National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Empagliflozin for treating chronic heart failure with reduced ejection fraction

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Comment 1: the draft remit

Section	Consultee/ Commentator	Comments [sic]	Action
Appropriateness	British Cardiovascular Society	Yes, this drug is of major interest to cardiologists and patients with heart failure.	Thank you for your comment. No action needed.
	Boehringer-Ingelheim	BI agree that this is appropriate.	Thank you for your comment. No action needed.
	British Society for Heart Failure	Yes. The EMPEROR-reduced trial showed significant benefit, in terms of morbidity and mortality reduction, with Empagliflozin, in addition to standard care, compared to placebo. There was a 25% reduction in the primary endpoint of cardiovascular death and hospitalisation for worsening heart failure in the empagliflozin group compared with placebo.	Thank you for your comment. No action needed.
	Pumping Marvellous Foundation	Yes, it is important that NICE appraises innovative technologies.	Thank you for your comment. No action needed.

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	Primary Care Cardiovascular Society	Yes. It is appropriate that NICE appraise the role of Empagliflozin in patients with Heart Failure with reduced ejection fraction (HFrEF) following the publication of the EMPEROR-Reduced trial. This trial shows significant benefit of adding Empagliflozin to standard therapy for HFrEF.	Thank you for your comment. No action needed.
Wording	British Cardiovascular Society	Yes	Thank you for your comment. No action needed.
	Boehringer-Ingelheim	BI agree with the wording.	Thank you for your comment. No action needed.
	British Society for Heart Failure	Yes. Wording is appropriate.	Thank you for your comment. No action needed.
	Pumping Marvellous Foundation	Yes.	Thank you for your comment. No action needed.
	Novartis	We suggest to add “symptomatic” before “chronic heart failure with reduced ejection fraction” in order to reflect the inclusion criteria of the empagliflozin clinical trial in heart failure.	Thank you for your comment. The scope has been updated.
	Primary Care Cardiovascular Society	Yes.	Thank you for your comment. No action needed.

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Timing Issues	British Cardiovascular Society	This drug is already in widespread use in the NHS and its use in heart failure is being expanded currently as part of the broader introduction of the entire class of SGLT2i's. This appraisal is therefore urgent, although there is an even greater need for a more comprehensive look at the overall field of heart failure management to clarify the most effective sequencing of introducing heart failure medications.	Thank you for your comment. NICE aims to provide draft guidance to the NHS within 6 months from the date when marketing authorisation for a technology is granted. NICE has scheduled this topic into its work programme. No action needed.
	Boehringer-Ingelheim	The SGLT2i class offers significant reductions in morbidity, mortality and hospitalisation in patients with heart failure with reduced ejection fraction (HFrEF) compared with current NHS standard care. Despite improvements in care for HFrEF over time, the 5-year mortality rate for patients in the UK remains high. Given the unmet need in the management of HF and the innovative nature of empagliflozin, and the SGLT2i class, the appraisal should be scheduled as soon as possible and in line with NICE's principle of appraisal timelines based on section 3.18 of VPAS. The VPAS agreement states that the appraisal for non-oncology treatments will match the timelines for oncology treatment, which means that the appraisal should be scheduled so that the first appraisal committee meeting occurs shortly following the anticipated Committee for Medicinal Products for Human Use (CHMP) opinion. Timely assessment and approval	Thank you for your comment. NICE aims to provide draft guidance to the NHS within 6 months from the date when marketing authorisation for a technology is granted. NICE has scheduled this topic into its work programme. No action needed.

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		of empagliflozin will result in meaningful benefits to patients as soon as possible following the marketing authorisation. The anticipated CHMP positive opinion is expected in [redacted] and Marketing Authorisation is [redacted]. This information is listed in the Regulatory Issues section below. BI have already engaged with NICE around timelines and appreciate NICE's proactively and willingness to offer solutions to expedite the process so that the committee meeting for empagliflozin is as close to the CHMP meeting as possible.	
	British Society for Heart Failure	Heart failure has a worse prognosis than many cancers and national level audit data shows that 32% of people are dead within a year of a heart failure hospitalisation. Therefore, the appraisal should be considered urgent due to the benefit demonstrated in the clinical trial EMPERORReduced. Delay in this process will prevent patients from receiving treatment that can improve mortality and morbidity in a syndrome with malignant outcomes.	Thank you for your comment. NICE aims to provide draft guidance to the NHS within 6 months from the date when marketing authorisation for a technology is granted. NICE has scheduled this topic into its work programme. No action needed.
	Pumping Marvellous Foundation	Urgent – we need to increase the options to optimise treatment in the NHS for people living with heart failure.	Thank you for your comment. NICE aims to provide draft guidance to the NHS within 6

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			months from the date when marketing authorisation for a technology is granted. NICE has scheduled this topic into its work programme. No action needed.
	Primary Care Cardiovascular Society	We would consider this appraisal to be urgent given the poor prognosis of patients diagnosed with HFrEF, typically similar to or worse than the prognosis of patients with common types of cancer. The significant morbidity and mortality benefits of using empagliflozin in HFrEF are seen within 4 weeks of starting therapy therefore delaying this review may result in adverse outcomes for many patients with heart failure who may have benefitted from this treatment.	Thank you for your comment. NICE aims to provide draft guidance to the NHS within 6 months from the date when marketing authorisation for a technology is granted. NICE has scheduled this topic into its work programme. No action needed.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	AstraZeneca	The background information section includes the recommendations for ivabradine and sacubitril valsartan. The recommendations for dapagliflozin	Thank you for your comment. The background section has

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		should also be included, as the TAG for dapagliflozin was published on the 24th Feb 2021 (https://www.nice.org.uk/guidance/ta679).	been updated as suggested.
	British Cardiovascular Society	Essentially correct. The figure of 30-40% mortality in the first year refers to patients who were hospitalised with heart failure at the point of diagnosis. One year mortality is likely to be lower in patients diagnosed without having been hospitalised.	Thank you for your comment. No action needed.
	British Society for Heart Failure	Information accurate and complete.	Thank you for your comment. No action needed.
	Pumping Marvellous Foundation	Dapagliflozin should be in the treatment pathway as per NICE TA (ID 1656).	Thank you for your comment. The background section has been updated as suggested.
	Primary Care Cardiovascular Society	The information in the draft scope seems both accurate and complete	Thank you for your comment. No action needed.
The technology/ intervention	British Cardiovascular Society	Yes	Thank you for your comment. No action needed.
	Boehringer-Ingelheim	Yes, BI agree with the description of the intervention. As stated in the draft scope, this appraisal aims to compare the addition of empagliflozin to standard care vs standard care alone for patients with HFrEF.	Thank you for your comment. No action needed.

