NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Dapagliflozin for treating heart failure with reduced ejection fraction [ID1656]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Dapagliflozin for treating heart failure with reduced ejection fraction [ID1656]

Contents:

The following documents are made available to consultees and commentators:

The **final scope** and **final stakeholder list** are available on the NICE website.

Pre-technical engagement documents

1. **Company submission** from Astrazeneca UK Ltd

2. **Clarification questions and company responses**

3. **Patient group, professional group and NHS organisation submissions** from:
   a. British Society for Heart Failure (endorsed by British Cardiovascular Society and the Royal College of Physicians)
   b. Pumping Marvellous Foundation

4. **Evidence Review Group report** prepared by **Kleijnen Systematic Reviews Ltd**

5. **Evidence Review Group report – factual accuracy check**

6. **Technical report**

7. **Technical engagement response from company**
   a. Company Technical Engagement response

8. **Technical engagement responses from experts:**
   a. Dr Klaus Witte – clinical expert, nominated by AstraZeneca UK
   b. Nick Hartshorne-Evans patient expert nominated by Pumping Marvellous Foundation

9. **Technical engagement responses from consultees and commentators:**
   a. British Cardiovascular Society (endorsed by Royal College of Physicians and British Cardiovascular Society)
   b. British Society for Heart Failure (endorsed by Royal College of Physicians and British Society for Heart Failure response)
   c. Cardiomyopathy UK
   d. MSD
   e. Primary Care Cardiovascular Society
   f. South Asian Health Foundation
   g. Novartis Pharmaceuticals UK Limited

10. Evidence Review Group critique of company response to technical engagement prepared by Kleijnen Systematic Reviews (KSR) Ltd

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

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Dapagliflozin for treating heart failure with reduced ejection fraction [ID1656]

Document B

Company evidence submission

May 2020

File name	Version	Contains confidential information	Date
NICE Document B_Dapagliflozin_HFrEF_FINAL [AIC]	1	Yes	22/05/20

Contents

Tables and figures

Abbreviations

ACEi	Angiotensin-converting-enzyme inhibitor
AE	Adverse event
AIC	Akaike information criterion
ALT	Alanine transaminase
ARB	Angiotensin receptor blocker
ARNI	Angiotensin receptor-neprilysin inhibitor
AST	Aspartate transaminase
BIC	Bayesian information criterion
BMI	Body mass index
CHD	Coronary heart disease
CHF	Chronic heart failure
CI	Confidence interval
COPD	Chronic obstructive pulmonary disease
CPRD	Clinical Practice Research Datalink
CRT	Cardiac resynchronisation therapy
CV	Cardiovascular
DKA	Diabetic ketoacidosis
DSA	Deterministic sensitivity analysis
DSU	Decision Support Unit
EASD	European Association for the Study of Diabetes
ECG	Electrocardiogram
EF	Ejection fraction
eGFR	Estimated glomerular filtration rate
EQ-5D (-3L/-5L)	European quality of life 5 dimensions (3 levels/5 levels)
ESC	European Society of Cardiology
ESS	Effective sample size
FAS	Full analysis set
FTA	Fast track appraisal
GP	General practitioner
GPwSI	General practitioner with a special interest
HF	Heart failure
HFS	Hypoglycaemia Fear Survey
HFrEF	Heart failure with reduced ejection fraction
HFmrEF	heart failure with mid-range ejection fraction
hHF	Hospitalisation for heart failure
HR	Hazard ratio
HRG	Healthcare Resource Group

HRQOL	Health-related quality of life
HSUV	Health state utility value
HTA	Health technology assessment
HUI3	Health Utilities Index Mark 3
ICD	Implantable cardioverter defibrillator
ICER	Incremental cost-effectiveness ratio
IP	Investigational product
IPD	Individual patient-level data
ITT	Intent-to-treat
IV	Intravenous
KCCQ	Kansas City Cardiomyopathy Questionnaire
LV	Left ventricle
LVAD	Left ventricular assist devices
LVEF	Left ventricular ejection fraction
LVSD	Left ventricular systolic dysfunction
LY	Life-year
LYG	Life-years gained
MAIC	Matching adjusted indirect comparison
MDT	Multidisciplinary team
MI	Myocardial infarction
MRA	Mineralocorticoid receptor antagonist
NHS	National Health Service
NT-proBNP	N-terminal pro B-type natriuretic peptide
NYHA	New York Heart Association
OR	Odds ratio
PACD	Primary analysis censoring date
PCI	Percutaneous coronary intervention
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
QALY	Quality-adjusted life year
QoL	Quality of life
RAASi	Renin-angiotensin aldosterone system inhibitor
RCT	Randomised controlled trial
SAE	Serious adverse event
SBP	Systolic blood pressure
SD	Standard deviation
SE	Standard error

SF-6D	Short form 6-dimensions
SGLT2	Sodium/glucose cotransporter 2
SGLT2i	Sodium glucose cotransporter 2 inhibitor
SLR	Systematic literature review
SmPC	Summary of Product Characteristics
SMR	Scottish Morbidity Record
SC	Standard care
STA	Single technology appraisal
T1DM	Type 1 diabetes mellitus
T2DM	Type 2 diabetes mellitus
TEM	Treatment effect modifier
TTO	Time trade-off
TSS	Total Symptom Score
uHFv	Urgent heart failure visit
UKPDS	United Kingdom Prospective Diabetes Study Group
ULN	Upper limit of normal
UTI	Urinary tract infection
WTP	Willingness to pay

B.1 Decision problem, description of the technology and clinical care pathway

B.1.1 Decision problem

The submission covers the technology's full marketing authorisation for this indication.

Table 1: The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adults with chronic heart failure with reduced ejection fraction.	As per scope.	NA
Intervention	Dapagliflozin in combination with SC (including treatment with an ACEi, ARB, mineralocorticoid receptor antagonist, beta blocker, sacubitril valsartan and/or an aldosterone antagonist).	Dapagliflozin in combination with SC, where SC is defined as: • ACEi or ARB, in combination with beta-blocker, ±MRA (according to patient's tolerance of MRA) • Sacubitril valsartan, in combination with beta-blocker, ±MRA (according to patient's tolerance of MRA)	The intervention is in line with the scope, with SC defined more clearly to reflect the two distinct places of therapy relevant for dapagliflozin in the treatment pathway for HFrEF patients.
Comparator(s)	Individually optimised SC without dapagliflozin. Standard care is defined as: • ACEi in combination with beta-blockers, and/or mineralocorticoid receptor antagonists • ARBs in combination with beta-blockers, and/or mineralocorticoid receptor antagonists • Sacubitril valsartan in combination with beta-blockers, and/or mineralocorticoid receptor antagonists	For the treatment of HFrEF patients on ACEi or ARB, in combination with beta-blocker, ±MRA, the comparators will be: • Sacubitril valsartan • Placebo For the treatment of HFrEF patients on sacubitril valsartan, in combination with beta-blocker, ±MRA, the comparators will be: • Placebo	In line with NICE TA388 and NG106, the relevant comparators at the two distinct places of therapy relevant for dapagliflozin in the treatment pathway for HFrEF patients (see 'intervention') are sacubitril valsartan and placebo. Background therapy (SC) will be the same in both the dapagliflozin arm and the comparator arm.
Outcomes	The outcome measures to be considered include: • symptoms of heart failure • hospitalisation for heart failure • all-cause hospitalisation	As per scope.	NA

