National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Dapagliflozin for treating heart failure with reduced ejection fraction

Response to consultee and commentator comments on the draft remit and draft scope (pre-referral)

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Comment 1: the draft remit

Section	Consultee/ Commentator	Comments [sic]	Action
Appropriateness	AstraZeneca	Yes	Thank you for your comment. No action required.
	Boehringer Ingelheim Ltd.	Yes, HF has significant morbidity and mortality in the UK&I.	Thank you for your comment. No action required.
	British Cardiovascular Society	The topic is highly appropriate for NICE appraisal. Heart failure is associated with significant mortality and morbidity despite optimal medical therapy. A recent, large, randomised, double blind phase III trial has shown mortality and symptom benefit of dapagliflozin compared for placebo for patients with heart failure therapy (EF < 40%) that was standard at the time of the trial initiation. Therefore, appraisal is both important and timely. Importantly this applies to patients both with and without diabetes,	Thank you for your comment. No action required.

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	British Society for Heart Failure	Yes. DAPA-HF showed significant benefit, in terms of morbidity and mortality reduction, with Dapagliflozin in addition to standard care compared to placebo.	Thank you for your comment. No action required.
	Novartis Pharmaceuticals UK Limited	No comments.	Thank you for your response. No action required.
Wording	AstraZeneca	Yes	Thank you for your comment. No action required.
	Boehringer Ingelheim Ltd.	Yes, seems appropriate.	Thank you for your comment. No action required.
	British Cardiovascular Society	The wording is appropriate.	Thank you for your comment. No action required.
	British Society for Heart Failure	Yes. Wording is appropriate.	Thank you for your comment. No action required.
	Novartis Pharmaceuticals UK Limited	We suggest to add “symptomatic” before “chronic heart failure with reduced ejection fraction” in order to reflect the inclusion criteria of the dapagliflozin clinical trial in heart failure.	Thank you for your comment. The remit states that dapagliflozin will be appraised within its marketing authorisation for treating adults with

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			chronic heart failure with reduced ejection fraction. Therefore, no change is required to the draft remit.
Timing Issues	AstraZeneca	Dapagliflozin offers significant reductions in mortality and hospitalisations in patients with heart failure with reduced ejection fraction (HFrEF) compared with current NHS standard care (1). Despite improvements in care for HFrEF over time, the 5-year mortality rate for patients in the UK remains high at 51.8% (2). Given the unmet need in the management of HF patients and the innovative nature of dapagliflozin as a first in class medicine for HFrEF patients (see Innovation section below), 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 the Voluntary Scheme for Branded Medicines Pricing and Access (VPAS) agreement. The VPAS agreement states that the appraisal timelines 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 positive Committee for Medicinal Products for Human Use (CHMP) opinion. Timely assessment and approval of dapagliflozin will result in meaningful benefits to patients as soon as possible following marketing authorisation. The anticipated CHMP positive opinion and market authorisation dates have previously been communicated to NICE and this information is also listed in the Regulatory Issues section below.	Thank you for your comment. No action required.

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		AstraZeneca also believe that dapagliflozin is an appropriate candidate for fast track appraisal by NICE, which is supported by preliminary economic analyses. Cost-effectiveness analysis has demonstrated an incremental cost-effectiveness ratio (ICER) <£10,000 per quality adjusted life year (QALY) for dapagliflozin compared to standard care alone (the comparator in the DAPA-HF trial). Results from scenario analyses show the cost-effectiveness of dapagliflozin to be robust to variations in model parameters.	
	Boehringer Ingelheim Ltd.	Timing is appropriate. Limited new therapies for HF. However, Worth Noting other SGLT2i have ongoing trials too. Still no clear treatment pathway for HFpEF which current scope will not cover as the License is only for HFrEF.	Thank you for your comment. No action required.
	British Cardiovascular Society	The appraisal should be a high priority given the high mortality and morbidity of heart failure despite current optimal medical therapy. Further data in this area are likely to add to the existing DAPA HF trial data for this class of drug. There are other ongoing dedicated HF trials (e.g. EMPEROR programme using Empagliflozin) which are yet to report and will add to the evidence base for this class of medications. Canaglifozin also has some data suggesting benefit in heart failure in the CANVAS study.	Thank you for your comment. No action required.
	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 DAPA-HF. 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. No action required.

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	Novartis Pharmaceuticals UK Limited	No comments.	Thank you for your response. No action required.
Additional comments on the draft remit	AstraZeneca	NA	Thank you for your response. No action required.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	AstraZeneca	AstraZeneca suggest the following additions to the background information: • In addition to coronary artery disease, it is important to note that there are many conditions which increase the risk of developing heart failure (HF), including ischemic heart disease (IHD), atrial fibrillation (AF), valve disease, hypertension, diabetes, chronic obstructive pulmonary disease (COPD), and asthma (3, 4). • HFrEF should be defined as left ventricular ejection fraction (LVEF) ≤40%, in line with NICE NG106 (5) and current European Society of Cardiology (ESC) guidelines (3). • The statement "67% of patients with heart failure had a reduced left ventricular ejection fraction" should be amended to 66% based on the most recent National Audit report (4). • It should be noted that the burden of HF is increasing; there was a 12% increase in HF diagnoses in the UK between 2002–2014 due to an increase in population size and an ageing population (6).	Thank you for your comments, the background section of the scope has been amended to reflect these. The definition of reduced ejection fraction has been updated in line with NICE guideline 106 for chronic heart failure in adults.