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	British Society for Heart Failure	Yes	Thank you for your comment. No action needed.
	Pumping Marvellous Foundation	Yes.	Thank you for your comment. No action needed.
	Novartis	Empagliflozin was studied in combination with standard care. Sacubitril/valsartan should be added to the treatments included in this description. In the EMPEROR trial roughly 20% of empagliflozin patients were receiving an angiotensin receptor–neprilysin inhibitor (i.e. sacubitril/valsartan) at baseline.[1] Sacubitril/valsartan is also part of standard of care for heart failure in the UK, as established in NICE NG106 for chronic heart failure and NICE ID1656. [1] Packer M, Anker SD, Butler J, et al. Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure. N Engl J Med. 2020;383(15):1413-1424. doi:10.1056/NEJMoa202219	Thank you for your comment. Sacubitril//valsartan were included in the description of standard care. No action needed.
	Primary Care Cardiovascular Society	Yes	Thank you for your comment. No action needed.
Population	British Cardiovascular Society	Yes	Thank you for your comment. No action needed.

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	Boehringer-Ingelheim	**Are there any subgroups of people in whom empagliflozin is expected to be more clinically effective and cost effective or other groups that should be examined separately?** Empagliflozin is intended as an add-on therapy to standard care for patients with HFrEF who continue to be symptomatic. All patients could benefit from empagliflozin, regardless of whether co-morbidities are present or not. The pivotal Phase III trial, EMPEROR-Reduced, showed a reduction in HHF or adjudicated CV-death (composite primary outcomes) across multiple subgroups, including age (<65yr/>65yr), sex (male/female), race (white, black, asian, other), body mass index, T2DM/no T2DM, and prior therapies (ARNI/no ARNI) as shown in F	Thank you for your comment. No action needed.

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		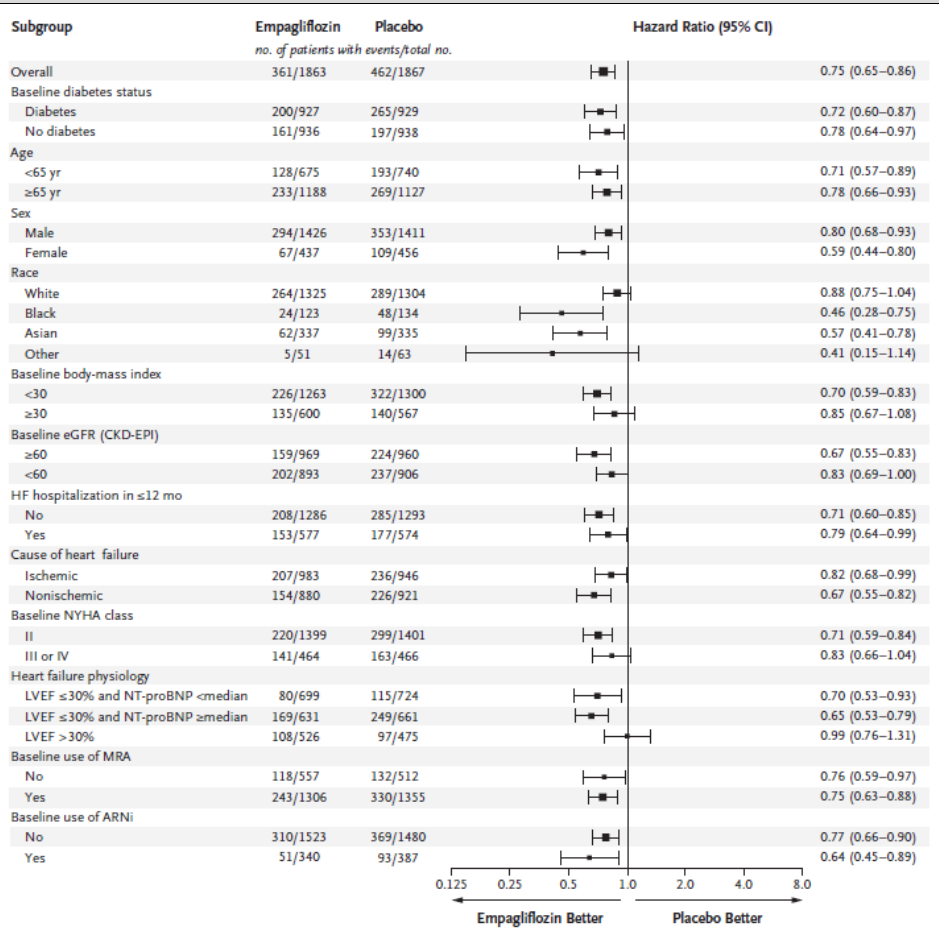	

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		Figure 1 [1]. Therefore, no subgroups will be considered separately in the economic analysis. The efficacy and safety results for trial participants from Europe in EMPEROR-Reduced will not be reported separately in the submission. The proportion of HF patients who identified as white was higher in the Europe subgroup than in the UK [redacted] [2] vs 91% [3], respectively). This difference only widened when compared to metropolitan areas (42.3% white in inner London boroughs) [4]. Therefore, by not considering this subgroup, we maintain consistency with NICE's Social Value Judgments and the Equality Act 2010 (race is one of the protected characteristics)[5].	

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		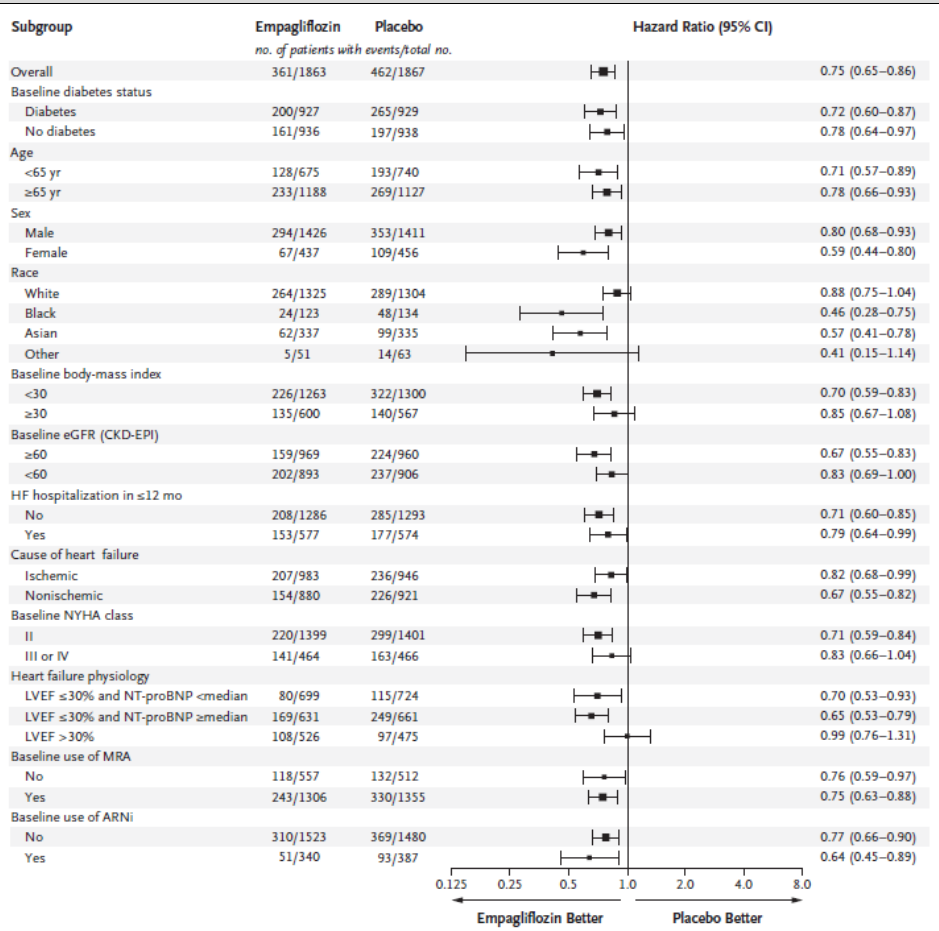	

