in hospitalisation, a significant element in that, however, achieved. Unfortunately, a whole class of drugs that promise to improve our QoL has been rejected with no apparent justification other than subjective economic assumption. We ask that the current decision is reversed and that SGLT2i are reimbursed. There are members in our HFpEF advisory committee that have benefited from this treatment. Pumping Marvellous UK HFpEF Advisory Board [redacted]
	Pumping Marvellous Foundation, Patient Educators (43 Expert Patients) Response This response comes from the Pumping Marvellous Foundation of Patient Educators (Expert Patients) in our community who have heart failure, a mixture of HFrEF, HFpEF and HFmrEF. Heart failure afflicts us all irrespective of the type. We total 43 patients across the UK and 4 Nations. We stand together as a community of humans with the same debilitating issues; those of us with HFrEF are fortunate enough to have medications that make a difference to us daily. We have

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	hope for a better future & the decision from this appraisal has essentially removed that from people who have HFpEF. Below is a mixture of quotes from some of our Patient Educators – **[redacted] summarises [redacted] thoughts here.** "I feel that blocking these meds is playing with people's lives. These meds could potentially be someone's lifeline, but by blocking them, in my opinion, it feels like a kick in the teeth to those patients that could benefit from them". **[redacted] summarises [redacted] thoughts.** "In turning your backs on the use of these drugs for HFPEF patients, despite their benefits identified in large RCT's, primarily on the grounds of cost, will NICE be issuing guidance to clinicians on how to assist patients in amortising/depreciate their quality of life? Will the cost of mental health support for those patients who feel they have no hope for an improved QOL outweigh the cost of allowing these patients to access these medications?" **The feeling from our community is confusion & a colossal disappointment.** **[redacted] summarises [redacted] thoughts.** "I'm incredibly disappointed that NICE has decided not to approve SGLT2i's for heart failure patients that have preserved ejection fraction when they have already approved it for those of us that have HF with reduced ejection fraction. The chance to finally prescribe medication that can help improve the quality of life for a group of patients with so few treatment options feels like a missed opportunity." **A missed opportunity is precisely how this feels. We worry that it could also impact future research for treatments for patients with HFpEF, why invest? Research that is desperately needed & that would also have long-term cost benefits to the NHS. These patients deserve every opportunity to live better with their condition, and this decision goes against that fundamentally.** **[redacted] summarises [redacted] thoughts.** "Whilst NICE's recommendation to withdraw SGLT2i's from patients with HFpEF doesn't affect me personally, I kindly request that the decision is reviewed with a reversal in mind as I'm aware of many fellow heart failure patients whose quality of life will be affected by this decision. Heart failure is tough enough to live with, and the prospect of increased symptoms due to the non-prescribing of the drugs mentioned above is both unnerving and irresponsible". **It is unnerving to think that NICE would make this decision despite clinicians, patients & the heart failure community, in general, knowing that these treatments would be a positive and necessary addition to our arsenal of tools in the fight to live with heart failure. As patients, we want to live, not just exist. Although we often hear that with a diagnosis of heart failure, patients feel that their lives are diminished, this decision is another blow to people who are often already living a physically & mentally difficult life. This decision impacts that difficulty massively for many of us & we are saddened to think of the far-reaching implications it will have.**

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	[redacted] **summarises** [redacted] **thoughts, on behalf of us all.** "I am astonished to hear about the recent decision by NICE to not recommend SGLT2i's for those Heart Failure Patients with Preserved Ejection Fraction or mildly reduced ejection fraction. I believe, the reason for this is that this treatment is not deemed to be cost-effective. I cannot see why cost would be an issue when clinical trials have shown benefits such as improved Quality of Life, reduced hospital admissions and improved outcomes regarding life expectancy. I urge NICE to reconsider their decision and give this group of patients the opportunity they deserve". We appreciate your consideration on this matter; we hope this response will go some way to a reconsideration of this decision.
	Section 3.27 Committee cost-effectiveness estimates We would also like to note that Patients with heart failure and an ejection fraction more than 40% should not be held to the lower end of the willingness to pay threshold of £20000 per QALY but instead should have access up to the £30,000 per QALY. NICE would not deny patients with cancer, who have a comparable prognosis as patients with heart failure with an ejection fraction of more than 40%, access to innovations up to and sometimes exceeding the £30000 per QALY threshold. It is clear thst the decision is inappropriate, for a population of patients that does not have any other form of treatment.

Insert extra rows as needed

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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.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is [redacted] and information that is [redacted]. If confidential information is submitted, please submit a second version of your comments form with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the NICE Health Technology Evaluation Manual (section 5.4) for more information.
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Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	[**British Cardiovascular Society**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	[**None**]

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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.
Example 1	We are concerned that this recommendation may imply that ……..
1	Section 3.3 - "Symptomatic treatments for comorbidities are also offered to people with heart failure with preserved ejection fraction, including angiotensin converting enzyme inhibitors, angiotensin II receptor blockers, beta blockers or mineralocorticoid receptor antagonists." This statement appears incorrect, in that these medications are used to treat comorbidities which co-exist in patients with HFpEF/HFmrEF (such as hypertension) on an indication by indication basis. Symptoms from these co-morbidities may improve but this is not the main aim. Prognosis or prevention of hospitalisation are some examples depending on the condition/co-morbidity being treated.
2	Section 3.7 – "This pooled analysis showed that dapagliflozin significantly reduced cardiovascular mortality compared with placebo (hazard ratio 0.86, 95% confidence interval 0.76 to 0.96; Jhund et al. [2022]). In this pooled analysis there was no evidence that the effect of dapagliflozin differed by level of ejection fraction. The committee noted that evidence from the pooled analysis was not incorporated into the economic model." If there is evidence, independent of ejection fraction, demonstrating reduced cardiovascular mortality, was this used in modelling by the EAG? If not, please could this be explained.
3	Section 3.8 - The group of patients with previously reduced ejection fraction that is now >40% were specifically considered in the DELIVER trial and appeared to have significant benefit, over and above the benefit shown in the whole group. A specific recommendation for this group could have been given and would avoid them falling between the two different NICE SGLT2i appraisals (HFrEF & HFpEF). The current statement in the explanatory text does not make the position clear enough. Currently there are patients with HFrEF who have their LVEF re-evaluated following initiation of first line medications and the EF has improved to >40 prior to commencing a SGLT2i. Current guidance would exclude this group from being prescribed a SGLT2i.
4	Symptoms and quality of life are valid targets for treatment, particularly in a largely elderly group of patients with multiple co-morbidities. It is not clear to BCS that the economic modelling adequately represents this benefit from a patient perspective, particularly given the lack of other therapies.
5	Section 3.17 – The opinion on disutility attributed to a patient following a heart failure hospitalisation clearly varied across the discussion. BCS would prefer that a full evidence search was completed to inform this input more accurately and then used across both SGLT2i appraisals.

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	Disutility should probably not solely apply after an index hospitalisation. There is also the period of deterioration prior to the hospitalisation which may be of variable length and severity.
6	Section 3.21 – "The EAG noted that because of fewer treatments being available for this group (see section 3.3), approximately 6 GP or other primary care visits would be expected per year." BCS does not consider the lack of specific treatments for HFpEF to mean that healthcare contacts will be fewer. The opposite could equally be true. An evidence based approach would be preferable.
7	Section 3.26 – "The committee considered that there was uncertainty regarding whether it was appropriate to use non-elective inpatient costs taken from NHS reference costs 2019/2020 and inflated to the 2020/2021 cost year, or from NHS reference costs 2020/21, because of the unknown impact of the COVID-19 pandemic (see section 3.18)." BCS considers it unfortunate that it is difficult to agree the correct NHS reference cost and concerned regarding the subsequent impact this may have had on the decision.
8	Section 3.27 – "The lower bound of the threshold (£20,000 to £30,000 per QALY gained) was preferred by the committee given the large impact of the uncertainties relating to survival estimates on the ICER." BCS is concerned that the decision on which willingness-to-pay threshold to use is subjective and not fully explained. It would be preferable, if possible, to aim to resolve some of the uncertainty in the modelling through further evidence appraisal and expert discussion and fully explain why, in this case, a higher threshold is not thought appropriate.
9	Section 3.30- "the cost-effectiveness estimates for dapagliflozin are likely higher than what NICE considers a cost-effective use of NHS resources" BCS would prefer a more definitive statement that communicates less uncertainty around the decision. Ideally a statement that dapagliflozin is or is not cost effective. If there is inadequate evidence to make a decision then this could also be described.

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	**British Society for Heart Failure**

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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:	The Board of the British Society for Heart Failure, [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.
Example 1	We are concerned that this recommendation may imply that ……..
1	**Section 3.3 Treatment options** - We are concerned that this recommendation may imply that Frusemide and medications used to treat co-morbidities in HFpEF, offer treatment options that can act as comparators to Dapagliflozin for the treatment of HFpEF. Diuretics are used for the treatment of fluid overload in any type of heart failure however they are not indicated in the absence of fluid overload as the are not disease modifying treatments (i.e. Have not been shown to improve outcomes in patients with heart failure). The comorbidities that accompany HFpEF (hypertension, diabetes, chronic kidney disease) do not usually cause heart failure symptoms and hence treatment for comorbidities does not necessarily amerliorate symptoms in HFpEF either. We feel that it is important to acknowledge that there is simply no other disease modifying therapy available for HFpEF and SGLT2i currently represent the 1st treatment option that has become available to alleviate symptoms as well as prevent adverse outcomes, for a condition affecting nearly half a million people in the UK.
2	**Section 3.4 Comparators**– concerns as above that diuretics and treatment of comorbidities are not appropriate comparators for SGLT2i
3	**Section 3.5 Data sources and generalisability** This section seems to imply that the trial population in DELIVER was much younger than that seen in clinical practice. This is inaccurate as >40% of patients in DELIVER were ≥75 years, 77% were ≥65 yrs and the recruited population represented a broad spectrum of age groups (Peikert A, et al. Circ Heart Fail. 2022 Oct;15(10):e010080). Among 6263 randomized patients (aged 40–99 years, mean age 71.7±9.6 years which was older than many of the previous HF trials), 338 (5.4%) were <55 years, 1007 (16.1%) were 55–64 years, 2326 (37.1%) were 65 to 74 years, and 2592 (41.4%) were ≥75 years.Older patients in DELIVER had the highest LVEF with more patients whose LVEF ≥60%. The benefits of