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
	• mortality • cardiovascular mortality • adverse effects of treatment (including diabetic ketoacidosis, genital infections, Fournier's gangrene, amputations and fractures) • health-related quality of life.		
Economic analysis	Health economic analysis.	As per scope.	NA
Special considerations including issues related to equity or equality	None stated.	Equality issues related to current use and availability of dapagliflozin in T2DM patients.	Dapagliflozin is currently available across primary and secondary treatment settings for T2DM patients, including T2DM patients with comorbid HFrEF. A positive recommendation for dapagliflozin in HFrEF is expected to improve equality by extending the benefits of dapagliflozin for the treatment of all eligible HFrEF patients with and without comorbid T2DM. Similarly, initiation of dapagliflozin for the treatment of HFrEF in the primary care setting would improve equality of access without relying on access to specialist care, which currently varies by geography.

B.1.2 Description of the technology being appraised

A draft summary of product characteristics (SmPC) for dapagliflozin is provided in Appendix C; details of the technology being appraised in the submission, including the method of administration, dosing and related costs, are provided in Table 2.

Table 2: Technology being appraised

UK approved name and brand name	Dapagliflozin (Forxiga®).
Mechanism of action	Dapagliflozin is a highly potent, selective and reversible inhibitor of SGLT2. Inhibition of SGLT2 by dapagliflozin reduces reabsorption of glucose from the glomerular filtrate in the proximal renal tubule with a concomitant reduction in sodium reabsorption leading to urinary excretion of glucose and osmotic diuresis. However, the cardio-renal benefits of dapagliflozin are not solely dependent on the blood glucose-lowering effect and not limited to patients with diabetes. In addition to the osmotic diuretic and related hemodynamic actions of SGLT2 inhibition, potential secondary effects on myocardial metabolism, ion channels, fibrosis, adipokines and uric acid may be mechanisms underlying the cardio-renal beneficial effects of dapagliflozin.
Marketing authorisation/CE mark status	Marketing authorisation is expected late July / early August 2020.
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	*Indication of relevance to this submission:* Dapagliflozin is indicated in adults for the treatment of symptomatic heart failure with reduced ejection fraction. [expected wording] *Other indications:* Dapagliflozin is indicated in adults for the treatment of insufficiently controlled type 2 diabetes mellitus as an adjunct to diet and exercise • as monotherapy when metformin is considered inappropriate due to intolerance. • in addition to other medicinal products for the treatment of type 2 diabetes. Dapagliflozin is indicated in adults for the treatment of insufficiently controlled type 1 diabetes mellitus as an adjunct to insulin in patients with BMI ≥ 27 kg/m^2, when insulin alone does not provide adequate glycaemic control despite optimal insulin therapy.
Method of administration and dosage	10 mg oral dapagliflozin once daily.
Additional tests or investigations	None.
List price and average cost of a course of treatment	£36.59 for a 28-tablet pack Annual treatment cost of £476.98
Patient access scheme (if applicable)	Not applicable

B.1.2.1 Appraisal route

AstraZeneca (AZ) strongly believe that dapagliflozin is an appropriate candidate for fast track appraisal (FTA). Dapagliflozin for HFrEF satisfies the criteria for FTA:

- The cost-minimisation analysis of dapagliflozin versus sacubitril valsartan showed that **dapagliflozin** was associated with **cost-savings compared to sacubitril valsartan**
    - This analysis was based on the outcomes from a matching-adjusted indirect comparison (MAIC), which demonstrates there to be **no statistically significant differences** in outcomes between dapagliflozin and sacubitril valsartan, with numerical differences **favouring dapagliflozin** for the key endpoints that drive cost-effectiveness (including cardiovascular [CV]-mortality and heart failure [HF] hospitalisation); additionally, the **cost of dapagliflozin is approximately 60% less** than the cost of sacubitril valsartan
- The cost-effectiveness analysis of dapagliflozin as an add-on to standard care, as specified in the National Institute for Health and Care Excellence (NICE) scope, showed the incremental cost-effectiveness ratio (ICER) to be **less than £10,000/ quality adjusted life year (QALY)**
    - Scenario analyses demonstrate the cost-effectiveness of dapagliflozin to be **highly robust and maintained under variations in model input parameters**
    - As such, it is highly likely that the most plausible ICER is **less than £20,000 per QALY gained** and it is highly unlikely that the ICER is greater than £30,000 per QALY gained

One in five people over 40 years old will develop HF in their lifetime (1), with a 5-year mortality rate for patients in the UK of 54.5% (2). The burden of HF is expected to rise in the future (3), with hospital admissions related to HF projected to rise by 50% over the next 25 years (4). Dapagliflozin for heart failure with reduced ejection fraction (HFrEF) reduces mortality and hospitalisations compared with current standard care and has a favourable safety profile. In addition, the efficacy of dapagliflozin is evident from the very early stages of treatment, as shown by the early separation of the Kaplan-Meier (KM) curves for the primary endpoint, with a hazard ratio (HR) corresponding to a p-value of <0.05 from day 28 onwards (exploratory analysis) (5). Providing access to dapagliflozin as swiftly as possible is therefore likely to be highly beneficial for patients in the National Health Service (NHS). AstraZeneca consequently believe that there is a strong clinical rationale for FTA of dapagliflozin.

Dapagliflozin also offers benefits beyond efficacy compared with standard care; it has no requirement for dose titration (a limitation of beta-blockers, angiotensin-converting-enzyme inhibitors (ACEis) / angiotensin receptor blockers (ARBs) and mineralocorticoid receptor antagonist [MRAs]) and is not associated with hypotension and hyperkalaemia (a limitation of ACEis, MRAs and sacubitril valsartan). In addition, there is extensive experience of the use of dapagliflozin within the NHS, along with its safety profile, as a result of years of use for dapagliflozin as a treatment for type 1 and type 2 diabetes.

Providing access to dapagliflozin as swiftly as possible is therefore likely to be highly beneficial for HF patients in the context of the high hospitalisation rate and high mortality rate Company evidence submission template for dapagliflozin for HFrEF.

associated with HF. AstraZeneca consequently believes that there is a strong clinical and cost-effectiveness rationale for FTA of dapagliflozin.