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		Figure 1. Primary outcome in pre-specified subgroups in EMPEROR-Reduced	
	British Society for Heart Failure	Yes. This is in line with previous heart failure studies.	Thank you for your comment. No action needed.
	Pumping Marvellous Foundation	Yes – all heart failure, whether with Type 2 Diabetes or not.	Thank you for your comment. No action needed.
	Novartis	It should be noted that the EMPEROR trial population consisted of patients with symptomatic chronic heart failure with reduced ejection fraction with left ventricular ejection fraction (LVEF) ≤40% and NYHA functional class II-IV, therefore this should be the population considered within the appraisal.[1] This population is aligned with the populations assessed in both TA388 and TA679. [1] Packer M, Anker SD, Butler J, et al. Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure. N Engl J Med. 2020;383(15):1413-1424. doi:10.1056/NEJMoa202219	Thank you for your comment. The population is usually left broad. The committee will consider the clinical evidence presented to it and make recommendations based on that.
	Primary Care Cardiovascular Society	Yes. The population defined is appropriate and reflects that seen in the EMPEROR -Reduced trial where patients are optimally treated on standard therapy	Thank you for your comment. No action needed.
Comparators	AstraZeneca	The formatting in the draft scope is unclear and it is ambiguous which therapies are considered to be standard care and which therapies are considered to be comparators.	Thank you for your comment. The list of comparators has been

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		Specifically, it should be clarified that dapagliflozin is a comparator. The description of dapagliflozin as a comparator should be updated to align with the dapagliflozin TAG: Dapagliflozin as an add-on to optimised standard care with: • angiotensin-converting enzyme (ACE) inhibitors or angiotensin-2 receptor blockers (ARBs), with beta blockers, and, if tolerated, mineralocorticoid receptor antagonists (MRAs), or • sacubitril valsartan, with beta blockers, and, if tolerated, MRAs. It also should be clarified whether digoxin, ivabradine and hydralazine in combination with nitrate are considered comparators or as components of standard care.	updated to conform with NICE style.
	British Cardiovascular Society	Yes, although the full picture is more complex – see comments below.	Thank you for your comment. The appraisal committee will discuss the most appropriate comparators during the development of this appraisal. This will depend on the final marketing authorisation, the current treatment pathway, clinical and cost effectiveness evidence and current clinical practice.
	Boehringer-Ingelheim	**Which treatments are considered to be established clinical practice in the NHS for heart failure with reduced ejection fraction?**	Thank you for your comment. The list of comparators has been

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		The National Clinical Guideline 106 (NG106) published in 2018 [6] recommends a sequential approach to HF management. It states that patients with HFrEF should be treated with ACEi or ARBs plus BBs following diagnosis. An MRA can be added if symptoms continue. If symptoms persist despite these first line treatments, it is advised to refer to a HF specialist to initiate either sacubitril/valsartan, ivabradine, hydralazine and nitrate or digoxin. If sacubitril/valsartan is initiated, treatment with an ACEi should discontinue (Figure 2). HCPs are advised to reach the target dose for each drug class before prescribing another drug class [6]. For patients who have HFrEF and chronic kidney disease (eGFR <45ml/min/1.73m2), consider lower doses and/or slower titration of dose of ACEI inhibitor or ARBs, MRAs and digoxin. Figure 2. NG106: Chronic heart failure: management *Figure 2. NG106: Chronic heart failure: management*	updated to remove digoxin, ivabradine and hydralazine in combination with nitrate. Dapagliflozin might be standard practice at the time of the appraisal so has not be removed. The appraisal committee will discuss the most appropriate comparators during the development of this appraisal. This will depend on the final marketing authorisation, the current treatment pathway, clinical and cost effectiveness evidence and current clinical practice.

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		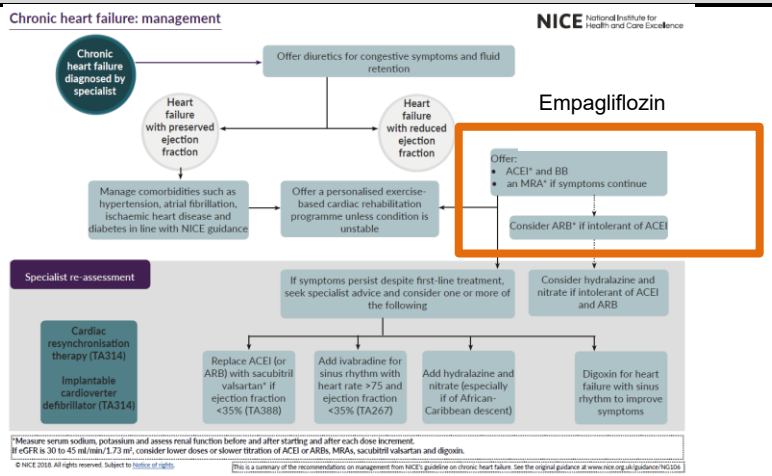 **Where do you consider empagliflozin will fit into the existing NICE pathway, chronic heart failure?** The optimal place for empagliflozin in the NICE pathway is as an add-on to ACEI or ARBs plus BB, MRA (Figure 2). Early use of empagliflozin can maximize the expected outcomes for patients [7]. Empagliflozin has shown to be an effective add-on to first line therapies, regardless of the dose used for these therapies. Unlike empagliflozin, these first line treatments often require a downward dose adjustment, due to poor tolerability and the presence of co-morbidities [6, 8]. Lower doses of ACEI and ARBs are associated with a higher risk of CV-death and hospitalisation than higher doses, as reported in the HEAAL and ATLAS trials [8-10]. Empagliflozin has an established safety profile [1, 11, 12], requires no dose adjustment [11] and thus no additional clinical time is needed to optimise a	