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	Dapgliflozin on reduction of primary composite outcome measure and improvement of symptoms, were irrespective of age. DELIVER not only randomised older patients but also a significant number of patents with HFpEF and frailty (≈63%), according to a pre-specified analysis (Butt JH et al. Ann Intern Med. 2022 Jun;175(6):820-830.) The beneficial outcomes were seen irrespective of degree of frailty but more importantly patients with the greatest frailty experienced the most improvement in symptoms, physical function, and quality of life
4	**Section 3.7**. **Impact of treatment on cardiovascular and all-cause mortality** The pooled analysis by Jhund et al (Nature Medicine 2022; volume 28, pages 1956–1964) also showed that Dapagliflozin reduced all-cause mortality by 10% (HR 0.90 (95% CI 0.82–0.99); P = 0.03) irrespective of ejection fraction. Similarly, another pre-specified analysis of the effect of Dapagliflozin on cause-specific mortality showed significant reductions in cardiovascular mortality irrespective of ejection fraction (attributable both due to reductions in HF death and sudden death - Desai AS, et al. JAMA Cardiol. 2022;7(12):1227–1234) A meta-analysis of 12,251 participants from DELIVER and EMPEROR-Preserved (Vaduganathan M, et al. Lancet 2022 Sep 3;400(10354):757-767), demonstrated significant reductions in the composite of cardiovascular death or first hospitalisation for heart failure (hazard ratio 0·80 [95% CI 0·73-0·87]) with consistent reductions in both components: cardiovascular death (0·88 [0·77-1·00]) and first hospitalisation for heart failure (0·74 [0·67-0·83]). As DELIVER was not powered to detect a reduction in cardiovascular or all-cause mortality, findings from the pooled pre-specified analyses as well as meta-analyses provide a more meaningful statistical estimate on cardiovascular and all-cause mortality benefit irrespective of ejection fraction. It is also important to note that in contrast to HFrEF, patients with HFpEF and HFmrEF, experience a greater proportion of non-cardiovascular mortality (mainly due to greater multimorbidity burden -Vaduganathan M et al. J Am Coll Cardiol. 2017;69(5):556-569). For a condition such as HFpEF which is associated with a constellation of comorbidities and which has not had such benefits noted from other therapies, this finding is important and cannot simply be glossed over.
5	**Section 3.8** Amongst the DELIVER population of patients, a minority (18%) had HF with improved EF (HFimpEF). In a pre-specified analysis (Vardeny et al Nature Medicine 2022, volume 28, pages 2504–2511) Dapagliflozin reduced the primary composite end point compared to placebo in participants with HFimpEF (HR = 0.74, 95% CI = 0.56–0.97) to a similar extent as patients with LVEF consistently over 40% (HR = 0.84, 95% CI 0.73–0.95; interaction P = 0.43). The benefits were similar and irrespective of age age ≥75 versus <75 years.. It is also important to note that the event rate (worsening HF, cardiovascular or all-cause death) was similar in the HFimpEF cohort and LVEF consistently>40% cohort indicating comparable risk profiles. There was also similar symptom benefit in the 2 groups (although those with HFimpEF were less symptomatic at baseline). These benefits are significant as this unique cohort of patients with HFimpEF has not been studied previously, however it is important to emphasise that inclusion of this cohort in DELIVER, does not accentuate the benefits seen in those with LVEF consistently >40%.
6	**Quality of life** People with HFpEF suffer from poor quality of life, significant burden of symptoms and physical limitation and improving symptomatic status is an important goal of heart failure guidelines. Results from the DELIVER Trial in its pre-specified sub-study (Kosiborod et al. JACC Volume 81, Issue 5, 7 February 2023, Pages 460-473), through evaluation of KCCQ-TSS, Physical Limitations (PLS), Clinical Summary (CSS), and Overall Summary (OSS) domains, show that Dapagliflozin use in HFpEF leads to an early (within 1 month) and sustained, significant improvement in symptoms and health status. We are concerned about the rationale for questioning KCCQ as a valid questionnaire to assess quality of life, when there is a weath of evidence that it is a robust measure in all types of HF (G-CHF Study.

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	Circulation. 2021;143:2129–2142, Spertus et al. JACC 2020, Joseph S et al. Circ Heart Fail. 2013 Nov;6(6):1139-46, Sepehrvand N, J Am Heart Assoc. 2020;9(17):e017278.) to detect meaningful change in health status and also has a better prognostic value in comparison to NYHA Class which is a more subjective and non-patient-centric score (Greene et al JAMA 2021). Our Pumping Marvellous "Living with Heart Failure" patient survey responses indicate that most important outcome for patients is to improve day-to-day quality of life (78.5% of patients), followed by increasing life expectancy (72.5% of patients), http://pumpingmarvellous.org/wp-content/uploads/2018/02/Pumping-Marvellous-Living-With-Heart-Failure-Infographic.pdf The importance of quality of life for a person living well with heart failure is emphasised by patients, carers and clinicians surveyed in the Pumping Marvellous "Living Well with Heart Failure "report https://pumpingmarvellous.org/wp-content/uploads/2022/04/Living-well-with-heart-failure-report-FINAL.pdf Similarly we are also concerned that the symptomatic benefit of Dapagliflozin in DELIVER is seemingly trivialised again due to the factor that the KCCQ use as a predictor of cause and cardiovascular mortality, has been questioned. SGLT2i are the 1st in class of therapies that have shown symptomatic benefit in people with HFpEF (despite associated multimorbidity, frailty).
7	**Section 3.10 Health state transition** The modelling approach for health state transition is similar to that approved for NICE TA 679. As also described below in Section 3.17, it is our opinion that currently there is no fool-proof modelling approach available to account for the transient and time-bound nature of HRQoL assessment.
8	**Section 3.11 Modelling of treatment effect on cardiovascular and all-cause mortality** Points made in Section 3.7 are also relevant here. Based on the totality of evidence outlined above, we are concerned that impact of the significant reduction in cardiovascular mortality in particular due to Dapagliflozin use in people with HF and LVEF>40% (and in particular HFmrEF as opposed to HFpEF), is being excluded by the committee. This is all the more relevant due to the inherent limitations of both sensitivity and scenario analyses being used to compute incremental cost-effectiveness ratios.
9	**Section 3.13 Ability of the model to replicate observed all-cause and cardiovascular survival outcomes** We find it confusing that when time-updated model covariate and a treatment effect coefficient were used in NICE TA for Dapagliflozin and Empagliflozin in HFrEF TA679 [TA773], yet the committee did not consider this a standard modelling approach for HFpEF, despite the totality of evidence indicating that heart failure is a condition that represents a continuum and the beneficial effects of SGLT2i are seen across the range of ejection fraction.
10	**Section 3.14 Modelling of treatment effect on HF events** We are concerned by the EAG statement "DELIVER data did not convincingly support a benefit of dapagliflozin in reducing urgent hospitalisation for heart failure" and on this basis the exclusion of dapagliflozin treatment effect on urgent hospitalisation for heart failure in its base case. DELIVER and other SGLT2i trials have shown a significant reduction in HF hospitalisation.
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	frequent event in HFpEF), nature of hospitalisation (HF versus other causes due to multimorbidity and the impact of individual patient characteristics upon disutility (Di Tanna, G.L.,et al. PharmacoEconomics 39, 211–229 (2021). However previous studies have indicated that a HF related hospitalisation reflects a disutility period upto 12 months. We feel this is a more realistic estimate of the impact of HF hospitalisation on HRQoL due to additional effects of falls, delirum, muscle wasting, hospital acquired infections and effect on nutrion. This is particularly relevant for patients with HFpEF who are frequently older than those with HFrEF; HFpEF is also associated withgreater multimorbdity as well as frailty.
12	**Section 3.21 GP visits** We are concerned that there appears to be an underestimate of the healthcare resources by people with HFpEF in primary care. Evidence indicates that HFpEF is under diagnosed and less recognised in primary care as symptoms and signs may be mis-attributed to obesity, ageing, frailty etc *Hossain et al https://doi.org/10.1177/174239532098387). In our opinion 6 annual GP visits is therefore an underestimate, as these patients also frequently contact urgent care centres or community heart failure teams.
13	**Section 3.26 Committee preferred assumptions** We express concerns regarding some of the assumptions as follows: 1. Hospitalisation disutility of 6 months is an underestimate and disutlity of 12 months is more accurate as per explanation above in Section 3.17 2. GP visits of 6/year is a likely underestimate 3. Removal of treatment effect of dapagliflozin on cardiovascular and all-cause deaths (see section 3.11) or on urgent heart failure visit events
14	We are concerned that the ICER cut off of £20,000 is being used despite a threshold of £30,000 having been used previously for other therapies and though outcomes of HFpEF comparable/worse than some of the cancers, there does not appear to be the same consistency in application of criteria for recommendations BSH would like to alert the committee to the fact that not recommending empagliflozin for this indication will be a major disadvantage to a large number of patients in the UK with HFmrEF and HFpEF who have a high symptom burden and experience frequent and recurrent hospitalisation and currently have very limited treatment options. The SGLT2 inhibitors dapagliflozin and empagliflozin are the first drugs shown to improve symptoms and reduce heart failure hospitalisation in this population. [redacted]

Insert extra rows as needed

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- Please underline all confidential information, and separately highlight information that is [redacted] and information

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Dapagliflozin for treating chronic heart failure with preserved or mildly reduced ejection fraction [ID1648]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on 1 March 2023. Please submit via NICE Docs.

that is [redacted]. If confidential information is submitted, please submit a second version of your comments form with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the NICE Health Technology Evaluation Manual (section 5.4) for more information.

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	**Primary Care Cardiovascular Society (PCCS)**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**NIL**

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Name of commentator person completing form:	[redacted] on behalf of the PCCS
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.
Example 1	We are concerned that this recommendation may imply that ……..
1	The assumption that all patients with heart failure with improved ejection fraction will be already prescribed dapagliflozin (or empagliflozin) is suspect. Not all patients with a previous diagnosis of heart failure will have been reviewed over the last 2 years and may have missed out on this treatment option. Furthermore, this review may not have considered the previous ejection fraction as a comparator to identify those where the ejection fraction has improved. If this recommendation is made, they will be excluded from consideration of this disease modifying treatment.
2	The cohort studied in this trial do not have any disease modifying treatments available to them, only treatment of co-morbidities. If dapagliflozin is not recommended as a treatment for heart failure with preserved ejection fraction, patients and clinicians continue to have limited treatment options.
3	This patient group accounts for a large number of hospital admissions each year. In view of our ageing population and increasing prevalence of heart failure with preserved ejection fraction, the pressure of recurrent hospitalisations on health services will only increase in the future. We are concerned that this recommendation does not allow the use of a treatment that could reduce these hospitalisations.
4	We are concerned that currently a minority of the HFmrEF and HFpEF populations are routinely seen by HF Specialist services which significantly disadvantages their health care which is not in keeping with the NICE Chronic HF guideline of 2018: people with suspected HF should see a specialist. They therefore do not have the opportunity for HF Specialist teams to assess and make recommendations around managing their symptoms, provide relevant education/support, refer to other services such as Cardiac Rehab etc. For this reason the normally applied ICER threshold of £20k should be reconsidered as too low for a population poorly served at this point in time by health services.
5	We are concerned that an outcome that focusses on mortality is missing the fact that this cohort are elderly with many co-morbidities leading to hospitalisation.