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		• The one-year mortality rate for HF in the UK should be amended to 19.2%, with a 5-year mortality rate of 51.8% (2). The ivabradine guidance should be amended as it is not restricted to patients contraindicated or intolerant to beta-blockers (7).	
	Boehringer Ingelheim Ltd.	Seems reasonable.	Thank you for your comment. No action required.
	British Cardiovascular Society	The background is largely accurate and complete. The statement that "30-40 percent of people diagnosed with heart failure die within the first year" should be referenced and appears at the high end of a range of mortality rates.	Thanks you for your comment. The background section of the scope has been amended.
	British Society for Heart Failure	'…..may also be associated with preserved ejection fraction (minimum ejection fraction of 45%)' HF-PEF is typically defined as LVEF >50%' The Ivabradine statement is incomplete, as it can also be used in patients in combination with beta-blockers (see NICE 106 - 1.4.19)	Many thanks for your comments. The definition of reduced ejection fraction has been updated in line with NICE guideline 106 for chronic heart failure in adults.
	Novartis Pharmaceuticals UK Limited	According to the 2016 European Society of Cardiology (ESC) Guidelines for the diagnosis and treatment of acute and chronic heart failure, heart failure with preserved ejection fraction is typically defined as heart failure with a left ventricular ejection fraction (LVEF) of ≥50%.1	Many thanks for your comments. The definition of reduced ejection fraction has been updated in line with NICE guideline 106

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		The section on sacubitril valsartan should be aligned with the wording of NICE technology appraisal guidance 388, which recommends sacubitril valsartan as an option for treating symptomatic chronic heart failure with reduced ejection fraction, only in people: • with New York Heart Association (NYHA) class II to IV symptoms and • with a left ventricular ejection fraction of 35% or less and • who are already taking a stable dose of angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor-blockers (ARBs). The section on ivabradine does not fully reflect the recommendation of NICE technology appraisal guidance 267 with regard to the use of ivabradine in combination with standard therapy, and should be modified accordingly. References: 1 Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J 2016;37:2129-2200. DOI: 10.1093/eurheartj/ehw128	for chronic heart failure in adults. The background section has been amended accordingly.
The technology/ intervention	AstraZeneca	Dapagliflozin is a selective inhibitor of sodium–glucose cotransporter 2 (SGLT2) and an established oral anti-diabetic drug that blocks glucose reabsorption in the proximal tubule of the kidney and promotes glucosuria (8). The known mechanisms of action of dapagliflozin (associated with changes in HbA1c, blood pressure and cholesterol) do not seem to determine the overall benefits of dapagliflozin on cardiovascular outcomes in HFrEF (9). While the mechanism of action of dapagliflozin in HFrEF is not yet fully understood, several putative mechanisms have been hypothesised, including improvement in ventricular loading conditions through a reduction in preload and afterload; improvement in cardiac metabolism and bioenergetics;	Thank you for your comment, the technology section of the scope has been updated to reflect the comments.

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		myocardial Na^+/H^+ exchange inhibition; reduction of necrosis and cardiac fibrosis; and alteration in adipokines, cytokine production and epicardial adipose tissue mass (9). The statement "*It has been studied in combination with standard care in 3 randomised controlled trials compared with placebo, in adults with an established documented diagnosis of symptomatic heart failure with reduced ejection fraction (NYHA functional class II-IV) for at least 2 months, who had a left ventricular ejection fraction of 40% or less"* should be clarified as there is only one currently published trial in this population which will be relevant to the submission (DAPA-HF). While there is one additional study (DEFINE-HF) in a relevant population, the primary endpoint (NT-proBNP) is not a clinical endpoint and the study cannot be used to inform economic modelling. There is also an ongoing functions and symptoms study (DETERMINE-reduced), which includes outcomes which have either already been examined in DAPA-HF (KCCQ) or are unlikely to be relevant to the current decision problem (6-minute walking distance, mean movement intensity, time spent in light to vigorous physical activity). Please note the spelling of AstraZeneca is currently incorrect in the Technology section of Appendix B – Draft Scope.	
	Boehringer Ingelheim Ltd.	Description about technology to suggest Dapa 'prevents' reabsorption of glucose is correct (as this would suggest full inhibition of reabsorption). It only they reduce it, as binding to the receptor is ~ 90%.	Thank you for your comment. No action required.
	British Cardiovascular Society	The text states that the drug has been "studied in combination with standard care in 3 randomised control trials". We are unaware of any other dedicated HF outcome trials that has reported other than DAPA-HF. Kato *et al* Circulation. 2019 May 28;139(22):2528-2536. was a post hoc analysis of 3.9% of the DECLARE-TIMI population, but was not a dedicated HF trial overall.	Thank you for your comment. The technology section of the scope has been updated to reflect this.