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		patient's treatment. In EMPEROR-Reduced, 19.4% of patients receiving empagliflozin plus standard care vs 24.7% receiving standard care alone experienced either a HHF or CV-death event (ITT, HR 0.75, 95%CI 0.65 to 0.86, P<0.001). Empagliflozin plus standard care also demonstrated an improvement in kidney outcomes. A composite renal outcome (chronic dialysis or renal transplantation or a profound, sustained reduction in the eGFR) occurred in 30 patients (1.6%) in the empagliflozin plus standard care group and in 58 patients (3.1%) in the standard care alone group (ITT, HR 0.50, 95% CI 0.32 to 0.77). The annual rate of decline in the eGFR was slower in the empagliflozin group than in the placebo group (–0.55 vs. –2.28 ml per minute per 1.73 m2 of body-surface area per year, respectively P<0.001) [1]. Early use of empagliflozin does not diminish the efficacy of sacubitril valsartan if it is subsequently added. When compared with placebo, empagliflozin reduced the risk of CV-death or HHF by 36% in those receiving sacubitril/valsartan (HR 0.64, 95% CI 0.45 to 0.89, P = 0.009) and by 23% in those not receiving sacubitril/valsartan (HR 0.77, 95% CI 0.66 to 0.90 P = 0.0008). The slowing of the decline in eGFR was also maintained. Empagliflozin slowed the rate of decline in the eGFR by 1.92 ± 0.80 mL/min/1.73 m2 in patients taking sacubitril/valsaratan (P = 0.016) and by 1.71 ± 0.35 mL/min/1.73 m2 in patients not taking sacubitril/valsartan (P < 0.0001), interaction P = 0.81) [13]. **Have all relevant comparators for empagliflozin been included in the scope?** BI agrees that the comparator is standard care without empagliflozin. Consistent with NG106, first line standard care is ACEI or ARBs plus BB,	

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		MRAs. We believe that these are the relevant comparators for this health technology appraisal and have been included in the scope. We note that sacubitril/valsartan, ivabradine, hydralazine and nitrate, digoxin and dapagliflozin have also been included in the scope. These are not relevant comparators for the following reasons: • Ivabradine, hydralazine and nitrate, digoxin are used in a specialist setting. o Clinicians fed back during the Single Technology Appraisal for dapagliflozin that these treatments are not considered standard care. "Experts explained that these drugs are rarely prescribed in clinical practice. They said that ivabradine is primarily a heart rate lowering medicines for patients with LVEF who are in sinus rhythm and have a resting heart rate of over 75 beats per minute". "One clinical expert noted that hydralazine with nitrate is used in people with poor kidney function or for whom ACEi inhibitors are not suitable". Another clinical expert noted that "digoxin is used in atrial fibrillation and in worsening or severe heart failure with sinus rhythm when reduced kidney function means no other treatments are an option".[14] o The feedback at the dapagliflozin appraisal committee meeting is consistent with trends observed in clinical practice. [redacted] • Sacubitril/valsartan o Based on the feedback from the dapagliflozin single technology appraisal[14], BI will not provide an indirect treatment	

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		comparison vs sacubitril/valsartan. This is because empagliflozin does not replace sacubitril/valsartan, but could be used in addition. • Dapagliflozin does not yet reflect standard care and therefore is not a relevant comparator. o Inclusion of dapagliflozin is not consistent with the aim of this appraisal which is to compare the addition of empagliflozin to standard care vs standard care alone. We know that NICE and advisory committees will endeavour to follow published processes during an appraisal, as this will support consistency in decision making [16]. Section 6.2.3 of the NICE Guide to Methods states “the committee will normally be guided by established practice in the NHS when identifying appropriate comparators”[17]. “The Committee's overall decision on whether it is a valid comparator will be guided by whether it is recommended in other extant NICE guidance, and/or whether its use is so embedded in clinical practice that its use will continue unless and until it is replaced by a new technology.”[14] Evidence suggests that dapagliflozin is not yet standard care. Its market share in HFrEF is <1% in 2020 [18] and it is not included in NG106. If dapagliflozin was included in the scope, it would introduce more uncertainty into the evidence base and offer limited additional value. A head to head trial of empagliflozin vs dapagliflozin in HFrEF has not been conducted. An unpublished Bucher indirect treatment comparison showed the composite primary endpoint outcome was comparable for	

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		empagliflozin vs dapagliflozin ([redacted] **Would people who are eligible for empagliflozin already be on an optimised treatment regime?** The clinical trial protocol for EMPEROR-Reduced does not provide a definition of optimised care. It only states that patients must have received all appropriate treatments for heart failure (as available and tolerated) and the doses should be stable for at least 1 week prior to screening and remain constant during the screening period until randomisation, which was between 4 to 28 days [19]. During the randomised period, background therapies were given at clinically appropriate doses in line with local/international guidelines; which varied globally[20].	
	British Society for Heart Failure	Empagliflozin should be seen as an add-on treatment to standard care rather than a comparator. Standard care includes betablocker, ACEI/ARB or ARNI, MRA. Dapagliflozin will be an alternative option once approved by NICE.	Thank you for your comment. The appraisal committee will discuss the most appropriate comparators during the development of this appraisal. This will depend on the final marketing authorisation, the current treatment

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			pathway, clinical and cost effectiveness evidence and current clinical practice.
	Pumping Marvellous Foundation	Yes	Thank you for your comment. The list of comparators has been updated.
	Novartis	The EMPEROR trial studied empagliflozin as add-on to standard care.[1] Standard care was most recently defined in TA679 as: • ACE inhibitors in combination with beta-blockers (BB), and/or mineralocorticoid receptor antagonists (MRA) • ARBs in combination with BB, and/or MRA • Sacubitril/valsartan in combination with BB, and/or MRA[2] TA679 recommends dapagliflozin, a similarly studied sodium-glucose co-transporter 2 (SGLT-2) inhibitor, as an option for treating symptomatic chronic heart failure with reduced ejection fraction in adults, only if it is used as an add-on to optimised standard care. The CaReMe treatment algorithm, an algorithm created by a collective body of societies and endorsed by the British Cardiovascular Society and British Society for Heart Failure also positions dapagliflozin as an add-on therapy.[3] This algorithm recommends dapagliflozin as an add-on to an ACE inhibitor (ARB if intolerant to ACEi) with a BB and MRA, or sacubitril/valsartan with a BB and MRA, in patients with LVEF equal to or less than 35%. Based on the EMPEROR trial and recent SGLT2 inhibitor placement in the UK, it is anticipated that empagliflozin, if recommended, will also be positioned as an add-on therapy to an ACE inhibitor (ARB if intolerant to	Thank you for your comment. Dapagliflozin might be standard practice at the time of the appraisal so has not be removed. The appraisal committee will discuss the most appropriate comparators during the development of this appraisal. This will depend on the final marketing authorisation, the current treatment pathway, clinical and cost effectiveness evidence and current clinical practice.