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	In many areas in England heart failure services are only commissioned for the management of the HFrEF leaving primary care to manage the remaining heart failure population. This cohort often have worse QoL than HFrEF patients and more co-morbidities (4.5 at diagnosis and increasing with time: Conrad et al https://doi.org/10.1016/S0140-6736(17)32520-5) and have frequent touch points in primary care and more frequent hospital/rehospitalizations. As the only treatment option for HFpEF these patients often have a high burden of loop diuretics which inconvenience patients, have no outcome benefits and negatively affect renal function (unlike SGLT2i which slow down renal decline and are nephroprotective). By addition of dapagliflozin (alongside a loop diuretic – for which a lower dose may be possible) the trials show, for the first time, a medicine that will improve QoL in HFmrEF and HFpEF.
6	We feel that the NICE modelling for primary care contact at 6/year is likely an underestimate given the number of co-morbidities in this ageing population and is an underestimated cost in the model. A treatment that improves QoL/ symptoms will have a positive impact on the need for primary care resource. The evidence from the relevant trials suggests and improvement in KCCQ which is significant in managing any patient with HF and may have other positive health and social care benefits which are not accounted for.
7	We are concerned that there is a mismatch in the weighting of outcomes on mortality. Patient preference is for improved quality of life over mortality benefits. This includes avoiding hospital admissions (each admission reduces prognosis; is expensive to overall healthcare system; inconveniences patients, family, and carers; risks hospital acquired infection and will contribute to reduced acute hospital flow and the need for social care). NICE suggest that the impact of hospitalisation for HF will last less than a year before recovery, but that clinician experience suggests that a patient typically never recovers fully post hospitalisation whether this be reflected in their exercise tolerance or general well- being which emphasises the significance of a hospitalisation and the need to avoid if possible.

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):	UK Clinical Pharmacy Association
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	Nil

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Name of commentator person completing form:	[redacted] and [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	We are concerned that the recommendation does not differentiate between patients with mildly reduced ejection fraction and a preserved ejection fraction. Patients with an ejection fraction between 40% and 50% may benefit more from treatment with dapagliflozin than those with an ejection fraction greater than 50%. This large group of patients will be denied an effective therapy that improves quality of life and reduces hospitalisations.
2	The assumption that all patients with Heart failure with improved ejection fraction will be already prescribed dapagliflozin (or empagliflozin) is suspect. Not all patients with a previous diagnosis of heart failure with reduced ejection fraction will have been reviewed over the last 2 years and may have missed out on this treatment. If this recommendation is made they will be excluded from consideration of this disease modifying treatment.
3	The cohort studied in this trial do not have any disease modifying treatments available to them, only treatment of co-morbidities. If dapagliflozin is not recommended as a treatment for Heart failure with preserved ejection fraction, patients and clinicians continue to have limited treatment options.
4	This patient group accounts for a large proportion of hospital admissions. In view of our ageing population and increasing prevalence of heart failure with preserved ejection fraction, the pressure of recurrent hospitalisations on health services will only increase in the future. This recommendation does not allow the use of a treatment that could reduce these hospitalisations.
5	It is estimated that patients with mildly and preserved ejection fraction have between 6-12 GP visits per year. Dapagliflozin has been shown to improve the QOL with significant improvement in KCCQ scores. This could reduce the number of GP visits this patient group might need. There was a numerical reduction in cardiovascular mortality (not powered to show a significance) and an improvement in KCCQ scores is indirectly linked to reducing the risk of death.

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):	[**Insert organisation name**]
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	[**No disclosures to declare**]

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Name of commentator person completing form:	**[Lisa Anderson, Clinical Expert for this technology assessment (TA)]**
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.
Example 1	We are concerned that this recommendation may imply that ……..
1	The TA committee was satisfied that dapagliflozin significantly reduced the combined risk of cardiovascular death or first heart failure event in HFpEF and HFmrEF (heart failure with mildly reduced EF) and there are currently no disease-modifying treatments available. Heart failure (HF) is the commonest cause for admission in over 65-year-olds and heart failure admissions increased by one third in the five years before the pandemic.[1] Health education England project a doubling of admissions for cardiology patients in the next 25 years[2] – and this picture will be dominated by HFpEF, as effective medications for HF with reduced EF (HFrEF) has led to reduced admissions for this subgroup.[3] HF is one of the leading causes for readmission – currently 22% in 28 days. HF admissions are long and costly and there is an existing capacity crisis in the NHS. NHS England is investing in experimental alternatives to hospital admission to try and mitigate this crisis (Virtual Ward funding for 22/23, £200m, for 23/24 estimated £250m). Dapagliflozin reduces admission risk in a dominant condition contributing to the NHS bed crisis, but the legacy costing measures used in this TA are unable to take account of this benefit in terms of improved opportunity cost (ability to admit other patients to hospitals which are otherwise at capacity) or the reduced need for NHS investment in untested service models.
2	Plausibility for reduced mortality. Dapagliflozin significantly reduced heart failure admissions/worsening HF events (hazard ration 0.79). In England, a heart failure admission carries a 10% inpatient mortality and a further 33% post discharge 1 year mortality (total = 43% 12 month mortality).[1] Dapagliflozin's ability to reduce admissions means that it is highly plausible that dapagliflozin will lead to a reduction in mortality.
3	The resource use estimate for hospitalisation is not correct. The HRG cost is not based on length of stay but on the number of comorbid conditions. The complications and comorbidities for each HRG subchapter are updated annually and for heart failure (EB subchapter) can be taken from a defined list only. The 2020/21 NHS National Cost Collection data shows that heart failure is highly comorbid and the commonest associated HRG is EB03B – with 11-13 comorbidities. A weighted average of the annual admission cost is the most appropriate cost to use and can be considered conservative, as HFpEF patients are generally older than HFrEF patients and have even more comorbidities. The HRG code EB03E was used in only 3.5% of admissions in 2020/21.

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	<table><tr><td>HRG</td><td></td><td>Activity</td><td>Total Cost</td></tr><tr><td>EB03A</td><td>Heart Failure or Shock, with CC Score 14+</td><td>46,097</td><td>£187,752,739</td></tr><tr><td>EB03B</td><td>Heart Failure or Shock, with CC Score 11-13</td><td>46,620</td><td>£134,096,477</td></tr><tr><td>EB03C</td><td>Heart Failure or Shock, with CC Score 8-10</td><td>38,787</td><td>£84,288,556</td></tr><tr><td>EB03D</td><td>Heart Failure or Shock, with CC Score 4-7</td><td>29,746</td><td>£49,585,591</td></tr><tr><td>EB03E</td><td>Heart Failure or Shock, with CC Score 0-3</td><td>6,017</td><td>£6,899,584</td></tr></table> Use of a weighted average would also be consistent with the method used in TA679.
4	Severity: the committee should consider employing the severity modifier to give more weight to health benefits in the most severe conditions such as HFpEF. Dapagliflozin reduces HF admissions in HFpEF, a condition with a >40% 12-month mortality following admission and HF is a leading cause for readmission (22% within 28 days). There are no existing treatments available so the introduction of a novel disease modifying therapy would have a wider secondary impact on improved treatment pathways as there is currently no specialist service provision for HFpEF in most ICSs. 1. National HF Audit NICOR NICOR | Heart Failure (Heart Failure audit) 2. Https://eproduct.hee.nhs.uk/ 3. Owan, Theophilus E., et al. Trends in prevalence and outcome of heart failure with preserved ejection fraction. New England Journal of Medicine 355.3 (2006): 251-259 4. NHS England » National Cost Collection for the NHS
5	
6	

Insert extra rows as needed

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Single Technology Appraisal

Dapagliflozin for treating chronic heart failure with preserved or mildly reduced ejection fraction [ID1648]

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

Name	[redacted]
Organisation	University Hospitals Southampton and Portsmouth Hospitals University NHS Trusts
Conflict	N/A
Comments on the DG:	

To those it may concern,

Regarding NICE GID-TA10942 (Dapagliflozin for treating chronic heart failure with preserved or mildly reduced ejection fraction).

I am writing on behalf of the South Coast Heart Failure departments (Trust and community). Our hospitals and community services (University Hospitals Southampton, Isle of Wight and Portsmouth Hospitals University NHS Trust) serve a combined population of approximately 2.7 million patients.

Heart failure is a condition that necessitates a relatively long length of stay, at double the average LOS for all conditions. The changing population demographics and co-morbidity burden mean that heart failure with mildly reduced and preserved ejection fraction is set to become the dominant subtype. Following an admission with decompensated heart failure there are high rates of mortality and readmission and markedly impaired quality of life. At present the only treatment option available is to manage symptoms by decongestion with loop diuretics.

As heart failure Cardiologists and Physicians working with the wider MDT, we are acutely aware of the growing pressure on the emergency and acute medical departments at our respective hospitals. Any treatment which has the capability to reduce rates of heart failure hospitalisation should be considered within the wider pressures on the NHS. Deliver-HF has demonstrated an early risk reduction in heart failure hospitalisation, with separation of the treatment and placebo curves seen within the 0-3 month period.

Patients with heart failure with preserved ejection fraction are more likely to be elderly and co-morbid. The consequence of an inpatient episode in this cohort is often functional decline. Frail patients are likely to develop sarcopenia, suffer complications of inpatient management such as falls and infection and lose mobility. In our experience many patients never regain

the quality of life they enjoyed before being hospitalised with heart failure. Often a heart failure admission is followed by a readmission at a point before quality of life has recovered to baseline, beginning a ‘step-wise’ decline in overall health. For this reason, we contest that the impact of a heart failure hospitalisation is limited to 6 months post discharge.