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	British Society for Heart Failure	States - dapagliflozin has been studied in comparison to standard of care in patients with heart failure in 3 RCTs. Only one of these studies, DAPA-HF, studied a population of purely heart failure patients. The other studies had sub-sets of heart failure patients only (e.g. Declare-TIMI 58 was a cardiovascular trial not a comparative heart failure study). Intervention reads 'Dapagliflozin in combination with standard care (including treatment with a beta blocker and an aldosterone antagonist).' This should be: 'Dapagliflozin in combination with standard care (including treatment with an ACEI/ARB/ARNI, beta blocker and an aldosterone antagonist)'.	Thank you for your comment. The technology section of the scope has been updated to reflect this.
	Novartis Pharmaceuticals UK Limited	The technology: The description of the mechanism of action of SGLT2 inhibitors in the draft scope relates to the diabetes indication. To our knowledge, the mechanism of action of SGLT2 inhibitors in heart failure is currently unknown. In addition to having an established documented diagnosis of symptomatic heart failure with reduced ejection fraction (NYHA functional class II-IV) for at least 2 months and a LVEF of ≤40%, as already described in the draft scope, patients also had to be optimally treated with pharmacological and/or device therapy, as indicated, in order to be eligible for inclusion in the dapagliflozin main clinical trial 'DAPA-HF'.2	Thank you for your comments. The description of the technology has been updated in the scope.

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		Intervention: Dapagliflozin was investigated in the DAPA-HF trial in addition to individually optimised background standard of care therapy. Unless contraindicated or not tolerated, standard care consisted of an ACE inhibitor, or ARB or sacubitril valsartan, and a beta-blocker and, if considered appropriate by the treating physician, a mineralocorticoid receptor antagonist (MRA).2 For the technology appraisal, the intervention should be defined in line with how it was investigated in the clinical trial. We propose the following wording to describe the intervention: “Dapagliflozin in addition to individually optimised standard care (unless contraindicated or not tolerated, including treatment with an ACE inhibitor or ARB or sacubitril valsartan, and a beta-blocker and, if considered appropriate, a mineralocorticoid receptor antagonist (MRA)).” References: 2 Protocol for: 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	
Population	AstraZeneca	Yes	Thank you for your comment. No action required.
	Boehringer Ingelheim Ltd.	Yes	Thank you for your comment. No action required.

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	British Cardiovascular Society	The population described is appropriate. Patients with Type 1 diabetes are not suitable for this treatment however, even with heart failure. Importantly the DAPA-HF trial recruited patients both with and without diabetes and the benefits were observed in both patient groups. Previous trails of SGLT2 inhibitors have concentrated specifically on patients with type 2 diabetes with or at risk of atherosclerotic vascular disease (EMPA-REG, CANVAS, DECLARE TIMI 58). All 3 trials have shown a reduction in heart failure hospitalisations in the study population, a non-heart failure population.	Thank you for your comment. No action required.
	British Society for Heart Failure	Yes. This is in line with previous heart failure studies.	Thank you for your comment. No action required.
	Novartis Pharmaceuticals UK Limited	In order to represent the clinical trial population2 more accurately, we propose to add "[…] with LVEF ≤40% and NYHA functional class II-IV despite optimal treatment with pharmacological and/or device therapy". References: 2 Protocol for: 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	Thank you for your comment. The technology will be appraised according to its marketing authorisation and taking into account the available evidence. No changes to the population section are required.
Comparators	AstraZeneca	NICE NG106 guidelines recommend HFrEF patients to receive treatment with diuretics, an angiotensin converting enzyme inhibitor (ACEi) and a beta-blocker, and if symptoms continue a mineralocorticoid receptor antagonist (MRA). Treatment with an angiotensin receptor blocker (ARB) should be considered in patients who cannot tolerate an ACEi. In line with NG106, triple therapy with a beta-blocker, an ACEi or ARB and an MRA is considered a key	Thank you for your comment, the comparators section of the scope has been amended.

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		performance indicator in the National Heart Failure Audit. However, the use of MRAs is limited by their poor tolerability profiles, including hyperkalaemia and hypotension (10, 11). Additionally, sacubitril valsartan is recommend by NICE in patients with ejection fraction ≤35% as a treatment intensification in patients who still have symptoms after ACEi/ARB and beta-blocker ± MRA. Ivabradine and digoxin are recommended as treatment intensifications in patients with sinus rhythm >75 beats per minute and ejection fraction ≤35%, and sinus rhythm, respectively. Hydralazine in combination with nitrate is recommended as an alternative to ACEi/ARB in patients who cannot tolerate ACEi nor ARB. Hydralazine in combination with nitrate can also be considered in patients of African or Caribbean family origin with moderate to severe (NYHA III–IV) heart failure despite ACEi/ARB and beta-blocker ± MRA therapy. In the majority of patients, standard pharmacological therapy for the treatment of HFrEF consists of the following treatment combinations: • ACEi/ARB and beta-blocker ± MRA • Beta-blocker and sacubitril valsartan ± MRA Ivabradine, hydralazine/nitrate and digoxin are not commonly used in UK clinical practice to treat patients with HFrEF. In clinical practice, standard care for patients in the UK with HFrEF will vary depending on patients' symptoms and how well they tolerate each treatment. Data from the 2017/18 National Heart Failure Audit show standard care to consist of a combination of beta-blockers (89% of patients), ACEi and/or ARB (~85% of patients), and MRA (~55% of patients) (4). Dapagliflozin will be used in clinical practice in addition to established standard care therapies, and the most appropriate comparator for this decision problem is therefore standard care alone as per the DAPA-HF trial.	