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		ACEi) with a BB and MRA, or sacubitril/valsartan with a BB and MRA in patients with LVEF equal to or less than 35%. In conclusion, dapagliflozin is the most relevant comparator for this appraisal. [1] Packer M, Anker SD, Butler J, et al. Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure. N Engl J Med. 2020;383(15):1413-1424. doi:10.1056/NEJMoa202219 [2] National Institute for Health and Care Excellence (2020). Final Appraisal Document: Dapagliflozin for Treating Chronic Heart Failure with Reduced Ejection Fraction [ID1656]. Retrieved from: https://www.nice.org.uk/guidance/gid-ta10560/documents/html-content-2 **[3] CaReMe Heart Failure Algorithm. Available at: https://www.britishcardiovascularsociety.org/__data/assets/pdf_file/0028/24697/CaReMe-HF-Algorithm-Final-Nov-2020.pdf. (Accessed 19 January 2021)**	
	Primary Care Cardiovascular Society	Empagliflozin should not be compared with the standard therapies (ACE/ARB or ARNI, Beta blocker and Mineralocorticoid Receptor Antagonist) but as an additional therapy as reflected in the EMPEROR -Reduced trial. We do not believe Dapagliflozin should be considered as a comparator as there are no relevant head to head trials	Thank you for your comment. Dapagliflozin might be standard practice at the time of the appraisal so has not be removed. The lack of head to head trials is not a reason for a technology not to be included as a comparator. The appraisal committee will discuss the most appropriate comparators during the development of this appraisal. This will depend on the final

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			marketing authorisation, the current treatment pathway, clinical and cost effectiveness evidence and current clinical practice.
Outcomes	British Cardiovascular Society	Yes	Thank you for your comment. No action needed.
	Boehringer-Ingelheim	**Are the outcomes listed appropriate?** BI consider the outcomes listed in the scope appropriate. **The key trial for empagliflozin included people with LVEF of 40% or less, are outcomes likely to vary according to LVEF? If so, would this limit who is likely to receive empagliflozin in practice?** In EMPEROR-Reduced, the proportion of patients with a LVEF of ≤30 was 71.8% (1337/1863) for the empagliflozin group and 74.6% (1392/1867) for the placebo group [11]. Across the primary composite endpoint (adjudicated HHF or CV-death) and key secondary endpoints ([1] adjudicated HHF and [2] CV-death), the efficacy observed in patients with varying degrees of severity in LVEF (Table 1) was numerically similar to that observed in the ITT population. Therefore, empagliflozin is suitable for all patients regardless of the LVEF and no limit to its use in clinical practice is necessary (Table 1). *Table 1. Composite primary endpoint results by LVEF subgroup*	Thank you for your comment. No action needed.

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		Outcome	**Subgroup**	**Empa 10mg, n/N, %**	**Placebo, n/N, %**	**Hazard ratio (95% CI)**	
		Composite primary outcome					
		Time to first event of adjudicated CV-death or adjudicated HHF[a]	**All patients**	361/1863 (19.3%)	462/1867 (24.7%)	0.75 (0.65 to 0.86)	
			LVEF ≤30% & NT-proBNP < median	80/699 (11.4%)	115/724 (15.8%)	0.70 (0.53 to 0.79)	
			LVEF ≤30% & NT-proBNP ≥ median	169/631 (26.8%)	249/661 (37.6%)	0.65 (0.53 to 0.79)	
			LVEF >30%	108/526 (20.5%)	97/475 (20.4%)	0.99 (0.76 to 1.31)	
		Key secondary endpoints					
		Time to the occurrence of adjudicated heart failure hospitalisation (first and recurrent)[a]	**All patients**	388/1863 (20.8%)	553/1867 (29.6%)	0.7 (0.58-0.85)	
			LVEF ≤30% & NT-proBNP < median	69/699 (9.8%)	122/724 (16.8%)	0.59 (0.41 to 0.85)	
			LVEF ≤30% & NT-proBNP ≥ median	206/631 (32.6%)	309/661 (46.7%)	0.66 (0.5-0.88)	

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	LVEF >30%	112/526 (21.2%)	118/475 (24.8%)	0.84 (0.59 to 1.22)	
Adjudicated CV-death	**All patients**	187/1863 (10.0%)	202/1867 (10.8%)	0.92 (0.75 to 1.12)	
	LVEF ≤30% & NT-proBNP < median	49/699 (7.0%)	45/724 (6.2%)	1.12 (0.75 to 1.69)	
	LVEF ≤30% & NT-proBNP ≥ median	76/631 (12.0%)	110/661 (16.6%)	0.72 (0.53 to 0.96)	
	LVEF >30%	58/526 (11.0%)	47/475 (9.9%)	1.10 (0.75 to 1.62)	
HHF, heart failure hospitalisation; LVEF a. Joint frailty model					

Do you consider that the use of empagliflozin can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation?
No

Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits.
N/A

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	British Society for Heart Failure	Yes.	Thank you for your comment. No action needed.
	Pumping Marvellous Foundation	Yes	Thank you for your comment. No action needed.
	Primary Care Cardiovascular Society	Yes	Thank you for your comment. No action needed.
Economic analysis	British Cardiovascular Society	Standard measures appropriate	Thank you for your comment. No action needed.
	Boehringer-Ingelheim	BI considers the proposed approach to the economic analysis to be appropriate.	Thank you for your comment. No action needed.
	British Society for Heart Failure	The analysis appears appropriate.	Thank you for your comment. No action needed.
	Pumping Marvellous Foundation	I believe the economic analysis is appropriate but see comments below	Thank you for your comment. No action needed.

Section	Consultee/ Commentator	Comments [sic]	Action
	Primary Care Cardiovascular Society	The proposed analysis appears appropriate	Thank you for your comment. No action needed.
Equality and Diversity	British Cardiovascular Society	No real issues, although note comments below.	Thank you for your comment. No action needed.
	Boehringer-Ingelheim	**Reducing the gap inequality in access to heart failure care through broad prescribing of SGLT2i's in primary and secondary care** BI support NICE's commitment to producing guidance that supports the reduction of health inequalities, consistent with the Social Value Judgments[5]. Principle 9 of NICE's Social Value Judgments states that due regard must be given to reducing inequalities. It states that equality should be considered in relation to the nine protected characteristics in the Equality Act 2010 (age, disability, gender reassignment, race, religion or belief, sex, sexual orientation, marriage and civil partnership, pregnancy and maternity) and socio-demographic factors [20]. Broad prescribing of SGLT2i across primary and secondary care can support the reduction in disparity in access to HF care across socio-economic groups within the UK. Waiting for a cardiologist to initiate a SGLT2i would likely widen the gap in health inequalities and lead to a delay as there is limited capacity in secondary care. This is important because lower socio-economic status is associated with increased risk of heart failure, hospital admissions, mortality and co-morbidities and a reduced likelihood of seeking medical attention in secondary care. Socio-economic class, sex, age and race are risk factors for the development of heart failure. Conrad et al 2018 [21] reported on a HES-linked CPRD study	Thank you for your comment. No action needed.