B.1.3 Health condition and position of the technology in the treatment pathway

B.1.3.1 Background

Heart failure is a clinical syndrome caused by structural or functional cardiac abnormalities which result in symptoms and signs such as difficulty breathing, fatigue, ankle swelling, and oedema (6). Mortality associated with HF is high, with approximately half of patients dying within 5 years of diagnosis (2). There are numerous causes of HF, such as left ventricular dysfunction (the most common), and abnormalities of the valves, pericardium, endocardium, and cardiac conduction and heart rhythm (e.g. atrial fibrillation). The most common causes of left ventricular dysfunction, which can be either predominantly systolic (reflecting contraction and emptying of the chamber) or diastolic (reflecting relaxation and filling), are ischaemic heart disease (IHD) and hypertension, although the cause in many patients is not known. Diabetes is also associated with a higher risk of developing HF, and comorbid diabetes is associated with poorer functional status and worse outcomes after HF develops (6). This is particularly relevant as the prevalence of diabetes has more than doubled in the UK over the past 20 years and is projected to increase further over the next 10 years (7); it is likely that this increase will therefore be associated with an increase in the incidence of HF and severity of prevalent HF.

HF is broadly divided into two types, differentiated on the basis of measurement of left ventricular ejection fraction (EF). Measurement of EF is a means of quantifying the fraction of blood ejected by the left ventricle, into the arteries, each time the heart contracts. If the EF is substantially lower than normal (<40%) the patient is said to have HF with reduced EF (HFrEF). The principal underlying problem in these patients is systolic dysfunction. Up to half of patients with HF do not have a clearly reduced EF and are generally described as having HF with “preserved” EF (HFpEF) i.e. not clearly reduced but not always normal (>50%). In many of these patients the predominant problem may be diastolic dysfunction. Recently patients with EF in the “borderline” area between 40% and 50% have been described as having HF with “mid-range” or “mildly-reduced” EF (HFmrEF) to reflect the possibility that some may have mild systolic dysfunction (4, 6). As outlined in the scope, this submission is concerned with treatment of patients with HFrEF.

B.1.3.2 Burden of HF

Heart failure represents one of the most significant healthcare problems in the UK; one in five people over 40 years old will develop HF in their lifetime (1) and their five-year mortality rate post-diagnosis is 54.5% (2). This mortality rate is higher than for many forms of cancer (e.g. leukaemia, bladder, colon) (8), with a one-year mortality rate for HF in the UK of 24.1% (2). Cardiovascular disease has been identified by the NHS as the single biggest condition where lives can be saved; the current NHS Long Term Plan consequently aims to prevent >150,000 heart attacks, strokes and dementia cases over the next 10 years (9). Improving treatment outcomes in HF will help meet this long-term NHS goal.

HF can lead to a range of symptoms, including difficulty breathing, fatigue, and ankle swelling (6). These symptoms, in addition to the emotional burden of living with a chronic

condition, reduce quality of life (QoL) significantly and increasingly as the patient's disease progresses (10), and the QoL of patients with HF is similar to diseases such as multiple sclerosis and rheumatoid arthritis, and lower (worse) than for breast cancer (11, 12). This burden places considerable stress on patients, and depression and anxiety are common comorbidities in HF (13). Hospitalisation for HF also has a significant impact on the QoL of patients; in a randomised controlled trial (RCT) of sacubitril valsartan patients with hospitalisation for heart failure (hHF) had a significant worsening in Kansas City Cardiomyopathy Questionnaire (KCCQ)[1] overall summary score (including the QoL domain) and clinical summary score from baseline at 8 months, while those who did not have a hHF event had improvements in these scores from baseline (14). Avoiding hHF will therefore have substantial QoL benefits for patients. Furthermore, a study of HF patients showed that patients' mental and physical QoL scores are predictive of long-term mortality, further emphasising the importance of maintaining HF patients' QoL (15).

HF is the leading cause of hospitalisations in people aged >65 years (16) and is the leading cause of rehospitalisation in the general population (17). The economic burden of HF is consequently high, and estimates of the annual cost to the NHS range from £650 million (18) to approximately 2% of the annual NHS budget (£2.6 billion) (4, 19). Based on 2019/20 NHS National Tariff and Reference Costs (EB03A–E), the average cost per hHF is £2,436 (20, 21) with an average length of stay of 9.1 days (22). In addition to direct costs, HF also contributes substantial indirect costs as a result of mortality, lost productivity, and the need to provide long-term domiciliary of institutional care for some patients (23).

The burden of HF will rise in the future, in part due to an ageing population and improved survival from other CV and other chronic diseases (24), and hospital admissions related to HF are projected to rise by 50% over the next 25 years (4). Despite improvements in clinical care and the introduction of new treatments for HF, many patients still experience disabling symptoms (25) and mortality rates remain high (26). In addition, HF admissions in England rose by 33% between 2013/14 and 2018/19, three times the percentage increase in overall admissions during this period (27). There is consequently an unmet need for easily accessible new treatments for HF which can lower mortality, reduce hospitalisation rates and improve symptoms and quality of life for patients with HF.

B.1.3.3 Epidemiology

The prevalence of HF in the UK is estimated to be 0.93% (28); based on 2018 population estimates there are therefore approximately 550,000 patients with HF in England and Wales (29). While the overall crude incidence rate for HF per 100 000 population in the UK decreased by 7% between 2002 and 2014, incidence increased in the oldest age group (≥85 years) and the number of individuals with new-onset HF increased by 12% over this period due the increase in population size and change in age structure (3). The age- and sex-standardised prevalence, which, in part, reflects survival of people developing heart failure, remained relatively stable between 2002 and 2014, although the number of people living with heart failure grew by 23% over the same period (3, 26).

[1] The KCCQ assesses a patient's health function and is discussed further in Section B.1.3.5.

Of 68,266 patients admitted to hospital due to HF in England and Wales between April 2017 and March 2018, 66% had HFrEF (26); based on the estimate of 550,000 patients with HF in England and Wales (29), there are therefore approximately 364,000 patients with HFrEF in the UK.