We would like to highlight that heart failure with mildly reduced and preserved ejection fraction is a spectrum of disease severity. Some patients will be higher risk and this can be determined by NYHA class, magnitude of NT-proBNP (or BNP) elevation, requirement for inpatient management, and presence of co-morbidities. We would like to ensure that our high-risk patients do not miss out on a treatment which may improve quality of life and reduce readmissions because it has been determined not be cost effective in the population as a whole. It is important to reiterate that for patients with HFPEF, still a high risk group, there is no other life changing therapy. The trial point estimate of benefit is in a position that would normally be considered and approved by NICE. In addition, published meta-analysis demonstrates no modification of effect according to ejection fraction. It is vital that patients do not have inequitable access to heart failure care solely based on their ejection fraction.

As heart failure specialists we have positive experience of using SGLT2 inhibitors widely in heart failure with reduced ejection fraction. From this basis we would like to be able to recommend the use of SGLT2 inhibitors in heart failure with mildly reduced and preserved ejection fraction to improve quality of life and reduce risk of heart failure hospitalisation.

On behalf of the Trust base and community heart failure teams at University Hospitals Southampton, Isle of Wight and Portsmouth Hospitals University NHS Trust.

[redacted]

Name	[redacted]
Conflict	N/A
Comments on the DG:	

Question: Has all of the relevant evidence been taken into account?

Response: No, it doesn't appear to have been. The pre-specified individual patient level data pooled analysis demonstrating a clear, consistent, and

meaningful cv mortality benefit, for the first time in this population of patients, who to date have had no evidence-based therapies does not appear to have been fully appreciated.

Question: Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

Response: The cost-effectiveness interpretations appear to assume no cv benefit (see above) nor recognise the prognostic importance of symptomatic deterioration nor heart failure hospitalisation in this cohort of patients. From the national heart failure audit, in-patient mortality from heart failure is 9%. Heart failure represents the condition with single biggest cost to the NHS, predominantly via hospitalisations. Patients with heart failure often have very prolonged and complicated hospital admissions and to date there has been nothing to prevent these prior to these data. Hospitalisations in DELIVER were reduced within two weeks, which if translated to a decrease in NHS hospitalisations would be welcomed by all given the current stresses on services.

Question: Are the recommendations sound and a suitable basis for guidance to the NHS?

Response: No, prior to the DELIVER trial, other than loop diuretics, patients with HF with an EF>40%, who represent a broad range of cardiomyopathy patients, had no other treatment options, and had a prognosis that is worse than most cancers. The DELIVER trial represents a paradigm shift in the management of this patient group, with evidence of both symptomatic relief and CV mortality benefit.

Dapagliflozin should be recommended in patients with HF>40% and given the familiarity in primary care of the drug and the number of such patients within primary care, patients should not have to wait for specialist advice before being prescribed Dapa for this condition. Hospital specialist MDTs do not currently have capacity and re-referral of already diagnosed patients who should be initiated in primary care.

Question: Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Response: HF with preserved ejection fraction tends to affect the elderly (although the young too in those with inherited cardiac conditions) and therefore, given the same relative risk reduction in mortality is seen in the younger patients with reduced ejection fraction in Dapa-HF as in older cohort of preserved ejection fraction in DELIVER, HFpEF should be approved in the same way as HFrEF is approved.

Were the current recommendations to persist, those patients with diabetes or CKD and HFpEF would have access to this disease-modifying agent and those without would not.

Name	[redacted]
Conflict	N/A
Comments on the DG:	

Question: Has all of the relevant evidence been taken into account?

Response: Yes I have looked at all the evidence.

Question: Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

Response: I agree with the cost effectiveness evidence. They are reasonable.

Question: Are the recommendations sound and a suitable basis for guidance to the NHS?

Response: I am in disagreement with the guidance.

I am the first HCP in the UK to set up a Cardio Metabolic Clinic in the NHS. I have had persoanl experience in managing HfpEf patients , hundreds of them. I can vouch that SGLT2i as per evidence and reseach have played very important role in managing these complex patients. All range of heart failure patients should get SGLT2i as part of their four pillars."

The recommendations should be to use in Hfpef patients as per research globally. When the whole world is using it for hfpef and it is in the best interest of the patient. I have personally used this in many Hfpef patients & they have shown several advantages which will lead to improvement in morbidity & mortality of these group of patients.

Question: Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Response: There is no discrimination in the document. No all good in this section.

Name	[redacted]
Organisation	Leeds Teaching Hospitals NHS Trust (Heart Failure Team)
Conflict	N/A
Comments on the DG:	

Question: Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

Response: The data is hard to use to persuade us it has a Quality of Life (QoL)/symptomatic improvement. The outcome is mainly driven by reduced hospitalisation for heart failure or worsening heart failure episode - both of these could be argued to improve QoL for patients. There is a significant numerical change between KCCQ score but it is not possible to see if the KCCQ change from baseline in the Dapagliflozin arm is >5 points (which is deemed a significant change in QoL). We feel the assumption of 6 GP visits per year is not evidenced based and, therefore, not a reliable marker of cost. The meta-analysis of Dapagliflozin across all HF syndrome shows a significant CV death reduction RRR 14% and we feel also that dapagliflozin does reduce hospitalisations, improve QoL and symptoms for patients with HFmEF and HFpEF.

Question: Are the recommendations sound and a suitable basis for guidance to the NHS?

Response: We feel NICE should focus on the QoL benefits to patients as QoL matters. Achieving prognostic benefit in this heterogeneous group is difficult. We think that the effect of a long (> 1 week) hospitalisation for a probably elderly, co morbid patient is very difficult to assess and we suspect has a very long impact on the QoL. Furthermore, we know that longer hospitalisations are likely to have an impact on consumption of social care resource when patients decondition so we think that reduction in HF hospitalisation for these patients is long, and the economic impact almost certainly underestimated. We believe very strongly that a focus on analysis of effect on QoL is actually the most important metric to a patient and, that given the number of other medical complaints that these patients have, any beneficial effect on QoL is of high importance. We feel that dapagliflozin does reduce hospitalisations. improve QoL and symptoms for patients with HFmEF and HFpEF.

Name	[redacted]
Organisation	Medicines Optimisation Team, NICE
Conflict	N/A

Comments on the DG:

Comment on Section 1 Recommendations, Section 1.1:

Second paragraph under 'Why the committee made these recommendations' last sentence was difficult to follow on first read. Consider changing to "It is not clear whether dapagliflozin plus standard care reduces the likelihood of dying from any cause or specifically from cardiovascular causes."

Name	[redacted]
Conflict	N/A
Comments on the DG:	

Question: Has all of the relevant evidence been taken into account?

Response: There is significant unmet need, with trials of all other classes of agent e.g. ARB/ ARNI/ Digoxin/ MRA failing to demonstrate any benefit in patients with HF and EF>40%

- Jund et al. demonstrate consistent RRR in mortality across the range of ejection fraction with no attenuation at higher EFs
- Vaduganathan et al. demonstrated that dapagliflozin can add up to 2.4 years of event-free survival in this highly morbid, currently untreated group of patients.
- Kosiborod et al. and Ostrominski demonstrated significant improvement in quality of life as measured by KCCQ and NYHA respectively with comparable magnitude of effect as seen in Dapa-HF and Paradigm studies.
- Butt et al. demonstrated that even frailest of patients derive benefit from Dapagliflozin and that it was as well tolerated as placebo even in the frailest of patients

Question: Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

Response: There is a clear and established causative link between heart failure hospitalisations and mortality in heart failure.

- Heart failure symptoms are highly predictive of overall prognosis
- Patients with HF and ejection fraction>40% do not currently have access to any evidence-based therapies and therefore Dapagliflozin represents true innovation
- Patients with HF and ejection fraction>40% should not be held to the lower end of the willingness to pay threshold ie £20000 per QALY but instead should have access up to the £30000 per QALY threshold
- Patients with cancer have a comparable prognosis as patients with HF and ejection fraction>40% and have access to innovations up to and sometimes exceeding the £30000 per QALY threshold

Question: Are the recommendations sound and a suitable basis for guidance to the NHS?

Response: Dapagliflozin is widely prescribed in primary care for diabetes and CKD at the same dose and frequency and with the same counselling as for HF>40%

- People with HF>40% have been discharged to primary care due to the lack of evidence-based therapies and lack of commissioning of secondary care services
- Secondary care are overwhelmed managing patients that require specialist input and expertise e.g., HF with EF<40% where other treatment options are available
- Dapagliflozin should be available to any patient diagnosed with HF >40% and initiation should not depend on specialist advice which is time-consuming and represents significant opportunity costs for the specialist

Question: Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Response: HFpEF tends to be a disease of elderly women and therefore this group of patients should have equitable access to Dapagliflozin as the younger more gender-balanced diabetes and CKD cohorts are routinely initiated in primary care

Name	[redacted]
Conflict	
Comments on the DG:	

I am writing this purely to provide what I hope is useful information.

I will be [redacted] years of age on 9th March 2023 and attend a local heart care clinic plus a local physical play group, both, generally on a weekly basis,in an effort to keep me fit for as long as possible. (I played tennis until nearly [redacted])

My EF is around 20% and was first evident about August 2018, and since the first echogram I have been taking Entresto, Bisoprolol, Atorvastatin as well as Warfarin and Finasteride.

My Cardiologists have recently advised me to take Dapagliflozin which I have now commenced.

My query , to be answered is, am I now taking too many tablets, and duplicating.

NICE recommendations are that Dap can be taken with the other drugs. Ignoring my own status, it would seem to me that physical fitness may have a significant effect on HF

Dapagliflozin for treating chronic heart failure with preserved or mildly reduced ejection fraction (ID1648)

EAG response to company draft guidance comments

March 2023

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1 Introduction

This document provides the Evidence Assessment Group (EAG)'s critique of the company's response to the draft guidance (DG) document produced by the National Institute for Health and Care Excellence (NICE) for the appraisal of dapagliflozin for treating chronic heart failure with preserved (HFpEF) or mildly reduced ejection fraction (HFmrEF) (ID1648).

Section 2 presents the EAG's critique of the issues covered by the company in response to the DG, the company's updated results are presented in Section 3 and Section 4 presents the EAG's updated base case and scenarios. Issues are discussed according to issue number as per the company's response document to DG. Table 1 below summarises these issues, including which area of the DG they relate to and EAG comment, as well as reference to which section they are discussed in more detail.

Table 2 below summarises the EAG's preferred assumptions within the EAG report, committee preferences/comments from the DG and the company's updated base case assumptions following DG.