Section	Consultee/ Commentator	Comments [sic]	Action
		of 4 million adult patients. A subset of these later developed heart failure (n=45,671). At the same age and sex, patients in the most deprived socio-economic quintile were more likely to experience incident heart failure than more affluent individuals (IRR 1·61, 95% CI 1·58 to1·64). Further, patients from the most deprived socio-economic quintile were about 3·5 years younger at diagnosis than those from the least deprived group (mean age at diagnosis 74·5 years [SD 13·3] for most deprived vs 77·8 years [SD 12·1]; adjusted difference −3·51 years, 95% CI −3·77 to −3·25). Lawson et al 2020 [3]reported in another HF HES-linked CPRD study that age at HF onset differed significantly by race with younger onset in South Asian group (72 years) and black group (68 years) compared with the older white group (78 group). Following adjustment, age differences compared with the white group were −5.7 years (95% CI, −6.2 to −5.2) for the South Asian group and −9.0 years (95% CI, −9.9 to −8.2) for the black group. There is also a disparity across socio-economic groups in mortality outcomes and the risk of co-morbidities. Lawson et al 2020 [3] reported that HF patients from the most deprived group compared to the least deprived group had significantly higher prevalence of most co-morbidities; the biggest difference was for obesity (28% versus 19%), diabetes mellitus (30% versus 23%) and chronic obstructive pulmonary disease (25% versus 14%).This trend was also observed for mortality. Witte et al 2018 reported in a UK prospective cohort study that that the risk of death increases for HFrEF patients in lower socio-economic classes. Age-sex adjusted Cox regression analyses indicated every 10-unit increase in the UK Index of Multiple Deprivation score was associated with 6% higher risk of all-cause mortality (95% CI 2% to 10%, P=0.004), a 9% higher risk of non-cardiovascular mortality (95% CI 3% to 16%, P=0.003) and a non-significant 3% higher risk of cardiovascular mortality (95% CI −2% to 9%, P=0.21) [22].	

Section	Consultee/ Commentator	Comments [sic]	Action
		Socio-economic status has an impact on access to secondary care in the UK, and subsequently access to heart failure treatments. Moscelli et al 2016 reported a statistically significant difference in waiting times across socio-economic groups for patients who attend the same hospital: patients living in more income deprived areas waited longer (35% difference, or 43 days) than patients who lived in less deprived areas. As well as waiting longer, CHD patients in a lower socio-economic class were admitted to hospital less often than those in a higher class. McCartney et al 2013 reported on a prospective study of 7049 and 8353 women in the west of Scotland followed up for 37 years. The likelihood of a hospital admission for CVD was 21% higher for female patients in socio-economic class IV and V than patients in class I and II. Those patients in class IV and V also stayed 25% longer in hospital (589 vs 736 bed day/1000 person years, respectively)[23]. However, this trend was not observed in men of different socio-economic classes. Socio-economic factors also impact access to HF treatments. In a Danish Heart Failure registry of 17,122 HFrEF patients, a lower income was associated with a 20% lower odds of a prescription of ACEI/ARBs than those with a higher income [24]. These studies indicate that if patients in lower socio-economic classes utilize secondary care less often, their opportunity to access HF medications would also be lower if they are solely prescribed in secondary care. Redistribution of resources within NHS hospitals due to COVID-19 and cancellation of non-urgent care may exacerbate pre-existing inequity in access to secondary care. In a discussion paper, Propper et al 2020[25] noted that disruptions to emergency care and cancellation of elective care are most likely to affect the elderly and those from deprived areas. Emergency admissions among those in the more deprived areas in England were considerably higher than those among the less deprived (110 vs 180 admissions per 10% population), although elective procedures were evenly distributions across deprivation deciles.	

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		Delayed presentation of CV emergencies in UK hospitals due to COVID-19 emphasizes the need for preventative pharmacological interventions, such as SGLT2is, that can be accessed in primary care. Fersia et al 2020 [26] reported a 50% drop in the number of patients presenting to cardiology departments in a district hospital in Dumfries and Galloway. Additionally, the number of patients referred from primary care to cardiology outpatient clinics dropped by 80%. All areas of cardiology service provision sustained significant reduction, which included outpatient clinics, investigations and procedures. The authors expect that there will be another surge of patients seeking cardiology care and that services need to plan to treat these patients early and urgently to prevent long term complications. **In this health technology appraisal, it will be important that all eligible patients with HFrEF across socio-demographic groups are considered eligible for treatment with SGLT2is. To enable this, a broad recommendation by NICE that facilitates prescribing across primary and secondary care and the classification as green on local/regional formularies will be important. This in turn, will support a broader goal of reducing inequity in access to care for HFrEF patients, in line with NICE's Social Value Judgments.**	
	British Society for Heart Failure	Empagliflozin was found to be of benefit across different ethnic groups in the EMPEROR-Reduced trial. The proposed remit and scope does not appear to need changing to reflect this.	Thank you for your comment. No action needed.
	Pumping Marvellous Foundation	I don't think the scope needs changing but we are concerned with these points here –	Thank you for your comment. NICE is required by law to look at any protected

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		• could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed; • could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g., by making it more difficult in practice for a specific group to access the technology. We believe there should be consideration in the scoping around who prescribes this technology. That equality of access should not be restricted by a different process to how it is prescribed for people with Type 2 Diabetes and heart failure currently under existing NICE protocols.	characteristics and whether any recommendation could cause unlawful discrimination. The appraisal committee will consider any equality issues.
	Primary Care Cardiovascular Society	We do not think that the remit and scope needs changing in respect of equality or discrimination.	Thank you for your comment. No action needed.
Other considerations	British Cardiovascular Society	There are ongoing studies with this agent that will likely broaden its utility.	Thank you for your comment. No action needed.
	Pumping Marvellous Foundation	Equity of prescribing	Thank you for your comment. No action needed.
Innovation	British Cardiovascular Society	Yes, as part of the wider impact of the entire class of SGLT2i medications. It is of course not the only agent in this class with evidence of benefit in heart failure.	Thank you for your comment. No action needed.

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	Boehringer-Ingelheim	**Do you consider empagliflozin to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)?** Early use of SGLT2i supports a step-change in the management of HFrEF. Delivering an integrated care service is a core objective of the NHS Long Term Plan[27] and is reflected in a recent white paper to strengthen its implementation [28]. Further, NICE recently published a report on implementing NG106. It noted that patients with heart failure often have other problems such as diabetes and kidney disease and may end up attending a number of specialist clinics. SGLT2i's offer an opportunity to promote a more holistic approach to treatment of adults with T2DM.[29] Empagliflozin is already indicated for the T2DM[30], and with a marketing authorisation expected in August/September 2020 for HFrEF, this objective can be supported. **Do you consider that there will be any barriers to adoption of this technology into practice? If yes, please describe briefly.** Additional guidance by NICE on what an integrated diabetes and HF pathway might look like in the future with support for its implementation will further accelerate a holistic pathway. With the update of the ESC Clinical Practice Guidelines for Chronic Heart Failure [31] this year, 2021 offers an opportunity to update NG106 guidelines to ensure consistency. In addition to update of NG106, a broad evidence based recommendation by NICE for prescribing across primary and secondary care will accelerate uptake for SGLT2i's, especially if it is listed as green on local formularies.	Thank you for your comment. No action needed.