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		Therefore, AstraZeneca would like to ask NICE to amend the comparators in the final scope to the following, to reflect NICE guidance and to reflect standard care received by the majority of patients in UK clinical practice: • Standard care consisting of ACEi/ARB and beta-blocker ± MRA • Standard care consisting of beta-blocker and sacubitril valsartan ± MRA Some of the comparators proposed in the draft scope are not in line with existing NICE clinical guidelines and technology appraisal guidelines (5, 7). The following statements are inaccurate and should be removed from or corrected in the final scope: • "*For people in whom an ACE inhibitor is unsuitable: […] Mineralocorticoid receptor antagonist (MRA) in addition to an ACE inhibitor (or ARB) and beta-blocker*". This statement is self-conflicting. MRA therapy is not restricted to patients who are intolerant to ACEi. • *"For people in whom ACE inhibitors and ARBs are unsuitable: […] ivabradine in combination with standard therapy".* This statement is incorrect. Ivabradine is not restricted to patients who are intolerant to ACEi. • *"For people in whom beta-blocker therapy is contraindicated or not tolerated: Sacubitril valsartan in combination with standard therapy."* This statement is inaccurate. Sacubitril valsartan is not restricted to patients who are intolerant of beta-blockers. Sacubitril valsartan is restricted to patients on stable doses of ACEi or ARB (12). *"Standard care includes treatment with a beta blocker and an aldosterone antagonist."* This statement is inaccurate. Please see above for a description of the standard care and the pharmaceutical therapies used in standard care.	

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	Boehringer Ingelheim Ltd.	Yes	Thank you for your comment. No action required.
	British Cardiovascular Society	The comparator groups require clarification and amendment. Dapagliflozin was compared to patients receiving either angiotensin-converting–enzyme (ACE) inhibitor, an angiotensin-receptor blocker (ARB), or sacubitril–valsartan in addition to a beta-blocker, unless contraindicated. 72% of patient also received a mineralocorticoid receptor antagonist (MRA). Therefore, comparator groups should be: ACE, Beta-blocker, MRA ARB, Beta-blocker, MRA Sacubitril-Valsartan, Beta-Blocker, MRA Empagliflozin has also been noted as a treatment with likely benefit on heart failure endpoints in the European heart failure guidelines, based on the EMPA REG trial, at least in diabetic patients. This would seem a relevant comparator to dapagliflozin, a drug from the same class (as is canagliflozin). All patients in EMPA REG had proven atherosclerotic disease. The Ivabradine statement is incomplete, as it can also be used in patients in combination with beta-blockers	Thank you for your comment the comparators section of the scope has been amended.
	British Society for Heart Failure	The comparators listed are incorrect. These are the current recommended guideline treatments for heart failure however; they are not alternatives to dapagliflozin.	Thank you for your comment the comparators section of

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		DAPA-HF was a study of dapagliflozin compared to placebo, as an adjunct to standard care. Standard care comprises of Angiotensin Converting Enzyme inhibitors (ACEi) or Angiotensin II Receptor Blockers (ARB) plus Beta-blockers (BB) and Mineralocorticoid Receptor Antagonists (MRA). Alternative established treatment includes Angiotensin receptor Naprilysin Inhibitor (ARNi) in place or ACEi or ARB. Ivabradine in place of, or in addition to, a BB, and device therapy including Cardiac resynchronisation therapy. Standard care is not correctly defined within the draft scope.	the scope has been amended.
	Novartis Pharmaceuticals UK Limited	In the DAPA-HF trial, 94% of patients received background medication of ACE inhibitor, ARB or sacubitril valsartan, 96% beta-blocker, and 71% MRA.3 Dapagliflozin (or placebo) was given in addition to these treatments.2 Consequently, based on the available evidence, the before-mentioned treatments do not qualify as alternatives to dapagliflozin and are thus not considered suitable comparators for this technology appraisal. Instead, when used as add-on therapy as per the DAPA-HF clinical trial, we consider the appropriate comparator to be best supportive care, based on the placebo comparator arm in the trial. (Separately, we would like to highlight that the description of comparators in the draft scope is in parts not consistent with the recommendations of the NICE guideline Chronic heart failure in adults: diagnosis and management (2018) and related technology appraisals. For example, these do not restrict the use of sacubitril valsartan to people in whom beta-blocker therapy is	Thank you for your comment. The comparators section of the scope has been updated.