Within the DG, the committee highlighted areas of remaining uncertainty relating to the modelling of survival which could be resolved through consultation by the company submitting scenarios in relation to:

- exploring the exclusion of a direct and/or indirect treatment effects of dapagliflozin on cardiovascular mortality (CVM) and all-cause mortality (ACM);
- providing evidence that the economic model can reproduce the outcomes observed in DELIVER.

Table 1. Summary of issues covered in company's response to DG

Issue in company DG response		Relevant sections of DG	Company response	EAG comment
1	Removal of CVM and ACM treatment effects as scenarios	3.7, 3.11, 3.26	• Rationale for why treatment effects should be included reiterated • Scenarios requested by committee provided	The EAG acknowledges arguments put forward by the company, but notes that they do not rule out the possibility of no treatment effect on these outcomes given [redacted] in the DELIVER trial. Scenarios requested by the

				committee have been provided and should help inform decision-making. The EAG's rationale for removing CVM benefit from the base case was also based on [redacted] between those with and without a prior LVEF ≤40%. (Section 2.1 below)
2	Appropriateness of the model	3.13, 3.26	• Notes similar structure to previous dapagliflozin and empagliflozin appraisals • States that economic model is consistent with results in the DELIVER trial	The EAG agrees with the company that the model is in line with previous appraisals which were accepted by committee and at each stage of the model neither NICE nor the EAG raised any concern. In efforts of validating the company's observed and predicted results comparisons, the EAG raises concern over the alignment of the trial and model results. (Section 2.2 below)
3	Model structure contributing to a sustained treatment effect	3.15	• Provides comment on use of transition probabilities prior to and after the discontinuation of dapagliflozin • Concludes that the modelling approach does not introduce bias of CE results in favour of dapagliflozin	The effect of dapagliflozin on KCCQ-TSS health state leads to a sustained treatment effect over time, which is unlikely to be clinically plausible. The company's assumption that dapagliflozin patients experience SoC transition probabilities after discontinuation is only partially conservative and leads to a sustained relative treatment effect for patients in KCCQ-TSS 4 in the model over time. (Section 2.3 below)
4	Correct use of NHS reference costs	3.18, 3.26	• Concludes that 2020/2021 reference costs should be used in the base case	Given the gross increase in costs associated with non-elective inpatient costs compared to previous years, which is most likely in part to be due to COVID-19, the EAG considers the costs from previous years inflated to the current cost year to be the

				most generalisable source of costs. (Section 2.4 below)
5	WTP threshold	3.2, 3.27	• Concludes that £30,000 WTP threshold is appropriate given the unmet need for new and effective treatment options	The most appropriate WTP threshold is a decision to be made by committee. Arguments put forward by the company are partly based on new scenarios provided in their response to DG, but the EAG does not consider uncertainty to be completely resolved. (Section 2.5 below)
6	Initiation of treatment and specialist involvement	3.29	• Provides arguments for initiation in primary and secondary care, without further specialist advice, once a diagnosis of HFpEF/HFmrEF has been confirmed by a specialist	The most appropriate setting for initiating dapagliflozin, and whether further specialist advice is required, is a decision to be made by committee. Arguments put forward by the company are the same as those prior to DG. (Section 2.6 below)

Abbreviations: ACM, all-cause mortality; CE, cost-effectiveness; CVM, cardiovascular mortality; DG, draft guidance; EAG, External Assessment Group; HFmrEF, heart failure with mildly reduced LVEF; HFpEF, heart failure with preserved LVEF; KCCQ-TSS, Kansas City Cardiomyopathy Questionnaire - Total Symptom Score; LVEF, left ventricular ejection fraction; NA, not applicable; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; SoC, standard of care; WTP, willingness to pay.

Table 2. List of assumptions and preferences following the EAG report and draft guidance.

EAG preferred assumptions	Committee preference / comments	Revised company base case assumptions
Age adjusted utilities	EAG assumption	EAG assumption
Multiplicative population adjusted utilities	EAG assumption	EAG assumption
Removal of amputation from adverse events	EAG assumption	EAG assumption
Non-elective inpatient (NEL) costs taken from NHS Reference Costs 2019/20 and inflated to the 2020/21 cost year	The committee concluded that both EAG and company preferred sources of NHS reference costs were plausible and was uncertain which NHS reference cost values were most appropriate, given the uncertain impact of the COVID-19 pandemic.	2020/2021 NHS reference costs
HHF disutility applied for 2.75 months	HHF disutility applied for 6 months	HHF disutility applied for 6 months
6 annual GP visits per year	EAG assumption	EAG assumption

Code cost associated with shorter HHF LoS used (EB03E)	EAG assumption	EAG assumption
Removal of dapagliflozin treatment effects from UHFV event calculations	The committee considered that a comparison of the hospitalisation for heart failure predictions from the economic model (including the impact of changes in KCCQ-TSS state over time) and the observed data from DELIVER is needed to determine whether the modelling approach was appropriate.	Inclusion of a dapagliflozin treatment effect in UHFV event calculations.
Removal of dapagliflozin treatment effects from CV and non-CV survival curve calculations	The committee considered that it may be appropriate to include a direct and/or indirect treatment effect of dapagliflozin on cardiovascular and all-cause mortality but noted that the model should be able to replicate the observed trial data.	Inclusion of a dapagliflozin direct and in-direct treatment effect in survival curve calculations.

Abbreviations: CV, cardiovascular; EAG, External Assessment Group; GP, general practitioner; HHF, hospitalisation for heart failure; ICER, incremental cost-effectiveness ratio; KCCQ-TSS, Kansas City Cardiomyopathy Questionnaire - Total Symptom Score; LoS, length of stay; NHS, National Health Service; QALY, quality adjusted life year; UHFV, urgent heart failure visit.

2 EAG's critique of company response to DG

2.1 Issue 1. Removal of CVM and ACM treatment effects as scenarios

The company have provided the scenarios requested by the committee in Section 3.26 of the draft guidance (DG), where indirect and/or direct treatment effects of cardiovascular mortality (CVM) and all-cause mortality (ACM) are removed from the economic model (see Sections 3 and 4 for the results of these scenarios when applied to the company's and External Assessment Group (EAG)'s preferred assumptions, respectively):

- Scenario 1 – dapagliflozin treatment effect removed as a candidate variable from regression models used to generate CVM and ACM extrapolations (removing direct effect of dapagliflozin on CVM and ACM vs placebo)
  Scenario 2 – dapagliflozin treatment effect (as above in scenario 1) removed, as well as removing Kansas City Cardiomyopathy Questionnaire (KCCQ) - Total Symptom Score (TSS) quartile as candidate variables from regression models used to generate CVM and ACM extrapolations (which removes indirect effect of dapagliflozin on CVM and ACM vs placebo).

Despite providing the requested scenarios described above, the company maintain that these scenarios are not appropriate for decision-making. Various arguments are put forward to support their conclusion; these are summarised in Table 3 below.

The company concludes that if the committee still considers there to be uncertainty present in terms of the treatment effect of dapagliflozin on CVM and ACM, scenario 1 should be considered the most relevant scenario analysis, as this is in line with precedent from TA773 where the direct effect of empagliflozin on mortality was removed from the base case analysis but the indirect effect was not removed and this was not requested by the committee. The EAG notes, however, that in TA773 the committee concluded that dapagliflozin was the most appropriate comparator for the appraisal (section 3.3 of the final appraisal document [FAD]), where based on an indirect treatment comparison similar effectiveness was concluded (section 3.6 of the FAD).[1]

Overall, the EAG concludes that:

- the company has provided the scenarios requested by committee in terms of removing indirect and/or direct treatment effects of dapagliflozin on CVM and ACM. When these two scenarios are applied to the company's revised base case and the EAG preferred

assumptions are similarly applied, the probabilistic incremental cost-effectiveness ratio (ICER) of both scenarios lie between the £20,000 and £30,000 willingness to pay (WTP) threshold;

- the EAG acknowledges arguments put forward by the company in terms of why [redacted] of dapagliflozin [redacted] in the DELIVER trial,[2, 3] and the existence of the pooled analysis with the DAPA-HF trial,[4] but does not consider this to resolve the uncertainty surrounding the effect of dapagliflozin on these outcomes specifically in the population with heart failure with preserved (HFpEF) or mildly reduced (HFmrEF) left ventricular ejection fraction (LVEF);
- some evidence has been put forward from an external study and a prespecified analysis of the DELIVER trial that baseline KCCQ scores may be linked to outcomes such as CVM and ACM,[5, 6] which may represent a biological mechanism through which a mortality benefit might be expected in the DELIVER trial (given improvements in KCCQ were seen vs placebo). However, this is not conclusive given limitations such as these analyses being based on baseline KCCQ rather than improvements, and improvements vs placebo in the DELIVER trial being smaller than the increments used in the external analysis;
- clinical expert feedback about the plausibility of the mechanism put forward by the company through which dapagliflozin might be expected to improve CVM and ACM, which includes improvements in KCCQ scores and reduction in hospitalisation for heart failure (HHF) observed in the DELIVER trial, would be useful for committee decision-making;
- the EAG agrees that there may be a rationale for why a CVM or ACM benefit for dapagliflozin might be expected, but does not consider that the evidence available from DELIVER proves the existence of a survival benefit over placebo;
- the EAG's decision to remove a treatment effect of dapagliflozin on CVM in its base case was also based on the [redacted] observed between those with and without a prior LVEF ≤40% in the DELIVER trial, given that, in clinical practice, people with a prior LVEF ≤40% that has since improved to be >40% would not be required to discontinue it if recommended while their LVEF was ≤40%. The point estimate for those with no prior LVEF ≤40% was [redacted], while [redacted] dapagliflozin was suggested for the group with a prior LVEF ≤40%.