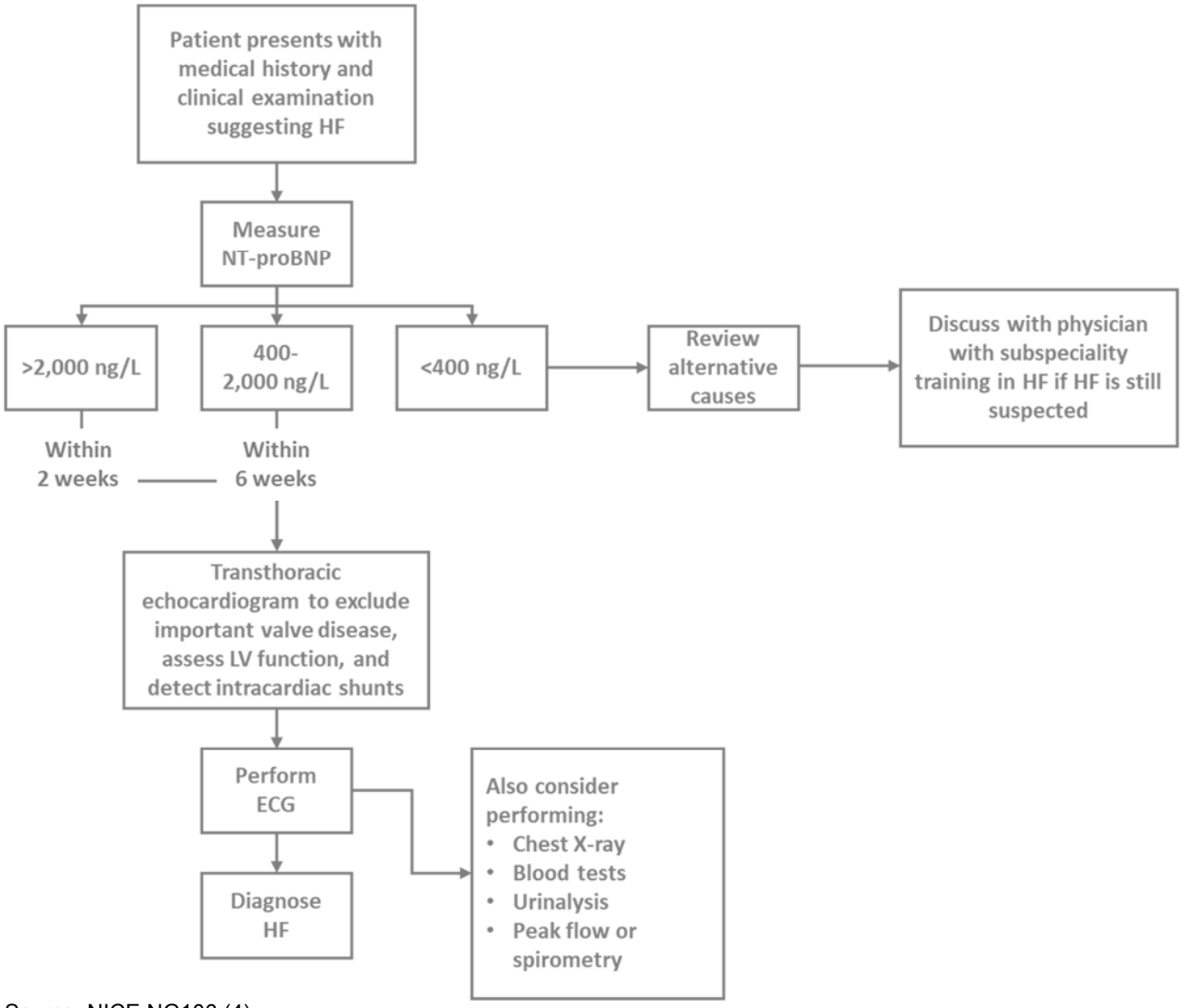
B.1.3.4 Healthcare settings for the management of patients with HF

NICE NG106 recommends that patients should receive care from both a primary care team, typically their local general practitioner (GP), and a specialist multidisciplinary team (MDT). The specialist MDT should include a lead physician trained in HF along with a specialist HF nurse; at least one member of the specialist MDT should have expertise in specialist prescribing for HF. The primary care team are responsible for coordinating the patient's care, ongoing monitoring and management following the initial diagnosis, and referring the patient to specialist HF services as and when required. NG106 recommends that the specialist MDT are responsible for diagnosing HF and initial management of newly diagnosed patients, management of patients with recently decompensated or advanced HF, initiating new medicines which require specialist supervision, and managing patients who are not responding to treatment.

B.1.3.5 Diagnosis of HF

Diagnosis of HF can be difficult because the typical symptoms and signs of heart failure are non-specific i.e. breathlessness fatigue, and swollen ankles, which can result in delays and under-diagnosis of the condition. NICE NG106 (Figure 1) provides guidance on the diagnosis of HF (4); briefly, patients with a medical history suggestive of HF should have a measurement of plasma N-terminal pro B-type natriuretic peptide (NT-proBNP) and referred for echocardiogram and electrocardiogram (ECG) if the NT-proBNP concentration is ≥400 ng/L.

Figure 1: NICE NG106 diagnostic pathway for HF



Source: NICE NG106 (4).
Abbreviations: ECG, electrocardiogram; HF, heart failure; LV, left ventricle; NT-proBNP, N-terminal pro B-type natriuretic peptide.

Clinical guidelines for diagnosis of HF from the European Society of Cardiology (ESC) have similar recommendations (6). Once diagnosis of HF is confirmed it is categorised as HFrEF (left ventricular ejection fraction [LVEF] <40%), heart failure with mid-range ejection fraction (HFmrEF; LVEF 40 to <50%) or HFpEF (LVEF ≥50%) (4, 6).

HF patients are routinely evaluated in clinical practice using the New York Heart Association (NYHA) Functional Classification (Table 3), which is based on physical limitations due to symptoms; however, symptom severity does not correlate closely with left ventricular (LV) function and patients with “mild symptoms” (NYHA class II) still have a substantial risk of hospitalisation and death (6). While the NYHA is useful as a short-hand description of a patient’s clinical status, it is highly subjective, poorly reproducible and not patient-centric (i.e. it is a clinicians assessment of the patients functional limitation) (30). Different cardiologists may have different assessments of the same patient (inter-rater concordance of 54–56% for mild to moderate symptoms) (30) and poor correlation between the NYHA classification and

more objective HF severity measures has been demonstrated (31), as well as very low reproducibility of the NYHA classification among trained cardiologists (32, 33). Inputs from clinical experts indicate that NYHA class has a limited impact on the treatments offered to patients in clinical practice, given the subjective nature of the classification criteria.

Table 3: NYHA Classification Criteria

NYHA stage	Criteria
I	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitations, or dyspnoea.
II	Slight limitation of physical activity. The patient is comfortable at rest. Ordinary physical activity results in fatigue, palpitations, or dyspnoea.
III	Marked limitation of physical activity. The patient is comfortable at rest. Less than ordinary activity causes fatigue, palpitations, or dyspnoea.
IV	Inability to carry on any physical activity without discomfort. Heart failure symptoms are present even at rest or with minimal exertion.

Abbreviations: NYHA, New York Heart Association

In contrast to the NYHA classification system, which provides only 4 score options, the KCCQ overall summary score provides a continuous measure with a potential score between 0 to 100, derived from answers to 23 questions covering 6 domains (physical limitations, symptoms, social limitations and QoL; Table 4) and is considered to provide a more comprehensive and robust assessment of a patient's health status and to be more responsive to change (34). Importantly, it is not biased by a physician's interpretation of patients' symptoms but gives a patient-reported and more granular assessment of the patient's symptoms and limitations. The KCCQ is consequently a more robust measure of changes in a patient's condition than NYHA class, especially in clinical trials, and has established thresholds which indicate clinically relevant changes in health status (35). Baseline KCCQ –Total Symptom Score (TSS) has been found to align with clinical outcomes, with patients with worse KCCQ-TSS at baseline having higher mortality and hHF rates (35). As a result, KCCQ rather than NYHA class, has become the standard tool used in clinical trials to evaluate patient-reported health status and response to treatment.