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		contraindicated or not tolerated. Please refer to our comments to the section 'Background information' for full details on the population in which sacubitril valsartan is recommended.) References: 2 Protocol for: 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 3 McMurray JJV, DeMets DL, Inzucchi SE, et al. The Dapagliflozin And Prevention of Adverse-outcomes in Heart Failure (DAPA-HF) trial: baseline characteristics. Eur J Heart Fail. 2019;21:1402-1411. DOI:10.1002/ejhf.1548	
Outcomes	AstraZeneca	Yes	Thank you for your comment. No action required.
	Boehringer Ingelheim Ltd.	Appropriate clinical outcomes. Could include BNP as a surrogate measure? In addition, will QoL be via NYHA or KCCQ?	Thank you for your comment. With regard to BNP (we assume you are referring to pro-B-type natriuretic peptide) levels, there is uncertainty about the reliability of this as a surrogate (Greene et al 2018; Circulation vol. 138, issue 10). No action required.

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			The EQ-5D is the preferred measure of health-related quality of life, in line with the NICE reference case., see guide to the methods of technology appraisal 2013 section 5.
	British Cardiovascular Society	The outcome measures are appropriate. Other “adverse effects of treatment” could include specific side effects of this class of drugs, including diabetic ketoacidosis, genital infections, Fournier’s gangrene, amputations and fractures.	Thank you for your comment. These outcomes have been included in the scope.
	British Society for Heart Failure	Yes	Thank you for your comment. No action required.
	Novartis Pharmaceuticals UK Limited	No comments.	Thank you for your response. No action required.
Economic analysis	AstraZeneca	No comments.	Thank you for your response. No action required.
	Boehringer Ingelheim Ltd.	Quick separation of HHF curves in Dapa-HF study suggests that early onset benefits will be observed.	Thank you for your comment. No action required.

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	British Cardiovascular Society	The economic analysis is appropriate.	Thank you for your comment. No action required.
	British Society for Heart Failure	-	-
	Novartis Pharmaceuticals UK Limited	No comments.	Thank you for your response. No action required.
Equality and Diversity	AstraZeneca	Dapagliflozin is currently available for type 2 diabetes mellitus (T2DM) patients, including T2DM patients with comorbid HFrEF. A positive recommendation by NICE for dapagliflozin in HFrEF is expected to improve equality by extending the benefits of dapagliflozin for the treatment of HFrEF to all patients with HFrEF, including patients with HFrEF but without comorbid T2DM.	Thank you for your comment. No action required.
	Boehringer Ingelheim Ltd.	Potential risk alongside diuresis in congestive HF will need careful titration and routine monitoring in community, especially in frail/elderly, fluid depleted states. Will need caution in low carb diets due to risk of ketosis.	Thank you for your comment. No action required.
	British Cardiovascular Society	The proposed remit and scope should not have an adverse impact on any particular group of people.	Thank you for your comment. No action required.
	British Society for Heart Failure	-	-

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	Novartis Pharmaceuticals UK Limited	No comments.	Thank you for your response. No action required.
Other considerations	AstraZeneca	Not applicable.	Thank you for your response. No action required.
	Boehringer Ingelheim Ltd.	N/A	Thank you for your response. No action required.
	British Cardiovascular Society	The appraisal should consider the optimal sequence of heart failure therapies and combination of heart failure therapies including ACE inhibitors/ARB, beta-blockers, aldosterone antagonist, sacubitril valsartan and dapagliflozin	Thank you for your comment. The remit of the appraisal is to appraise the clinical and cost effectiveness of dapagliflozin within its marketing authorisation for treating adults with chronic heart failure with reduced ejection fraction. Therefore, it is out of scope for this appraisal to make recommendations on the optimal sequence of heart failure therapies.

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	British Society for Heart Failure	-	-
	Novartis Pharmaceuticals UK Limited	No comments.	Thank you for your response. No action required.
Innovation	AstraZeneca	HFrEF poses a substantial challenge to the NHS over the coming years - one in five people over 40 years old will develop HF in their lifetime (13). Despite current treatment options, survival rates are less than some cancers, with approximately 50% of patients dying within 5 years post-diagnosis(14). The burden of HF is expected to rise in the future (15) and hospital admissions related to HF are projected to rise by 50% over the next 25 years (5). Dapagliflozin is an innovative treatment for HFrEF which reduces mortality and hospitalisations compared with current standard care and has a favourable safety profile. In particular, the beneficial effect of dapagliflozin was present across all subgroups considered, including sub-groups by comorbidities, LVEF, and background therapies. Dapagliflozin consequently offers clinical benefits for patients with HFrEF regardless of their current treatment for HFrEF, and does not have the safety limitations associated with many standard care therapies. Beta-blockers, ACEis/ARBs and MRAs require dose titration, and therefore require time to reach guideline-recommended doses, while dapagliflozin can be initiated at the recommended dose with statistically significant benefits observed from day 28 of treatment onwards. The use of beta-blockers, ACEis, and MRAs is also limited by treatment-related AEs such as hypotension and hyperkalaemia (ACEis, MRAs and sacubitril valsartan), which limit patients from reaching guideline-recommended treatment doses. Dapagliflozin is not associated with hypotension or hyperkalaemia and can therefore offer an effective and simple add-on therapy to existing treatments; it is consequently an important and innovative treatment which can help ease the burden of HFrEF to the NHS.	Thank you for your comment. No action required.