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	British Society for Heart Failure	Empagliflozin is in a new class of medicine in the treatment of heart failure therefore is felt to be innovative. It is possible that Empagliflozin may reduce the incidence of end-organ complications of diabetes mellitus such as diabetic eye disease, diabetic neuropathy or diabetic nephropathy in very long-term follow-up. In addition, the Cardiovascular (CV) Outcomes Trials showed that empagliflozin has the best in class reduction in CV mortality for DM patients with high CV risk.	Thank you for your comment. No action needed.
	Pumping Marvellous Foundation	This technology is innovative and is part of a new emerging drug class, SGLT2i's that has significant outcome benefits, including QOL, to patients with heart failure with reduced ejection fraction. This technology can be classed as a step change in the treatment of heart failure with reduced ejection fraction. It should be seen as a cost-effective addition to the armoury of treatment options. From a patient position, the way, NICE measure's a technology impact on a patient population only looks at the micro-health economic impact, not the broader macro impact that surrounds the patient's quality of life and their involvement in the wider society. I am not going to change this today though am I? Data available includes EMPEROR Reduced - https://www.nejm.org/doi/full/10.1056/NEJMoa2022190 and please take note of this as well regarding renal function of gliflozins https://www.nejm.org/doi/full/10.1056/NEJMoa2024816	Thank you for your comment. No action needed.
	Primary Care Cardiovascular Society	Empagliflozin is one of two SGLT2 inhibitors (in addition to Dapagliflozin) which have recently shown significant benefit when used in HFrEF and are novel therapies for this indication.	Thank you for your comment. No action needed.

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		Empagliflozin when used in patients with Type 2 Diabetes Mellitus may lower glucose and as a consequence may result in reduced complications seen in this condition related to cardiovascular disease and otherwise	
Questions for consultation	British Cardiovascular Society	**Have all relevant comparators for empagliflozin been included in the scope?** No, suggest also include canagliflozin. Sotagliflozin is another relevant comparator to consider (e.g. SOLOIST WHF trial, where ~50% of patients were commenced on study treatment in hospital following an acute exacerbation of HF.) There may also be some signal efficacy of this drug in in HFpEF. **Which treatments are considered to be established clinical practice in the NHS for heart failure with reduced ejection fraction?** Mainstay of treatment is now ACEi+BB+MRA. Patients symptomatic despite these will be swapped to BB+ARNi+MRA+/-dapagliflozin (or empa if diabetic). IV iron may be suitable for some symptomatic patients on top of standard drug therapy. Ivabradine, digoxin, hydralazine used extremely rarely. Patients meeting NICE guidance for device therapy (especially CRT which may improve symptoms as well as prognosis) will also be offered these alongside the medical therapy. Cardiac rehab and lifestyle modification is also to be recommended for all such patients. Some patients will be considered for revascularisation, particularly in light of the 10 year STICH trial findings. **Would people who are eligible for empagliflozin already be on an optimised treatment regime?**	Thank you for your comment. Canagliflozin and sotagliflozin are not recommended in this indication and so are not considered appropriate comparators. The appraisal committee will discuss the most appropriate comparators during the development of this appraisal. This will depend on the final marketing authorisation, the current treatment pathway, clinical and cost effectiveness evidence and current clinical practice.

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		Not necessarily. Many of these patients will be diabetic and so may well have a much lower threshold for starting empagliflozin (due to the findings in the Empa-REG trial), before any optimisation of other heart failure medications. **How should standard care be defined?** In broad terms the treatments outlined above represent current standard of care. However, there exists a concern that the order in which agents are introduced may no longer be correct in light of the emerging data from trials of newer agents, including empagliflozin. It would be of very great value if a more coherent overall strategy of how to use all these agents could be outlined by NICE, rather than looking at each drug in isolation. It may be that the sequential introduction of ACE+Beta blocker+MRA, then ARNi, then SGLT2i is no longer an appropriate way to manage such patients. It is noteworthy for example, that progressing in this manner will take many months and assumes that all patients will be progressed efficiently through all these steps. The more complex the pathway the more likely some patients will not be given opportunity and support to progress to the final steps and get the full benefit. One advantage of SGLT2i's is that the starting dose is the same as the target dose, making it easy and rapid to establish patients on an effective dose of this treatment. **Are the outcomes listed appropriate?** Yes	

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		The key trial for empagliflozin included people with left ventricular ejection fraction of 40% or less, are outcomes likely to vary according to left ventricular ejection fraction? Yes. Subgroup analysis of the trial has shown some interesting findings. Benefit was most marked in those patients with LVEF<30%, especially if also with a high BNP level. Those with an EF>30% did not show statistically significant improvement in outcome. Conversely, benefit appeared slightly less in those patients with the most severe symptoms in the trial (NYHA III or IV) **If so, would this limit who is likely to receive empagliflozin in practice?** It seems likely that the drug would be used in all those eligible for the trial - all those with EF<40% and ongoing symptoms, even if benefit was greatest in those with LVEF<30%. However, if there is a prioritisation as to which patients should be offered this treatment, it may be appropriate to offer it to those with EF<30% first.	

Section	Consultee/ Commentator	Comments [sic]	Action
		Are there any subgroups of people in whom empagliflozin is expected to be more clinically effective and cost effective or other groups that should be examined separately? Patients with diabetes may benefit more since the drug will also have a beneficial effect on their diabetes management independent of its effects on the heart. Frail elderly/those with many comorbidities should be studied for impact of polypharmacy. Withdrawal of excessive medications may be appropriate in patients nearing the end of life. Subgroup analysis of the trial also identified a possible ethnicity related effect – whereby patients of Black/Asian ethnicity benefited more than those who were white. **Where do you consider empagliflozin will fit into the existing NICE pathway, chronic heart failure?** In symptomatic non diabetic patients, after BB+ACEi/ARNi+MRA. In diabetic patients, alongside BB+ACEi/ARNi. However, see above comments about the risks of an unduly complicated sequential introduction of these medications. We note that the benefit of empagliflozin was approximately equal whether patients were taking ARNi or not and whether they were taking MRA or not.	
	Boehringer-Ingelheim	**Eligibility for the Fast Track Appraisal Process** Section 2.4.31 of the NICE process guide states that a technology can be considered for the fast track appraisal process if[17]:	Thank you for your comment. No action needed.

Section	Consultee/ Commentator	Comments [sic]	Action
		• The company's base-case incremental cost-effectiveness ratio (ICER) is less than £10,000 per QALY gained. • It is likely that the most plausible ICER is less than £20,000 per QALY gained, and it is highly unlikely that it is greater than £30,000 per QALY gained. It is expected that the ICER for empagliflozin vs standard of care will be less than £10,000/QALY and therefore this appraisal meets the eligibility for the fast track appraisal process. **Is the primary outcome that was measured in the trial or used to drive the model for the comparator(s) still clinically relevant?** The individual components of the composite primary endpoint, HHF and CV-death are used to drive the cost effective model are a clinically relevant outcome. **Is there any substantial new evidence for the comparator technology/ies that has not been considered? Are there any important ongoing trials reporting in the next year?** EMPEROR-Preserved will read-out in Q3 2021, and it is expected that a pooled meta-analysis with EMPEROR-Reduced will be conducted.	
	British Society for Heart Failure	Q. Where do you consider empagliflozin will fit into the existing NICE pathway, Chronic heart failure? A. We anticipate that empagliflozin will fit in the existing NICE pathway as an addition to standard of care with ACEi/ARB/sacubitril valsartan, beta-blocker and MRA as tolerated. It is likely to be initiated following recommendation by a member of the heart failure specialist team.	Thank you for your comment. No action needed.