Table 3. Summary of issues covered in company's response to DG

Point raised by company	Detailed rationale	EAG comment
[redacted] of the DELIVER trial	The company: • reiterate that the DELIVER trial [redacted] for dapagliflozin vs placebo in terms of CVM or ACM; • highlight limitations associated with p-values;[2, 3] • conclude that data included in the original CS do not support a conclusion that dapagliflozin would not reduce CVM compared to placebo.	The EAG acknowledges that the DELIVER trial [redacted] in survival for dapagliflozin over placebo (for either CVM or ACM). This could be interpreted as the DELIVER trial [redacted] in survival between dapagliflozin and placebo. The uncertainty around a survival benefit is why the scenarios provided by the company in response to DG are useful for decision-making.
Pooled analyses of DAPA-HF and DELIVER trials	The company: • highlight statistically significant results from a pooled analysis powered to detect a difference in CVM, for both CVM and ACM;[4] • note that there was no evidence of effect modification by LVEF value as a categorical or continuous variable; • highlight that the SmPC for dapagliflozin uses this pooled analysis and concludes that both studies contributed to the effect on CVM.[7]	The DAPA-HF trial included in this pooled analysis includes those with HFrEF, a population for which dapagliflozin has already been approved.[8] While the pooled analysis shows a statistically significant benefit of dapagliflozin in terms of CVM and ACM, given that this appraisal focuses on HFpEF/HFmrEF and not HFrEF, the EAG does not consider that this pooled analysis [redacted]. While no significant effect of LVEF on treatment effects was observed for CVM or ACM in this pooled analysis as a continuous or categorical variable, the EAG notes that categorical data is based on six LVEF categories rather than division into ≤40% and >40% LVEF groups. In figure 3 of this pooled analysis, the results indicate a statistically significant effect of dapagliflozin in the ≤40% group but not in the >40% group, [redacted]. Across the six LVEF categories, there is variation in the point estimate estimated for HRs for both outcomes. For example, the >44% to ≤51% and >51 to ≤60% groups had slightly higher HRs than groups ≤44% (though the EAG notes for the >60% group, the HR point estimate is similar to or lower than ≤44% groups for both outcomes). Therefore, the EAG does not consider this pooled analysis presents strong enough evidence to prove that

		[redacted] would be observed if the DELIVER trial [redacted] for these outcomes.
Biologically plausible mechanism through which dapagliflozin may reduce CVM and ACM vs placebo	The company note that: • [redacted] and clinically meaningful reductions in HHF and improvements in mean KCCQ score vs placebo provide a biologically plausible mechanism through which dapagliflozin may reduce CVM and ACM vs placebo; • the above mechanism is in line with clinical expert feedback received by the company; • HHF is associated with a substantial quality of life burden and risk of infection. Reducing this may be associated with a reduction in overall decline in heart function and quality of life that people with chronic HF typically experience over time; • the DELIVER trial demonstrated [redacted] KCCQ scores as early as 1 month [redacted] at 8 months, and [redacted] using dapagliflozin experienced clinically meaningful improvements in KCCQ scores (and [redacted] deteriorations) • external evidence for an association between KCCQ score and mortality exists;[5] • there is some evidence from within the DELIVER trial of links between KCCQ score and CVM and/or HHF[6]	The EAG acknowledges the biological mechanism put forward by the company and considers that feedback from the committee's clinical experts about the plausibility of this mechanism would be useful for decision-making. The EAG confirms that [redacted] reductions in HHF (median follow-up [redacted], and [redacted] in KCCQ scores (at month 8), vs placebo were observed in the DELIVER trial. Improvements in KCCQ scores were observed as early as month 1 and sustained until month 8, but it is unclear if improvements were [redacted] at all time-points as p-values were not provided for other time-points in the CS. It is also unclear if the differences in KCCQ scores vs placebo are clinically meaningful (the largest difference was 2.4 [1.5 to 3.3] for KCCQ-TSS at month 8 for dapagliflozin vs placebo). The EAG also confirms that for KCCQ-TSS, [redacted] between dapagliflozin and placebo were observed for proportions achieving certain thresholds of improvement or deterioration; [redacted] in the dapagliflozin experienced ≥5- and 10-point improvements, whereas [redacted] people in the dapagliflozin group experienced ≥5-point deteriorations. While the company refers to "extensive evidence in the published literature" to support a relationship between KCCQ score and mortality, only reference to one study is provided.[5] The EAG considers that this study provides some evidence to support a potential link between KCCQ score and mortality in heart failure with a sample size of 8850 patients specific to the LVEF ≥40% group; however, it notes that it is unclear whether this analysis is based on the KCCQ-TSS sub score, which is the score used in this appraisal, and that the median duration of the current analysis is 1.6 years, [redacted] DELIVER trial. Also, the analysis only assesses the impact of baseline KCCQ on outcomes, not the impact any improvements from baseline in KCCQ would have on outcomes, and statistically significant HRs are based on 10-unit decrements in HRQoL, whereas in the DELIVER trial the mean difference in change from baseline between dapagliflozin and placebo at 8 months was much lower than this (2.4 higher in dapagliflozin). No analysis of CVM is provided in this paper. This paper may provide some support to the idea that

		improvements in KCCQ score observed in the DELIVER trial could represent a biologically plausible mechanism for why an impact of dapagliflozin on CVM or ACM might be expected with a larger sample size, but the EAG does not consider it to be conclusive based on the limitations mentioned, particularly as an analysis of CVM was not included in this paper. The EAG acknowledges the pre-specified analysis of the DELIVER trial raised by the company,[6] which may suggest a link between baseline KCCQ-TSS and prior hospitalisation for HF as well as between baseline KCCQ-TSS and higher rates of CVM or worsening HF, with significant differences observed across KCCQ-TSS terciles for CV death alone. However, this analysis is also based on baseline KCCQ values and it is unclear whether improvements observed within the trial would necessarily lead to improvements in other outcomes as a result. The EAG acknowledges that there may be some evidence from this analysis to support the idea that improvements in KCCQ scores may impact on other clinical outcomes such as CVM, but this is not conclusive given the limitations described.
Use of observed DELIVER trial is more robust than arbitrary assumptions	The company: • reference previous NICE appraisals for dapagliflozin and empagliflozin (TA679 and TA773), where no preference for removal of direct or indirect effect on mortality was expressed by the committee;[1, 8] • highlight the NICE manual in terms of a strong preference for RCTs to inform relative treatment effects, which the company state including a treatment effect aligns with.	The EAG notes the points raised by the company, but highlights the following: • in the previous dapagliflozin appraisal (TA679),[8] a statistically significant effect of dapagliflozin on CVM and ACM vs placebo was observed in the DAPA-HF trial; • in the previous empagliflozin appraisal (TA773),[1] the EAG notes that the committee concluded that dapagliflozin was the most appropriate comparator for the appraisal (section 3.3 of the FAD), where treatment effects were concluded to be similar (section 3.6 of the FAD); • the EAG acknowledges the importance of RCTs in terms of informing relative treatment effects; however, in addition to the [redacted] between treatments for CVM and ACM in the DELIVER trial, the EAG's decision not to include a treatment effect for CVM in its base case was also based on the [redacted] between those with and without a prior LVEF ≤40% in the DELIVER trial, given that, in clinical practice, people with a prior LVEF ≤40% that has since improved to be >40% would not be required to

		discontinue it if recommended while their LVEF was ≤40% (Sections 3.3.5 and 4.2.6.4 of the EAG report, Section 3.8 of DG).
Uncertainty relating to magnitude of treatment effect already captured within the PSA	The company note that: • the PSA performed by the company in the CS already captures uncertainty with regards to treatment effect of dapagliflozin on CVM and ACM robustly; • across each PSA iteration, the magnitude of dapagliflozin treatment effect was varied based on probability distributions derived from the uncertainty surrounding the point estimates in the DELIVER trial; • average treatment effects modelled for dapagliflozin (in terms of HRs for CVM and ACM vs placebo) are [redacted] and [redacted] – replicating the observed HRs for CVM and ACM, respectively, in the DELIVER trial • the PSA already considers the probability of dapagliflozin being equal or worse than placebo at reducing CVM and ACM, with only [redacted] and [redacted]%, respectively, of iterations modelling this assumption.	The EAG acknowledges the additional arguments put forward by the company but does not change their base assumptions for the following reasons; • although the PSA includes the uncertainty around dapagliflozin treatment effects, it fails to resolve the uncertainty around the existence of a survival benefit. While a survival benefit may be plausible, a relationship has not been proven in the DELIVER trial. As such, a scenario analysis exploring this is not inconsistent with exploring the uncertainty in the PSA; • a scenario analysis is also appropriate considering the limitations of the PSA outcomes which are likely to be highly correlated (HHF and CVM, HHF and ACM, etc.) and yet are treated as independent variables within the PSA.
Extrapolations for CVM and ACM in response to new scenarios are not clinically valid when compared to observed KM data in the DELIVER trial	The company note that: • the extrapolations for CVM and ACM for scenario analyses requested by the committee are not clinically valid when compared to the observed KM data in the DELIVER trial; • CVM extrapolations in scenarios 1 and 2 underestimate the risk of CVM for SoC, while ACM extrapolations overestimate the risk of ACM for dapagliflozin; • Revised company base case CVM and ACM extrapolations closely match the observed KM data from the DELIVER trial (as discussed for issue 2 – Section 2.2).	The EAG aimed to identify the difference in CVM and ACM between DELIVER, the company base case and scenarios 1 and 2 using data from DELIVER and the model, the results of which are presented in Table 4. The results of this analysis show that scenarios 1 and 2 provide results and percentage increases over time which are comparable to the company base case is terms of difference from the DELIVER trial at up to 36 months. As such the EAG considers the results of scenarios 1 and 2 to be as clinically valid as the company revised base case but calls attention to the difference in all modelling scenarios over time compared to DELIVER.

Abbreviations: ACM, all-cause mortality; CS, company submission; CVM, cardiovascular mortality; DG, draft guidance; EAG, External Assessment Group; FAD, final appraisal document; HF, heart failure; HFmrEF, HF with mildly reduced LVEF; HFpEF, HF with preserved LVEF; HFrEF, HF with reduced LVEF; HHF, hospitalisation for heart failure; HR, hazard ratio; HRQoL, health-related quality of life; KCCQ, Kansas City Cardiomyopathy Questionnaire; KCCQ-TSS, Kansas City Cardiomyopathy Questionnaire-Total Symptom Score; KM, Kaplan-Meier; LVEF, left ventricular ejection fraction; NICE, National Institute of Health and Care Excellence; PSA, probabilistic sensitivity analysis; RCTs, randomised controlled trials; SmPC, summary of product characteristics; SoC, standard of care.

Table 4. Comparison of DELIVER CVM and ACM results to company base case and scenarios at 26 and 36 months.

	DELIVER study			Cost effectiveness model								
				Company revised base case			Scenario 1			Scenario 2		
CVM	Dapagliflozin	SoC	Incremental difference	Dapagliflozin	SoC	Incremental difference	Dapagliflozin	SoC	Incremental difference	Dapagliflozin	SoC	Incremental difference
	(N=3,131)	(N=3,132)		(N=3,131)	(N=3,132)		(N=3,131)	(N=3,132)		(N=3,131)	(N=3,132)	
Up to month 26	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Up to month 36	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Percentage increase between times	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ACM	Dapagliflozin	SoC	Incremental difference	Dapagliflozin	SoC	Incremental difference	Dapagliflozin	SoC	Incremental difference	Dapagliflozin	SoC	Incremental difference
	(N=3,131)	(N=3,132)		(N=3,131)	(N=3,132)		(N=3,131)	(N=3,132)		(N=3,131)	(N=3,132)	
Up to Month 26	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Up to Month 36	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Percentage increase between times	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ACM, all-cause mortality; CVM, cardiovascular mortality; SoC, standard of care.