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		The effect of dapagliflozin in HFrEF is independent of the glucose-lowering properties of SGLT2is, as demonstrated by the equivalence of the effect in patients with and without type 2 diabetes, and the early benefits observed with therapy. However, the exact mechanism of action of dapagliflozin in HFrEF is currently unknown and therefore the mechanism of action is likely to be a new and innovative. Mechanisms of action which have been postulated include effects on myocardial metabolism, ion transporters, fibrosis, adipokines, and vascular function (9).	
	Boehringer Ingelheim Ltd.	Potentially, yes along with other SGLT2 with ongoing clinical trials.	Thank you for your comment. No action required.
	British Cardiovascular Society	Yes. Dapagliflozin has the potential to improve the care of patients with heart failure and reduced ejection fraction by significantly reducing mortality, heart failure hospitalisations, symptoms, renal failure and improving quality of life in patients receiving the current standard of care. This is likely to represent a major change in the management of heart failure. It has the added benefit of improving glycaemic control in patients with heart failure and type 2 diabetes. McMurray JJV et al. Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction. N Engl J Med 2019;381:1995-2008. Kosiborod MN, et al. Effects of Dapagliflozin on Symptoms, Function and Quality of Life in Patients with Heart Failure and Reduced Ejection Fraction: Results from the DAPA-HF Trial. Circulation. 2019 Nov 17. doi: 10.1161/CIRCULATIONAHA.119.044138. [Epub ahead of print] Whilst dapagliflozin is the first drug in this class to be considered for a heart failure indication, we note the ongoing research interest with other SGLT2 drugs such as empagliflozin that will report in 2020	Thank you for your comment. No action required.

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	British Society for Heart Failure	Dapagliflozin is a new class of medicine in the treatment of heart failure therefore is felt to be innovative. It is possible that Dapagliflozin 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.	Thank you for your comment. No action required.
	Novartis Pharmaceuticals UK Limited	No comments.	Thank you for your response. No action required.
Questions for consultation	AstraZeneca	**Have all relevant comparators for dapagliflozin been included in the scope?** Please see the response to Comment 2: Comparators. **Which treatments are considered to be established clinical practice in the NHS for chronic heart failure with reduced ejection fraction?** NICE NG106 sets out the current pharmacological treatment pathway for patients with HFrEF in the UK (5). Briefly, patients are recommended to initiate treatment with beta-blockers and ACEis or ARB (if intolerant to ACEis) or hydralazine plus nitrate (if intolerant to ACEis and ARBs). If symptoms of HF continue it is recommended to add MRA to beta-blockers and ACEi/ARBs. Following optimisation of treatment with these therapies, patients may have ivabradine or sacubitril valsartan added if they are New York Heart Association (NYHA) stage II-IV and have LVEF ≤35%; ivabradine patients must also have sinus rhythm with heart rate ≥75 beats per minute. Hydralazine in combination with nitrate can be considered in patients of African or Caribbean family origin with moderate to severe (NYHA III–IV)	Thank you for your comments. The relevant section of the scope have been updated.

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		heart failure despite ACEi/ARB and beta-blocker ± MRA therapy. Digoxin can be considered for worsening or severe HFrEF despite ACEi/ARB and beta-blocker ± MRA therapy as treatment intensifications in patients with sinus rhythm. Due to their positioning in the treatment algorithm, the discrete clinical paramaters for which they should be used, ivabradine, hydralazine/nitrate and digoxin are not routinely used in UK clinical practice. Standard care therapy for the treatment of HFrEF in the UK should consequently be considered to consist of the following treatment combinations: • ACEi/ARB and beta-blocker ± MRA • Beta-blocker and sacubitril valsartan ± MRA Data from the 2017/18 National Heart Failure Audit show that beta-blockers are used by 89% of patients, ACEi and/or ARB by ~85% of patients, and MRA by ~55% of patients (4). **Is standard care defined appropriately?** The comparators are currently unclear and do not appear to reflect UK clinical practice. Please see the response to Comment 2: Comparators. As previously discussed, some of the comparators proposed in the draft scope are not in line with existing NICE clinical guidelines and technology appraisal guidelines. The inaccurate statements have been outlined in response to Comment 2 and the statements should be removed/corrected in the final scope. **Are the outcomes listed appropriate?** Yes.	