Section	Consultee/ Commentator	Comments [sic]	Action
		Q. Is there any substantial new evidence for the comparator technology/ies that has not been considered? Are there any important ongoing trials reporting in the next year? A. Another SGLT-2 inhibitor (Dapagliflozin) is being studied for the treatment of heart failure with reduced LV ejection fraction and also preserved LV ejection fraction.	
	Pumping Marvellous Foundation	OK with the process	Thank you for your comment. No action needed.
	Novartis	**Have all relevant comparators for empagliflozin been included in the scope?** Please see comments in 'Comparators' section above. **Which treatments are considered to be established clinical practice in the NHS for heart failure with reduced ejection fraction?** Please see comments in 'Comparators' section above. Established clinical practice currently includes the following: • ACE inhibitors in combination with BB, and/or MRA • ARBs in combination with BB, and/or MRA • Sacubitril/valsartan in combination with BB, and/or MRA **Would people who are eligible for empagliflozin already be on an optimised treatment regime?**	Thank you for your comment. No action needed.

Section	Consultee/ Commentator	Comments [sic]	Action
		The EMPEROR trial studied empagliflozin as an add-on to appropriately dosed and stable standard care, therefore in line with the available clinical data, patients eligible for treatment with empagliflozin should already be on an optimised treatment regime. This is also in line with the dapagliflozin pivotal trial where patients were clinically stable and optimised on heart failure therapies according to local guidelines.[1] **How should standard care be defined?** Please see comments in 'Comparators' section above. **Are the outcomes listed appropriate?** Yes. **The key trial for empagliflozin included people with left ventricular ejection fraction of 40% or less, are outcomes likely to vary according to left ventricular ejection fraction? If so, would this limit who is likely to receive empagliflozin in practice?** LVEF is a prognostic factor for heart failure patients. As stated in the 'Background' section of the Draft Scope, heart failure with reduced ejection fraction is defined using a LVEF of 40% or less as a bound. ESC guidelines consider patients with LVEF 50% or above as heart failure patients with preserved ejection fraction (pEF).[2] Patients with LVEF that ranges from 40 to 49% are labelled as heart failure patients with midrange ejection fraction (HFmrEF). These patients identified as PEF and HFmrEF are not covered in the EMPEROR trial, but are also considered different patient populations and would therefore have different outcomes to the population being appraised by NICE for ID3826.	

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		The EMPEROR trial includes patients with LVEF lower than 40% and the appraisal remit should be aligned to the available evidence for empagliflozin. As for outcomes varying according to LVEF across subgroups within the EMPEROR trial population (LVEF 40% or less), the trial data should reveal whether there is a difference in treatment effect for empagliflozin across those groups. **Where do you consider empagliflozin will fit into the existing NICE pathway, chronic heart failure?** As the second SGLT-2 inhibitor appraised by NICE for heart failure with reduced ejection fraction, empagliflozin is expected to fit into the same position as dapagliflozin. Both the Dapa-HF and EMPEROR trials evaluated the study drug as add-on therapy to standard of care in relatively similar patient populations. As mentioned above, the CaReMe treatment algorithm positions dapagliflozin as an add-on to an ACEi, ARB or sacubitril/valsartan with a BB and/or MRA for patients with LVEF equal to or less than 35%. A recent publication in the Lancet by Vaduganathan et al.[3] supports the combination use of an ARNI, BB, MRA, and SGLT2 inhibitor as a new therapeutic standard for HFrEF. Treatment of chronic heart failure is expected to follow this pathway, using a new comprehensive standard of care in order to achieve the best clinical outcome. **Do you consider that the use of empagliflozin can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation?**	

Section	Consultee/ Commentator	Comments [sic]	Action
		It is not believed that empagliflozin will result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation. [1] McMurray JJV, Solomon SD, Inzucchi SE, et al. Dapagliflozin in patients with heart failure and reduced ejection fraction. N Engl J Med 2019;381:1995-2008. DOI: 10.1056/NEJMoa1911303 [2] Ponikowski, P., Voors, A. A., Anker, S. D., Bueno, H., Cleland, J., Coats, A., Falk, V., González-Juanatey, J. R., Harjola, V. P., Jankowska, E. A., Jessup, M., Linde, C., Nihoyannopoulos, P., Parissis, J. T., Pieske, B., Riley, J. P., Rosano, G., Ruilope, L. M., Ruschitzka, F., Rutten, F. H., … ESC Scientific Document Group (2016). 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. European heart journal, 37(27), 2129–2200. https://doi.org/10.1093/eurheartj/ehw128 **[3] Vaduganathan M, Claggett BL, Jhund PS, et al. Estimating lifetime benefits of comprehensive disease-modifying pharmacological therapies in patients with heart failure with reduced ejection fraction: a comparative analysis of three randomised controlled trials. Lancet. 2020;396(10244):121-128. doi:10.1016/S0140-6736(20)30748-0**	
	Primary Care Cardiovascular Society	As stated above we believe that Empagliflozin should be considered as an additional therapy to standard therapy. Standard therapy again as outlined above includes Sacubitril -Valsartan which is commonly prescribed as an alternative first line therapy(to ACE inhibitors or ARB). Dapagliflozin has similar evidence for its use in patients with HFrEF but we would not consider it to be a comparator as the trial populations in DAPA-HF and EMPEROR-Reduced though similar are not identical.There are no head to head trials between Dapagliflozin and Empagliflozin in a HFrEF population	Thank you for your comment. No action required

Section	Consultee/ Commentator	Comments [sic]	Action
Additional comments on the draft scope	AstraZeneca	The section on 'related NICE recommendations and NICE pathways' should be updated to reflect NICE's recommendation for use of dapagliflozin in patients with HFrEF. The TAG for dapagliflozin was published on 24th Feb 2021 (https://www.nice.org.uk/guidance/ta679).	Thank you for your comment. The scope has been updated.
	British Cardiovascular Society	As above	Thank you for your comment. No action needed.
	British Society for Heart Failure	Given that many HCPs will have experience of this as a diabetic medication, we would welcome NICE to consider the need for an additional educational program post approval. Heart failure specialists may not be as confident with the co-prescription of other diabetic medicines, monitoring and implications of changing diabetic regimens. It is also necessary to consider education for implementation in non-diabetic patients and the potential requirement to adjust heart failure treatments to prevent adverse events. Not addressing this may delay/restrict uptake or lead to inappropriate prescribing leading to further complications in the future.	Thank you for your comment. No action needed.
	Primary Care Cardiovascular Society	We believe the question of who can prescribe this medication if of great importance. It is our opinion that the prescribing of empagliflozin (initiation or otherwise) should not be limited to Heart Failure specialists not least because it is currently prescribed by primary care clinicians and other Healthcare professionals for non heart failure related indications. It may though be appropriate for non Heart Failure specialists to seek the advice of a Heart Failure specialist prior to initiating empagliflozin in a patient with HFrEF.	Thank you for your comment. No action needed.

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

Heart UK responded to confirm receipt but would not be taking part in the consultation