Table 4: KCCQ questionnaire domains and summary scores

Domains	Description	Total Symptom Score	Clinical Summary Score	Overall Summary score
Physical limitations	Q1: measures the limitations patients experience, due to their heart failure symptoms, in performing routine activities.	Score does **not** include this domain	Includes this domain	Includes this domain
Symptoms (frequency, severity and change over time)	Q2–9: quantifies the frequency and burden of clinical symptoms in heart failure, including fatigue, shortness of breath, paroxysmal nocturnal dyspnoea and patients' oedema/swelling	Includes the frequency and severity sub-domains	Includes this domain	Includes this domain
Self-efficacy and knowledge	Q11–12: quantifies patients' perceptions of how to prevent heart failure exacerbations and manage complications when they arise.	Score does **not** include this domain	Score does **not** include this domain	Score does **not** include this domain
QoL	Q13–15: quantifies patients' assessment of their quality of life, given the current status of their heart failure.	Score does **not** include this domain	Score does **not** include this domain	Includes this domain
Social interference	Q16: quantifies the extent to which heart failure symptoms impair patients' ability to interact in a number of social activities.	Score does **not** include this domain	Score does **not** include this domain	Includes this domain

Source: Green et al. 2000 (34), Kosiborod et al. 2020 (35).
Abbreviations: QoL, quality of life

B.1.3.6 Current treatment options for HFrEF

NICE NG106 separates treatment for HFrEF into two groups, first-line treatment and specialist treatments.

First-line treatments

First-line treatments for HFrEF consists of a combination of diuretics, ACEi or ARB in patients who cannot tolerate an ACEi, and beta-blockers, followed by an MRA if symptoms continue (Figure 2). In clinical practice MRA initiation is often carried out by HF specialists, depending on the geographic region, due to the variable confidence amongst general practitioners in initiation of MRAs. This is primarily due to the common adverse events associated with MRAs, such as hyperkalaemia, hypotension, and worsening kidney function.

Similarly, ACEi/ARB initiation and up-titration in primary care is also variable and may instead take place during a HF specialist visit, depending on the geographic region. Further differences between NG106 and clinical practice are discussed in Section B.1.3.7.

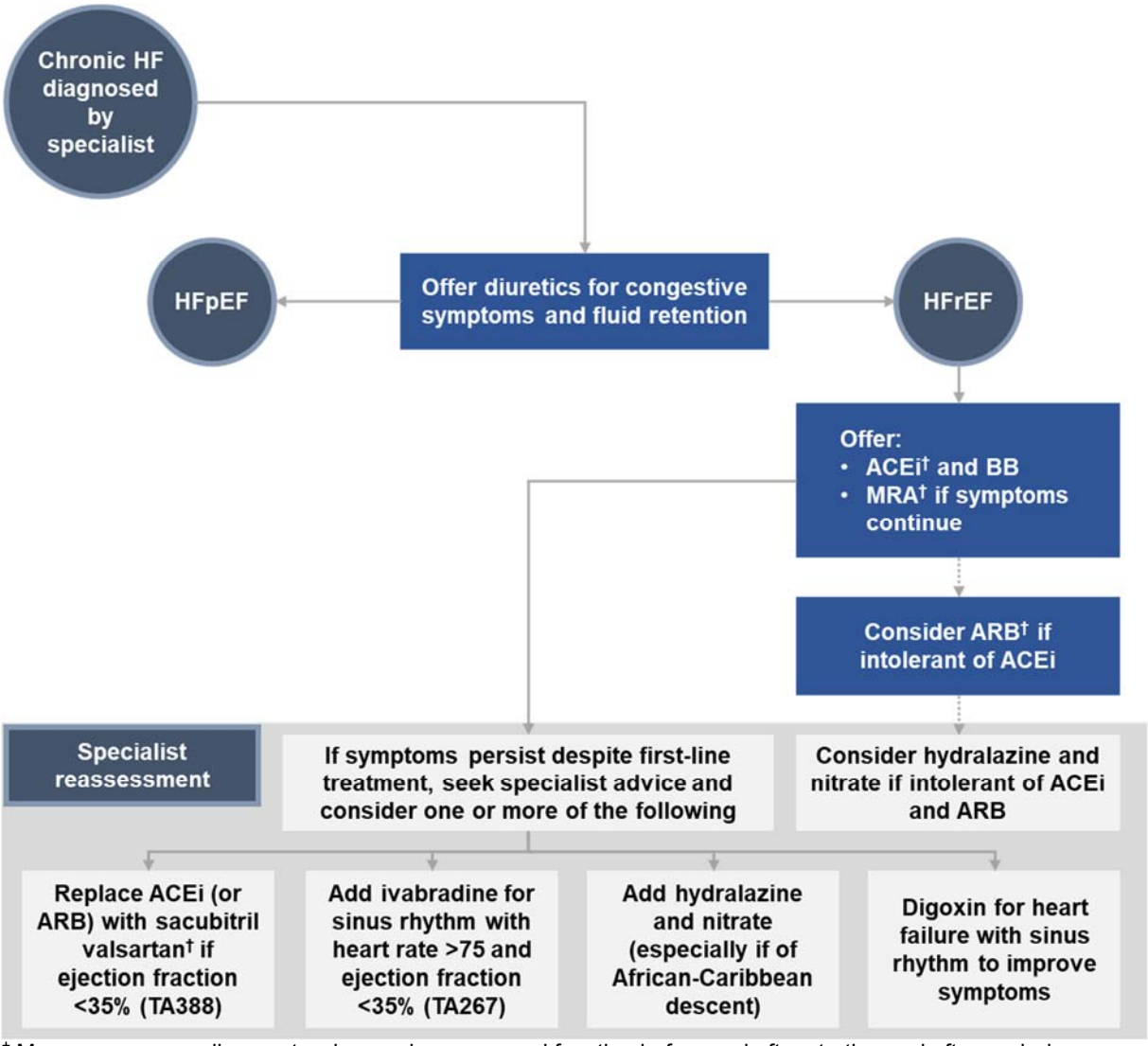
Specialist treatments

Specialist treatments are typically treatments which may be associated with more significant AEs or with which there is less clinical experience. NG106 specifies the treatments which can only be initiated under the supervision of the specialist MDT in patients who still have symptoms after ACEi/ARB and beta-blocker, ±MRA as (Figure 2):

- Sacubitril valsartan in patients with ejection fraction ≤35%.
- Ivabradine in patients with sinus rhythm >75 beats per minute and ejection fraction <35% despite first-line treatment for heart failure.
- 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 heart failure despite ACEi/ARB and beta-blocker, ±MRA therapy.
- Digoxin in patients with reduced ejection fraction despite first-line treatment for heart failure.

Ivabradine, hydralazine/nitrate and digoxin are not commonly used in UK clinical practice to treat patients with HFrEF (36).

Figure 2: Pharmacologic treatments for HFrEF recommended in NG106



† Measure serum sodium, potassium and assess renal function before and after starting and after each dose increment. If eGFR is 30 to 45 ml/min/1.73 m2, consider lower doses or slower titration of ACEI or ARBs, MRAs, sacubitril valsartan and digoxin.
Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blocker; EF, ejection fraction; HR, heart rate; MRA, mineralocorticoid-receptor antagonist.
Source: NG106 (4).