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		The key trial for dapagliflozin 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 dapagliflozin in practice? HFrEF is defined as HF with LVEF ≤40% (3); the DAPA-HF trial inclusion criteria are consequently based on the clinical diagnosis of HFrEF. The NICE guidance restriction in the sacubitril valsartan and ivabradine recommendations to patients with LVEF ≤35% was based on inclusion criteria in their pivotal trials relating to recruitment issues rather than due to clinical definitions (7, 12). In contrast, DAPA-HF included the full LVEF spectrum for patients with HFrEF, and dapagliflozin remained significantly more effective than standard care in subgroup analyses based on LVEF (≤median / >median and >35% / ≤35%). AstraZeneca consequently anticipates dapagliflozin being recommended based on the inclusion criteria of DAPA-HF, i.e. with no further restrictions based on LVEF. **Are there any subgroups of people in whom dapagliflozin is expected to be more clinically effective and cost effective or other groups that should be examined separately?** No treatment effect modifiers were identified in subgroup analyses of DAPA-HF; there are consequently no subgroups in which dapagliflozin is more effective than others. **Where do you consider dapagliflozin will fit into the existing NICE pathway, Chronic heart failure?** Dapagliflozin is expected to be used in clinical practice as per the DAPA-HF trial, i.e. in addition to current standard care, irrespective of the individual patient's background therapy. In UK clinical practice, the likely place of	

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		therapy for dapagliflozin will therefore be as an add-on therapy to current standard care consisting of the following treatment combinations: • ACEi/ARB and beta-blocker ± MRA • Beta-blocker and sacubitril valsartan ± MRA However, we recognise that not all patients in UK practice will receive treatment with the guideline recommended 'triple therapy' and therefore may receive mono or dual therapy. Based on data from the DAPA-HF trial and results from the cost-effectiveness analysis, we expect dapagliflozin to be considered a treatment option irrespective of the specific background therapy. **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 proposed remit and scope may need changing in order to meet these aims. In particular, please tell us if the proposed remit and scope:** • **could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which dapagliflozin 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;** • **could have any adverse impact on people with a particular disability or disabilities.** **Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts.** Dapagliflozin is currently available for T2DM patients, including T2DM patients with comorbid HFrEF. A positive recommendation for dapagliflozin in	

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		HFrEF is expected to improve equality, by extending the benefits of dapagliflozin for the treatment of HFrEF to all patients with HFrEF, including patients with HFrEF but without comorbid T2DM. **Do you consider dapagliflozin 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)?** Please see the response to Comment 2: Innovation. **Do you consider that the use of dapagliflozin can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation? Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits.** It is anticipated that all health-related benefits will be captured in the QALY calculation. **To help NICE prioritise topics for additional adoption support, do you consider that there will be any barriers to adoption of this technology into practice? If yes, please describe briefly.** Oral dapagliflozin has been widely used in the NHS, in both primary and secondary care settings, as a treatment for type 2 and type 1 diabetes since recommendation by NICE in 2013 and 2019, respectively. As such, both primary and secondary care clinicians have clinical experience in prescribing dapagliflozin, and therefore we anticipate no barriers to adoption in HFrEF.	

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		NICE intends to appraise this technology through its Single Technology Appraisal (STA) Process. We welcome comments on the appropriateness of appraising this topic through this process. (Information on the Institute's Technology Appraisal processes is available at http://www.nice.org.uk/article/pmg19/chapter/1-Introduction). AstraZeneca believe that appraisal of dapagliflozin via STA is appropriate but wish to make NICE aware that the appraisal satisfies the eligibility criteria for fast track appraisal based on the clinical efficacy and safety observed in the DAPA-HF trial, previous experience within the NHS with dapagliflozin in people with type 2 and type 1 diabetes, and preliminary economic analyses. Cost-effectiveness analysis has demonstrated an ICER <£10,000 per QALY for dapagliflozin compared with standard care alone (as per the DAPA-HF trial). Results from scenario analyses show the cost-effectiveness of dapagliflozin to be robust to variations in model parameters. **NICE has published an addendum to its guide to the methods of technology appraisal (available at https://www.nice.org.uk/Media/Default/About/what-we-do/NICE-guidance/NICE-technology-appraisals/methods-guide-addendum-cost-comparison.pdf), which states the methods to be used where a cost comparison case is made.** • **Would it be appropriate to use the cost comparison methodology for this topic?** Cost-comparison is not appropriate for the base case comparison of dapagliflozin versus standard care alone due to the significant differences in efficacy between the dapagliflozin arm and the standard care alone arm observed in DAPA-HF. AstraZeneca consequently intend to submit a cost-	

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		effectiveness analysis versus standard care alone (as per the DAPA-HF trial) in the base case. The results from the indirect treatment comparison will determine the most appropriate methodology for the cost-effectiveness evaluation of dapagliflozin versus sacubitril valsartan. • **Is the new technology likely to be similar in its clinical efficacy and resource use to any of the comparators?** [redacted] • **Is the primary outcome that was measured in the trial or used to drive the model for the comparator(s) still clinically relevant?** The primary outcome in the trial was a composite of cardiovascular death, hospitalisation for HF, or urgent HF visit; this outcome is highly clinically relevant. The economic model will consider all-cause mortality, hospitalisation for HF and urgent HF visit. • **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?** There is no additional evidence that has not been considered. The ongoing trial for dapagliflozin, DETERMINE-reduced, is not expected to report over the next year and includes outcomes which have either already been examined in DAPA-HF (KCCQ) or are unlikely to be relevant to the current decision problem (6-minute walking distance, mean movement intensity, time spent in light to vigorous physical activity).	