2.2 Issue 2. Appropriateness of the model

The DG (Section 3.13, Page 15) highlighted that the modelling approach used in this appraisal is, "*not a standard modelling approach and could affect model validity'* and noted that*, 'a patient-level multi-state simulation model may have been more appropriate because it generates a patient history and considers competing risk"*.

Following this critique by the committee, the company reiterated that the approach is directly aligned with the modelling approaches used in previous appraisals for dapagliflozin and empagliflozin for previous indications. The company discussed the proposed modelling approach for this appraisal with both the EAG and NICE in advance of the submission who confirmed they did not have any concerns with the approach aside from the adaptations needed to reflect the change in patient population from previous indications.

As such, following the DG the EAG's position has not changed on the suitability of the model structure and maintains its acceptability in inferring cost-effectiveness the of dapagliflozin treatment to HFpEF and HFmrEF populations.

In Section 3.13 of the DG the committee noted that, *"a model that does not replicate the trial data to an appropriate level of accuracy would lead to considerable uncertainty around the plausibility of the model results. The Committee concluded that a comparison of the overall survival and cardiovascular survival predictions from the economic model (which includes the impact of changes in KCCQ-TSS state over time) and the observed data from DELIVER is needed to determine whether the modelling approach was reasonable".*

The company response cited evidence provided in the CS (Figure 9 in the company response to the DG) which highlighted the extensive model validation process which was undertaken in development of the cost-effectiveness model with particular attention to the comparison of DELIVER KM data to the survival models used and their alignment. In efforts to further validate the model, the company visualised the concordance of the observed events rates from DELIVER versus the predicted even rates from the model and calculating a goodness-of-fit statistics (Figure 10 in the company response to DG). The company noted that as the observed event rates from DELIVER are unadjusted for covariate effects, a comparison using the unadjusted risk equations and survival are presented to fairly demonstrate concordance.

The EAG notes how the intercept of observed and predicted event rates lie across the 45˚ line, thereby suggesting the model is able to accurately predict the number of events given the observed events recorded in the model. However, the EAG was unable to replicate the results provided in Figure 10 by the company. As such, the EAG attempted to validate the accuracy of the prediction versus the observed events using the cost-effectiveness model and the DELIVER trial results. The EAG updated the cohort size of the cost-effectiveness model to reflect each arm of the DELIVER trial and compared the number of hospitalisation for heart failure (HHF) and urgent heart failure visit (UHFV) events up to 26 and 36 months, which was approximately the end of the trial. The EAG identified there was a difference in the predicted and observed HF events of [redacted] between the dapagliflozin and SoC arms, respectively, of the model and DELIVER at 26 months. This difference increased to [redacted] at 36 months (Table 5). Between the time points, the number of events increased in each trial arm in the cost effectiveness model by approximately 34%, while the average increase in the DELIVER trial arms were 14.5%. As the discrepancy between the observed and predicted outcomes increased substantially between 26 and 36 months, the EAG considers it likely that this over prediction in modelled results is likely to continue to increase over the remainder of the model time horizon.

For UHFV events the difference in dapagliflozin and SoC arms of the model and study increased from a difference of [redacted] to [redacted]. The EAG therefore considers that the model more accurately reflects the UHFV study events in comparison to HHF events. The EAG notes in particular the increase seen between the time points in the incremental difference between dapagliflozin and SoC treated arms in the model compared to DELIVER, from [redacted] compared to [redacted] in HHF events respectfully. The EAG therefore considers there to be some uncertainty in the model's ability to replicate HHF events observed in DELIVER, as this difference will be further exacerbated over time in the cost effectiveness model.

The EAG also notes how a comparison between the observed and predicted results was requested by committee in order to address the uncertainty around a UHFV dapagliflozin treatment effect. Given the additional evidence and analysis provided by the company and EAG, the EAG considers that this uncertainty has been addressed, with the evidence supporting the conclusion that dapagliflozin treatment does not substantially reduce UHFV events compared to SoC. As such this assumption has been incorporated into the EAG's base case in section 4.1.

Table 5. DELIVER and model HF and UHFV events at up to 26 and 36 months.

	DELIVER study			Cost-effectiveness model			Difference between predicted vs observed events		
HHF events	**Dapagliflozin (N=3,131)**	**SoC (N=3,132)**	**Difference**	**Dapagliflozin (N=3,131)**	**SoC (N=3,132)**	**Difference**	**Dapagliflozin**	**SoC**	**Difference**
Up to month 26	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Up to month 36	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Percentage increase between time points	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
UHFV events	**Dapagliflozin (N=3,131)**	**SoC (N=3,132)**	**Difference**	**Dapagliflozin (N=3,131)**	**SoC (N=3,132)**	**Difference**	**Dapagliflozin**	**SoC**	**Difference**
Up to month 26	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Up to month 36	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Percentage increase between time points	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: HF, heart failure; SoC, standard of care; UHFV, urgent heart failure visit.

To further validate the model, the company compared the modelled proportions of patients in each KCCQ-TSS quartile over time, to the observed results in the DELIVER trial. The company limited the DELIVER trial data used to only included patients with non-missing KCCQ-TSS data. Health states were based on KCCQ-TSS trial data, using quartile thresholds (Q1: TSS 0–54; Q2: TSS 55–72; Q3: TSS 73–87; Q4: TSS 88–100) and from mortality such that each patient at each timepoint was assigned a mutually exclusive health state (Q1, Q2, Q3, Q4 or death; Figure 10 in the company response). The company noted how the modelled traces showed good agreement with the DELIVER trial data, acknowledging that the greatest deviation was seen at Month 1 and was likely due to the averaging of observed transitions over the period from 0 to 4 months to generate the transition probability matrix used in the economic model.

The EAG agrees with the company that the DELIVER trial data and cost-effectiveness model traces are closely aligned, noting the discrepancy seen in the data sources around one month. At this time the model appears to slightly overestimate the proportion of patients in the KCCQ Q1 health state and underestimate the proportion of patients in the KCCQ Q4 health state for both placebo and dapagliflozin.

Given the above analysis provided by the company and validations conducted by the EAG, overall it appears that the model is able to replicate the trial KCCQ state patient proportions but provides overestimates of HF and UHFV events with the incremental difference in UHFV events being similar to the trial and the incremental difference in HF events being overestimated compared to the trial. Given the limited time available to review the company's updated model, the EAG is unclear if the issues affecting both survival and event equations are an artifact of poor parameterisation or a more issue with the model structure.

2.3 Issue 3. Model structure contributing to a sustained treatment effect

In the DG (Section 3.15, Page 16) the committee stated that the "*model structure may contribute to a sustained treatment effect for dapagliflozin, which may bias the cost-effectiveness results in favour of dapagliflozin*".

In response the company expanded on their arguments, indicating that treatment with dapagliflozin led to [redacted] KCCQ score verses placebo and that when patients discontinue from dapagliflozin in the model they are ascribed the equivalent health state transition probabilities as patients receiving SoC, in addition to having the same risks of mortality, HHF, UHFV

and AEs as patients receiving SoC. The company stated that as such the model does not allow for a sustained treatment effect after discontinuing with dapagliflozin and so no bias is introduced.

The EAG considers that the additional arguments put forward by the company do not address the key concerns of the committee. The effect of dapagliflozin on KCCQ-CSS health state (sustained by the combination of the proportion of patients in the better KCCQ-CSS states in the dapagliflozin arm and the low probability of disease progression for both SoC and dapagliflozin arms) leads to sustained treatment effect over time, which is unlikely to be clinically plausible.

The company's assumption that dapagliflozin patients experience SoC transition probabilities after discontinuation is only partially conservative and leads to a sustained relative treatment effect for patients in KCCQ-CSS 4 in the model over time. Due to the company's model structure, this assumption impacts the benefits associated with dapagliflozin on HHF and mortality, as these outcomes are dependent on patients' distribution across KCCQ-CSS states.

As such, the EAG does not consider that the company has appropriately addressed this issue in their response.

2.4 Issue 4. Correct use of NHS reference costs

As part of the DG (Section 3.18, Page 18), the Committee concluded that both sources of NHS reference costs (2020/2021 or 2019/2020 inflated to the current cost year) were plausible, and it was uncertain which NHS reference cost values were most appropriate, given the uncertain impact of the COVID-19 pandemic.

The company, with the preference of using the NHS 20/21 reference costs, expanded their argument for their use stating that due to the current economic climate in the UK and the high rate of inflation, there is no evidence that the NHS has returned to operating in line with pre-pandemic conditions. Adding that the current NHS clinical practice continues to be impacted by the effect of the COVID pandemic.

As outlined in the EAG report, costs relating to non-elective long term stay in the NHS references costs 20/21 appear to have grossly increased compared to the previous cost years, with COVID-19 and the reciprocal increase in demand for resources and hospital beds being a likely mechanism for the increase (Table 6). The EAG agrees that the percentage increase in cost is likely to be higher when compared to previous cost years but believes using the NHS reference costs from 2020/21 will

overestimate the costs relating to non-elective long term hospital stays, leading to the ICER being underestimated as dapagliflozin leads to a lower probability of these events.

Table 6. Comparison of NHS reference costs over time

	NHS reference cost year				
	2016/17	2017/18	2018/19	2019/20	2020/21
AKI weighted cost	£2,618	£2,674	£2,834	£3,011	£3,988
Percentage increase from previous year	-	2%	6%	6%	32%
HHF (NHS reference cost code EB03E)	£1,959	£1,795	£2,170	£1,973	£2,518
Percentage increase from previous year	-	-8%	21%	-9%	28%
Bone fractures weighted cost	£3,797.78	£3,682.56	£3,797.78	£4,066.55	£5,212.21
Percentage increase from previous year	-	-3%	3%	7%	28%

Abbreviations: AKI, acute kidney infection; HHF, hospitalisation for heart failure; NHS, National Health Service.

2.5 Issue 5. Willingness to pay (WTP) threshold

The DG (Section 3.27, Page 24) highlighted that the committee preferred the lower bound of the WTP threshold (£20,000 to £30,000 per QALY), given the large impact of the uncertainties relating to survival estimates on the ICER.