In clinical practice, standard care for patients in the UK with HFrEF varies depending on patients' symptoms and how well they tolerate each treatment. In the majority of patients, standard pharmacological therapy for the treatment of HFrEF consists of the following treatment combinations, in addition to a diuretic (see Section B.1.3.7, Table 5):

- ACEi/ARB, beta-blocker, ±MRA (with or without MRA, according to the patient's suitability for MRA)
- Sacubitril valsartan, beta-blocker, ±MRA

B.1.3.7 Clinical practice vs clinical guidelines

NG106 sets out recommendations for management of HFrEF (4); however, clinical practice does not always match guideline recommendations, which makes the choice of setting for initiation of dapagliflozin (primary or specialist) a highly relevant issue. Only 24% of patients with recorded HF symptoms have been found to follow a NICE guideline pathway to diagnosis, with only 4% completing the pathway within the recommended 6 weeks (37); most patients were found to be diagnosed in hospital following admission for acute symptoms (37).

There is also a discrepancy between clinical guidelines and clinical practice for setting of care. NG106 states that the specialist MDT should diagnose HF and prescribe any initial medications, with the primary care team then responsible for adding or adjusting any medications which do not require specialist prescribing (see Section B.1.3.6). Should the patient's HF fail to respond to treatment and require medications which require specialist initiation, the primary team should refer the patient to the specialist MDT. However, this does not consider GPs with a special interest (GPwSI) in HF, who are skilled in diagnosing and managing HF. GPwSI are typically part of large practices, and other GPs from their practice will typically refer any patients with suspected HF to the GPwSI (38). These GPwSI will initiate some treatments for HFrEF, such as ACEis / ARBs, beta-blockers, and MRAs, and may initiate sacubitril valsartan in coordination with specialist care; however, they would typically work in a community care setting, and depending on regional variation, may not be seen as part of the specialist MDT. Specialist HF nurses are part of the specialist MDT and are usually tasked with treatment titration, medicines management and follow-up following diagnosis by a HF specialist.

Once patients are diagnosed with HF, NG106 initially recommends triple therapy with a beta-blocker, an ACEi or ARB and an MRA, with such treatment considered a key performance indicator in the National Heart Failure Audit (26). However, beta-blockers, ACEis/ARBs and MRAs require dose titration and therefore require time and multiple appointments to reach guideline-recommended doses. Their use is also limited by treatment-related AEs such as hypotension (beta-blockers, ACEis/ARBs and MRAs) and hyperkalaemia (ACEis, and MRAs), which hinder patients from reaching guideline-recommended treatment doses (39, 40). Many hospitals consequently fall far short of prescribing benchmarks (26). 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) (26). However, these data are based on patients discharged following hHF who are likely to have more severe HF than the HF population as a whole. In the overall population, the proportion of patients on guideline-recommended treatments is even lower than National Heart Failure Audit, with only 70% of patients receiving ACEi or ARB, 51% receiving ACEi or ARB plus beta-blockers, and 16% receiving ACEi or ARB plus beta-blockers plus MRA (Table 5). In addition, of those patients on guideline-recommended treatments, the mean daily dose was only 42%, 20%, and 29% of the guideline-recommended dose for those receiving ACEi/ARB, MRA, and beta-blockers, respectively (41).

NICE NG106 provides recommendations for diagnosis, management, and treatment of patients with HF; however, in clinical practice many patients do not follow the diagnosis pathways outlined in NG106, and those who do are unlikely to be diagnosed within the Company evidence submission template for dapagliflozin for HFrEF.

recommended timelines (37). This can impact the availability of treatments to patients and reinforces the relevance of the setting for initiation of dapagliflozin (primary or specialist). As HF diagnosis is a prerequisite for pharmacological management of HF, especially with regards to specialist treatments, delays in HF diagnosis are likely to restrict patients' treatment options, particularly those initiated in specialist care, and thereby their disease progression (4). Once diagnosed, delays also occur in optimisation of patients' treatment; capacity issues, primarily due to a lack of HF nurses, delay referrals to specialist care, and a lack of experience and capacity may prevent GPs from up-titrating treatments which can be prescribed in primary care (36). It consequently takes approximately 3 months to titrate ACEis and beta-blockers, and up to 6 months to reach optimised specialist treatment with sacubitril valsartan (36). In the context of a condition with a 1-year mortality rate in the UK of 24.1% (2), such delays may have serious consequences for patients.

When assessing a new therapy which offers early and sustained efficacy benefits in patients with HF, such as dapagliflozin, it is therefore essential therapies with a favourable benefit-risk profile are not unnecessarily restricted to specialist initiation, which may impact patient care. Indeed, the choice to restrict a treatment to specialist initiation may have significant implications for patients' treatment options, with less than 5% of patients with HFrEF receiving treatments restricted to specialist initiation (Table 5). While it is unclear the extent to which this low level of uptake is due to the restriction, first-line therapies have much higher levels of uptake, although uptake remains below guideline-recommended levels. Treatments offering strong efficacy benefits along with a reassuring safety profile should not be unnecessarily restricted to specialist initiation if large number of eligible patients are to benefit, particularly in diseases with such high unmet need.

Table 5: Treatments for HF in UK clinical practice

Treatment†	n (%) (N=116,408)
Any HF treatment	107653 (92.5)
Diuretics	64662 (55.5)
ACEi	58893 (50.6)
ARB	25534 (21.9)
Beta-blockers	74771 (64.2)
MRA	25928 (22.3)
Sacubitril valsartan	1493 (1.3)
Ivabradine	2420 (2.1)
Hydralazine	927 (0.8)
Device therapy	13429 (11.5)
Therapy combinations†	
ACEi or ARB	81433 (70.0)
(ACEi or ARB) & beta-blocker	59116 (50.8)
MRA & (ACEi or ARB) & beta-blocker	18579 (16.0)
MRA & (NOT sacubitril valsartan)	24745 (21.3)
Sacubitril valsartan & (NOT MRA)	310 (0.3)

†It was not possible to differentiate HFrEF patients and HFpEF patients from the overall HF cohort from the CPRD, and therefore the proportion of patients on each treatment (combination) were calculated using the size of overall HF cohort as the denominator; it is expected that the proportion of patients on each treatment (combination) would have been higher in a HFrEF only cohort.
Source: Analysis of CPRD data from the 12-months prior to January 2019.
Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blocker; MRA, mineralocorticoid-receptor antagonist.

B.1.3.8 Proposed positioning of dapagliflozin in the HFrEF treatment pathway

In the pivotal DAPA-HF trial, dapagliflozin administered in addition to standard care demonstrated a significant reduction in CV mortality and hHF compared with placebo in addition to standard care. This was observed in both the overall population and in subgroups of patients based on their background therapies (Section B.2.7), along with a favourable safety profile. Standard care consisted of the treatments recommended in NICE NG106 (4); it should be noted that patients were not necessarily on NICE guideline-recommended doses of standard care but were instead optimised based on individual patient requirements.