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	Boehringer Ingelheim Ltd.	1. Outcomes are likely to vary based on LVEF? 2. If only prescribed based on firm diagnosis of rEF, will echo be a requirement? Will ruling out a reversible ischaemic cause be a requirement? 3. More effective in NYHA II and III? 4. Should fit once all other SoC have been implemented and still need for further therapy. 5. Adverse complications listed above. 6. Barriers may include cost and resource to introduce and monitor therapy. 7. There are other SGLT2i is which have ongoing HF trials in HFrEF and HFpEF (including empagliflozin) and based on comparative data so far, we expect these will have similar benefits.	Thank you for your comments. No action required.
	British Cardiovascular Society	None	Thank you for your response. No action required.
	British Society for Heart Failure	Q. Where do you consider dapagliflozin will fit into the existing NICE pathway, Chronic heart failure? A. We anticipate that Dapagliflozin will fit in the existing NICE pathway in a similar manner to Sacubutril-Valsartan but as an additional agent (i.e. not instead of sacubitril valsartan). It is likely to be initiated by a member of the heart failure specialist team.	Thank you for your comments. No action required.

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		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 (Empagliflozin) is being examined for the treatment of heart failure with reduced LV ejection fraction and preserved LV ejection fraction (EMPEROR trials).	
	Novartis Pharmaceuticals UK Limited	Have all relevant comparators for dapagliflozin been included in the scope? As outline above in our comments to the section 'Comparators', we consider best supportive care to be the relevant comparator in this technology appraisal given that dapagliflozin is expected to be used as add-on therapy as per the DAPA-HF clinical trial. Where do you consider dapagliflozin will fit into the existing NICE pathway, Chronic heart failure? Given that the evidence for the use of dapagliflozin in chronic heart failure comes from a trial in which dapagliflozin was administered in addition to optimised standard care including an ACE inhibitor, or ARB or sacubitril valsartan, and a beta-blocker and, if appropriate, an MRA, we believe the appropriate position for dapagliflozin in the treatment pathway is as add-on to these treatments, if patients remain symptomatic (NYHA II-IV) despite individually optimised therapy. As sacubitril valsartan has demonstrated superiority over ACE inhibitor in a head-to-head trial4, it could be argued that the most appropriate place for dapagliflozin in the treatment pathway is as add-on to sacubitril valsartan (in combination with a beta-blocker and, if appropriate, an MRA).	Thank you for your comments. The relevant sections of the scope have been updated.

Section	Consultee/ Commentator	Comments [sic]	Action
		References: 4 McMurray JJ, Packer M, Desai AS, et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure. N Engl J Med 2014;371:993-1004. DOI: 10.1056/NEJMoa1409077 NICE intends to appraise this technology through its Single Technology Appraisal (STA) Process. [...] Would it be appropriate to use the cost comparison methodology for this topic? Is the new technology likely to be similar in its clinical efficacy and resource use to any of the comparators? We consider the STA process as appropriate for this technology appraisal. The cost comparison approach does not seem to be suitable due to differences in the populations included in the clinical trials of treatments used for this indication. To our knowledge, no evidence exists to support the use of dapagliflozin in the same patient population as a NICE recommended treatment, precluding the assumption of similarity in terms of health outcomes which would be required for the cost comparison methodology.	
Additional comments on the draft scope	AstraZeneca	N/A	Thank you for your response. No action required.
	Boehringer Ingelheim Ltd.	-	-
	British Cardiovascular Society	Any additional comments on the draft scope • Would it be appropriate to use the cost comparison methodology for this topic? **BCS is happy with the proposed economic evaluation**	Thank you for your comments, the scope has been amended accordingly.

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		• Is the new technology likely to be similar in its clinical efficacy and resource use to any of the comparators? **It is likely to be similar in efficacy to empagliflozin and possibly canagliflozin, although these two have not had dedicated heart failure trials reported as yet.** **It may be similar in efficacy to sacubritil valsartan and it is unclear whether there is likely to be an additive benefit of the combination of dapagliflozin and sacubritil valsartan.** • Is the primary outcome that was measured in the trial or used to drive the model for the comparator(s) still clinically relevant? **Yes** • 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? • **As above – the ongoing EMPEROR trial will provide additional information in heart failure of the relative efficacy of empagliflozin**. We endorse also the following point made by the British society of heart failure. “Given that this is primarily a diabetic medication, we would welcome NICE to consider the need for an additional educational program post approval. Heart failure specialists may not be confident with the prescribing diabetic medicines, monitoring and implications of changing diabetic regimens. It is also necessary to consider education for implementation in non-diabetic	

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		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.”	
	British Society for Heart Failure	Given that this is primarily a diabetic medication, we would welcome NICE to consider the need for an additional educational program post approval. Heart failure specialists may not be confident with the prescribing 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.
	Novartis Pharmaceuticals UK Limited	-	-