Following the additional evidence provided by the company, in their response to the DG, the company believe that sufficient evidence has been provided to justify the appropriate modelling approach for the indication and as such there is no longer any rationale for the sole consideration of the lower bound of the WTP threshold. The company furthered their argument by highlighting the current unmet need for new treatments for the HFpEF and HFmrEF populations and the urgent requirements for treatments such as dapagliflozin. Particular attention was drawn to HF admissions and the wider benefits a treatment which reduces HF events may bring the NHS which is, “currently running at capacity”.

While the EAG acknowledges that the ability of a treatment to reduce the demand for hospital beds, given a treatment effect which reduces hospitalisation, is crucial in a climate where demand for

hospital beds is high and persistent. for a reduction in HHF events is already accounted for within the constraints of the NICE reference case.

While the company has provided two additional scenarios as requested by the committee, the underlying uncertainty around the effect of dapagliflozin on CVM and ACM and therefore the appropriateness of the direct and indirect treatment effect has not been reduced. The additional analysis provided by the EAG (Table 4, Table 5 and Table 6) highlights the uncertainty of the model in predicting CVM, ACM, HF and UHFV events in line with the observed events in the DELIVER trial and the most plausible costs of NHS resources given the COVID-19 pandemic. The company scenarios have shown that the ICER is highly sensitivity to the assumptions of direct and indirect treatment effects and is likely to be equally sensitive, if not more so, to changes in the incremental difference in HF events between treatments as this is the key driver of the incremental QALYs in the model. As such the EAG considers it not to be unreasonable for the committee to have a preference for the £20,000 WTP threshold.

2.6 Issue 6. Initiation of treatment and specialist involvement

The EAG does not consider any new arguments to have been supplied by the company that would change existing conclusions but considers this to be an issue that clinical experts would be best placed to comment on in terms of committee decision-making.

3 Company updated results

The company updated its base case assumptions with the following changes, with results presented in Table 7 below:

- Including age-adjusted and multiplicative population utilities;
- The hospitalisation for heart failure (HHF) disutility is applied for 6 months;
- The Healthcare Resource Group (HRG) cost code (EB03E), associated with less severe HHF, is used to cost HHF;
- The economic model assumes 6 annual general practitioner (GP) visits per year;

  Removal of amputation as an adverse event in the economic model.

Similarly, the results of the additional scenario under differing mortality assumptions as requested by committee are presented in

Table 8.

Table 7. Company's revised base case results post ACM 1. Replicated from Tables 3 and 5 in the company response to draft guidance.

Interventions	Total Costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Deterministic results							
Dapagliflozin plus SoC	£8,527	8.295	4.490	£2,117	0.370	0.236	£8,975
SoC	£6,410	7.926	4.255	-	-	-	-
Probabilistic results							
Dapagliflozin plus SoC	£8,496	-	4.497	£2,137	-	0.232	£9,226
SoC	£6,359	-	4.265	-	-	-	-

Abbreviations: ACM, appraisal committee meeting; ICER, incremental cost effectiveness ratio; LYG, life year gained; QALY, quality adjusted life year; SoC, standard of care.

Table 8. Additional scenario analysis results (run based on the company base case following the DG response). Replicated from Table 2 in the company's response to DG.

Results	Deterministic results		
	Inc. costs	Inc. QALYs	ICER
Company base case (following clarification questions)	£1,885	0.251	£7,519
Revised base case (following the DG response)	£2,117	0.236	£8,975

Scenario 1 (removal of dapagliflozin treatment effect from the regression models)	£1,928	0.100	£19,261
Scenario 2 (removal of dapagliflozin treatment effect and indirect effect via KCCQ from the CVM and ACM extrapolations)	£1,922	0.073	£26,435

Abbreviations: ACM, all-cause mortality; CVM, cardiovascular mortality; DG, draft guidance; ICER, incremental cost-effectiveness ratio; KCCQ, Kansas City Cardiomyopathy Questionnaire; QALY, quality-adjusted life year

4 EAG preferred assumptions

4.1 Correction to the EAG base case

Following the scenarios requested from the committee and that the EAG considers that insufficient evidence has been provided to suggest that the removal of the dapagliflozin direct or direct and indirect treatment effect is inappropriate (see Section 2.1), the EAG's preferred assumptions build on from the company ICERs for scenarios 1 (no direct treatment effect) and 2 (no direct and in-direct treatment effect) as outlined in Tables Table 9, Table 10, Table 11 and Table 12.

In addition to the exclusion of the direct and indirect treatment effects in the survival calculations, the EAG's preferred assumption of costing non-elective inpatient (NEL) events using the NHS Reference costs 2019/20 inflated to the 2020/21 cost year and removing the direct UHFV treatment effect have been applied.

Table 9. EAG's preferred model assumptions.

Preferred assumptions	Section in report	Company revised base case ICER (£/QALY)	Scenario 1 ICER (£/QALY)	Scenario 2 ICER (£/QALY)
Base case	Section 3	£8,975	£19,261	£26,435
2019/2020 NHS reference costs (1)	Section 2.4	£9,221	£19,961	£27,466
No direct UHFV treatment effect (2)	Section 2.2	£9,011	£19,384	£26,645
Assumptions 1 and 2	-	£9,250	£20,068	£27,655

Abbreviations: EAG, External Assessment Group; ICER, incremental cost effectiveness ratio; NHS, National Health Service; QALY, quality adjusted life year.

Table 10. EAG's preferred assumptions in combination with mortality scenarios, incremental differences and net health benefits

Mortality scenario*	Incremental costs	Incremental LYG	Incremental QALYs	ICER	Net health benefit £20,000 threshold	Net health benefit £30,000 threshold
Company revised base case (direct and indirect CVM and ACM treatment effect)	£2,179	0.370	0.236	£9,250	0.127	0.163
Scenario 1 (no direct CVM and ACM treatment effect)	£2,002	0.068	0.100	£20,068	0.000	0.033
Scenario 2 (no direct and no indirect CVM and ACM treatment effect)	£2,001	0.000	0.072	£27,655	-0.028	0.006

Abbreviations: ACM, all-cause mortality; CVM, cardiovascular mortality; EAG, External Assessment Group; ICER, incremental cost effectiveness ratio; LYG, life year gain; QALY, quality adjusted life year.

*As the updated model only allowed for the exploration of mortality scenarios applied to both CVM and ACM, the EAG was unable to provide additional scenarios where no direct or no direct and indirect treatment effect was only applied to either CVM or ACM.

Table 11. Deterministic and probabilistic scenario 1 (no direct CVM and ACM treatment effect) results with EAG preferred assumptions

Interventions	Total Costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Deterministic results							
Dapagliflozin plus SoC	£8,105	8.204	4.442	£2,002	0.068	0.100	£20,068
SoC	£6,103	8.137	4.342	-	-	-	-
Probabilistic results							
Dapagliflozin plus SoC	£8,144	-	4.442	£2,003	-	0.098	£20,360
SoC	£6,141	-	4.343	-	-	-	-

Abbreviations: ACM, all-cause mortality; CVM, cardiovascular mortality; EAG, External Assessment Group; LYG, life year gained; ICER, incremental cost effectiveness ratio; QALY, quality adjusted life year; SoC, standard of care.

Table 12. Deterministic and probabilistic scenario 2 (no direct and in-direct CVM and ACM treatment effect) results with EAG preferred assumptions

Interventions	Total Costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Deterministic results							
Dapagliflozin plus SoC	£8,233	8.426	4.509	£2,001	0.000	0.072	£27,655

SoC	£6,232	8.426	4.437	-	-	-	-
Probabilistic results							
Dapagliflozin plus SoC	£8,273	-	4.511	£2,006	-	0.072	£27,813
SoC	£6,267	-	4.438	-	-	-	-

Abbreviations: ACM, all-cause mortality; CVM, cardiovascular mortality; EAG, External Assessment Group; LYG, life year gained; ICER, incremental cost effectiveness ratio; QALY, quality adjusted life year; SoC, standard of care.

4.2 Scenarios around the EAG base case

As a scenario, the EAG was requested by NICE to cost CVM at £1,452. These results are provided below in Table 13, with limited or no impact on the EAG's base case results.

Table 13. Scenario analysis around the EAG base case.

Preferred assumptions	Scenario 1 (£/QALY)	Scenario 2 ICER (£/QALY)
EAG base case	£20,068	£27,655
Updated CVM cost (£1,452)	£20,071	£27,655

Abbreviations: CVM, cardiovascular mortality; EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year.

5 References

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Updated committee preferences, base case results and mortality scenarios

Following the committee's updated preferences post ACM 2, the EAG below highlights the outcomes of these preferences across the mortality scenarios discussed at ACM 2. Table 1. Updated committee preferences. ICER's and preferences.Table 1 shows the independent effects of the updated committee preferences on the ICER and Table 2 provides the cost, QALY, LYG of each trial arm for each scenario and the resulting ICER.

Table 1. Updated committee preferences. ICER's and preferences.

Preferred assumptions	Direct and indirect treatment effect on survival ICER (£/QALY)	Indirect treatment effect only on survival ICER (£/QALY)	No direct or indirect treatment effect on survival ICER (£/QALY)
Previous EAG base case	£9,250	£20,068	£27,655
(1) HHF weighted cost	£8,686	£18,535	£25,412
(2) CVM cost of £1,452	£9,280	£20,071	£27,655
Preferences 1+2	£8,715	£18,537	£25,412

Abbreviations: CVM, cardiovascular morality; HHF, hospitalisation for heart failure; ICER, incremental cost effectiveness ratio: QALY, quality adjusted life year.

Table 2. Updated committee preferences. Deterministic base case results.

Interventions	Total Costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Direct and in-direct treatment effect on survival							
Dapagliflozin plus SoC	£8,641	8.295	4.490	£2,053	0.370	0.236	£8,715
SoC	£6,589	7.926	4.255	-	-	-	-
Indirect treatment effect only on survival							
Dapagliflozin plus SoC	£8,558	8.204	4.442	£1,849	0.068	0.100	£18,537
SoC	£6,709	8.137	4.342	-	-	-	-
Indirect treatment effect only on survival							
Dapagliflozin plus SoC	£8,711	8.426	4.509	£1,839	0.000	0.072	£25,412
SoC	£6,872	8.426	4.437	-	-	-	-

Abbreviations: ACM, appraisal committee meeting; ICER, incremental cost effectiveness ratio; LYG, life year gained; QALY, quality adjusted life year; SoC, standard of care.