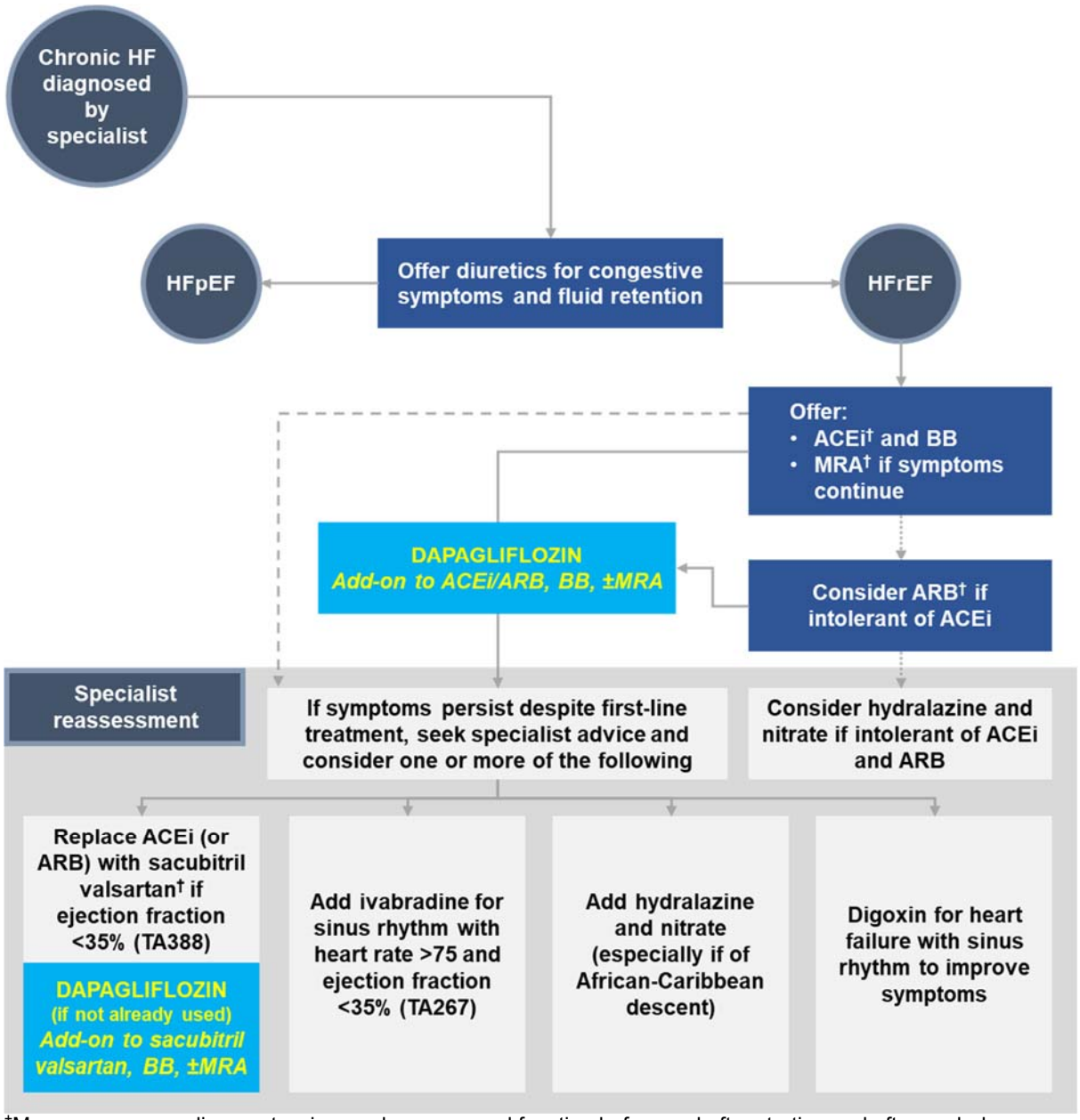
B.1.3.8.1 Positioning

Figure 3 shows the proposed positioning of dapagliflozin in HFrEF with respect to the NICE NG106 recommended treatment pathway. Based on the population studied in the DAPA-HF trial and the outcomes of the trial, along with clinical expert input, there are two appropriate positionings for dapagliflozin in the HFrEF treatment pathway:

- As an add-on therapy to patients who are already treated with ACEi or ARB, in combination with beta-blocker, ±MRA (with or without MRA, according to the patient's suitability for MRA)
- As an add-on therapy to patients who are already treated with sacubitril valsartan, in combination with beta-blocker, ±MRA

Discussions from a UK clinical advisory board and outcomes from subsequent 1:1 clinical expert interviews supported these positionings. Overall, UK clinical experts expressed a preference to use dapagliflozin before sacubitril valsartan in the treatment pathway, as well as to use dapagliflozin as an option after sacubitril valsartan, given the consistent treatment effect of dapagliflozin irrespective of background therapy and the favourable tolerability profile of dapagliflozin (42).

Figure 3: Current treatment pathway for HFrEF (NG106) and proposed place in therapy of dapagliflozin



†Measure serum sodium, potassium and assess renal function before and after starting and after each dose increment. If eGFR is 30 to 45 ml/min/1.73 m^2, consider lower doses or slower titration of ACEI or ARBs, MRAs, sacubitril valsartan and digoxin.
Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blocker; BB, beta-blocker; EF, ejection fraction; HR, heart rate; MRA, mineralocorticoid-receptor antagonist.

B.1.3.8.2 Comparators

As per TA388 and NG106, sacubitril valsartan is used for treatment intensification in patients who remain symptomatic despite treatment with ACEi/ARB, beta-blocker, ±MRA, and as such, sacubitril valsartan is a comparator for this appraisal (base case analysis #1). Prescribing data, CPRD data and input from UK clinical experts indicate that a large

proportion of patients who already receive treatment with ACEi/ARB, beta-blocker, ±MRA are not currently treated with sacubitril valsartan, and therefore placebo should also be a comparator in these patients (base case analysis #2).

The DAPA-HF trial also included patients who received treatment with sacubitril valsartan at baseline (11%), and subgroup analyses show that the treatment effect of dapagliflozin in the subgroups of patients with and without sacubitril valsartan at baseline was consistent. Based on these outcomes, dapagliflozin is also suitable as an add-on therapy in patients who already receive treatment with sacubitril valsartan, in combination with beta-blocker, ±MRA. The comparator to dapagliflozin as an add-on therapy in this positioning is placebo (base case analysis #3).

In summary, the relevant comparators to dapagliflozin for the treatment of HFrEF are sacubitril valsartan and placebo:

- Positioning 1: As an add-on therapy to patients who are already treated with ACEi or ARB, in combination with beta-blocker, ±MRA
    - Comparator (base case analysis #1): sacubitril valsartan
    - Comparator (base case analysis #2): placebo
- Positioning 2: As an add-on therapy to patients who are already treated with sacubitril valsartan, in combination with beta-blocker, ±MRA
    - Comparator (base case analysis #3): placebo

B.1.3.8.3 Treatment setting

As per Figure 3, initiation of dapagliflozin in symptomatic HFrEF patients should not replace referral to a specialist and disease management by a specialist HF multidisciplinary team. However, it is proposed that dapagliflozin could be initiated in primary care, in parallel with a specialist referral, so that patients with a confirmed diagnosis of HFrEF can benefit from treatment with dapagliflozin whilst awaiting specialist reassessment. Recent NICE appraisals in HF (ivabradine and sacubitril valsartan) have restricted these treatments to specialist initiation (43, 44), based in part on concerns over the safety profile and initiation practicalities of the treatments under assessment. As discussed in Section B.1.3.7, restriction to specialist initiation may affect uptake of treatments in clinical practice and should only be applied when appropriate based on concerns over the tolerability of, or clinical experience with, a new treatment. AstraZeneca believes that dapagliflozin is an appropriate treatment for initiation across different healthcare settings for HFrEF, including primary care, and should not be restricted to specialist initiation for the following reasons:

- There is extensive experience of safety profile of dapagliflozin, particularly from primary care, from its use for over 7 years as an anti-diabetes medication; in addition, HFrEF is a common comorbid condition of type 2 diabetes (45), and clinicians may already have experience in using dapagliflozin in patients with HFrEF who also have diabetes.
- Dapagliflozin has no titration requirements and can therefore be easily initiated in primary care.

Company evidence submission template for dapagliflozin for HFrEF.

- The clinical benefits of dapagliflozin are observed early on following initiation (in an exploratory analysis of cumulative data, the p-value was <0.05 for the primary endpoint from 28-days onwards) (5) and continue with prolonged treatment (45); restriction to specialist initiation will delay treatment, and patients may therefore miss out on early benefits associated dapagliflozin treatment.
- The treatment effect of dapagliflozin is consistent regardless of background therapy for HF (46).
- Dapagliflozin has a favourable safety profile, with no serious adverse events (SAEs) with a frequency of >1% occurring more frequently with dapagliflozin than with placebo in DAPA-HF (45).
- The cost of dapagliflozin is substantially lower than the cost of recently recommended specialist treatments for HFrEF.

B.1.3.8.4 Patients with comorbid type 2 diabetes mellitus

In patients with type 2 diabetes mellitus (T2DM), dapagliflozin is currently prescribed and initiated by primary care physicians for glycaemic control and cardiovascular protection. In line with the American Diabetes Association and European Association for the Study of Diabetes (EASD) consensus guidelines on managing hyperglycaemia in T2DM (47) and the ESC/EASD guidelines on diabetes, pre-diabetes and cardiovascular disease (48), clinical experts have indicated that dapagliflozin should be considered immediately following metformin in T2DM patients with cardiovascular disease, or even as the first oral anti-diabetes drug in drug-naïve patients (42). Thus, based on existing T2DM guidelines, clinical expert opinion and the efficacy and tolerability profile of dapagliflozin, it is important to recognise the value of GPs initiating dapagliflozin in the primary care setting in T2DM patients with comorbid HFrEF.

The current submission focuses on the overall HFrEF patient population, as per the final scope and decision problem. The current submission does not explicitly evaluate dapagliflozin in the T2DM-specific positioning and setting, given that dapagliflozin is already recommended for T2DM patients, including those with comorbid HF. Furthermore, it is likely that the ongoing update of NG28 will provide further details of role of dapagliflozin in patients with T2DM with comorbid HF.

B.1.4 Equality considerations

Dapagliflozin is currently available across primary and secondary treatment settings for T2DM patients, including T2DM patients with comorbid HFrEF. A positive recommendation for dapagliflozin in HFrEF is expected to improve equality by extending the benefits of dapagliflozin for the treatment of HFrEF to all eligible patients with HFrEF, including patients with HFrEF but without comorbid T2DM. Similarly, initiation of dapagliflozin for the treatment of HFrEF in the primary care setting would improve equality of access without relying on access to specialist care, which currently varies by geography.

B.2 Clinical effectiveness

- DAPA-HF was an event-driven, double-blind RCT with a median follow-up of 18.2 months which enrolled 4,744 patients and compared dapagliflozin (N=2,373) with placebo (N=2,371) for treatment of HFrEF, with patients also receiving current standard care for HFrEF in both arms
- Dapagliflozin significantly reduced the risk of the primary composite endpoint of CV death, hHF, or an urgent HF visit, compared with placebo (16.3% vs 21.2%, respectively, HR 0.74 [95% CI 0.65, 0.85; p<0.001])
- The efficacy of dapagliflozin was observed from the early stages of treatment, as shown by the early separation of the KM curves for the primary endpoint. In an exploratory analysis (5), the HR for the primary endpoint corresponded to a p-value of <0.05 when including data up to 28 days following randomisation and the p-value remained below 0.05 in analyses of cumulative data at subsequent daily cut-offs.
- Dapagliflozin also reduced the risk of each component of the composite endpoint, compared with placebo:
  - hHF – HR 0.70 (95% CI 0.59, 0.83; p<0.0001)
  - Urgent HF visit – HR 0.43 (95% CI 0.20, 0.90; p=0.0213)
  - CV death – HR 0.82 (95% CI 0.69, 0.98; p=0.0294)
- In addition, dapagliflozin was also superior to placebo for all secondary endpoints, except for worsening renal function:
  - Composite of CV death or hHF – HR 0.75 (95% CI 0.65, 0.85; p<0.001)
  - Death from any cause – HR 0.83 (95% CI 0.71, 0.97; nominal p=0.022)
  - Worsening renal function – HR 0.71 (95% 0.44, 1.16; p=0.1681)
  - KCCQ-TSS:
    - ◊ Change at 8 months – win ratio[2] 1.18 (95% CI 1.11, 1.26; p<0.001)
    - ◊ ≥5-point increase (improvement) in KCCQ-TSS at 8 months – odds ratio (OR)[3] 1.15 (95% CI 1.08, 1.23; p<0.001)
    - ◊ ≥5-point reduction in KCCQ-TSS score at 8 months – OR[4] 0.84 (95% CI 0.78, 0.90; p<0.001)
- The effect of dapagliflozin was generally consistent across subgroups, including standard care treatment at baseline (sacubitril valsartan [yes/no], not receiving MRA and not receiving sacubitril valsartan [yes/no], MRA without sacubitril valsartan [yes/no]), patients with and without diabetes, age (≤65 years/>65 years), LVEF (≤median/>median), and renal function (estimated glomerular filtration rate [eGFR] ≥60 mL/min/1.73 m^2 / <60 mL/min/1.73 m^2)

[2] Win ratio >1 indicates superiority of dapagliflozin over placebo.
[3] OR >1 for ≥5 point increase in KCCQ-TSS indicates superiority of dapagliflozin over placebo.
[4] OR <1 for ≥5 point reduction in KCCQ-TSS indicates superiority of dapagliflozin over placebo.

B.2.1 Identification and selection of relevant studies

Full details of the process and methods used to identify and select the clinical evidence relevant to the technology being appraised are provided in Appendix D.

A systematic literature review (SLR) was conducted to identify RCT evidence reporting on the efficacy and safety of dapagliflozin and relevant comparator treatments for chronic HF (NYHA class II-IV) with reduced LVEF.

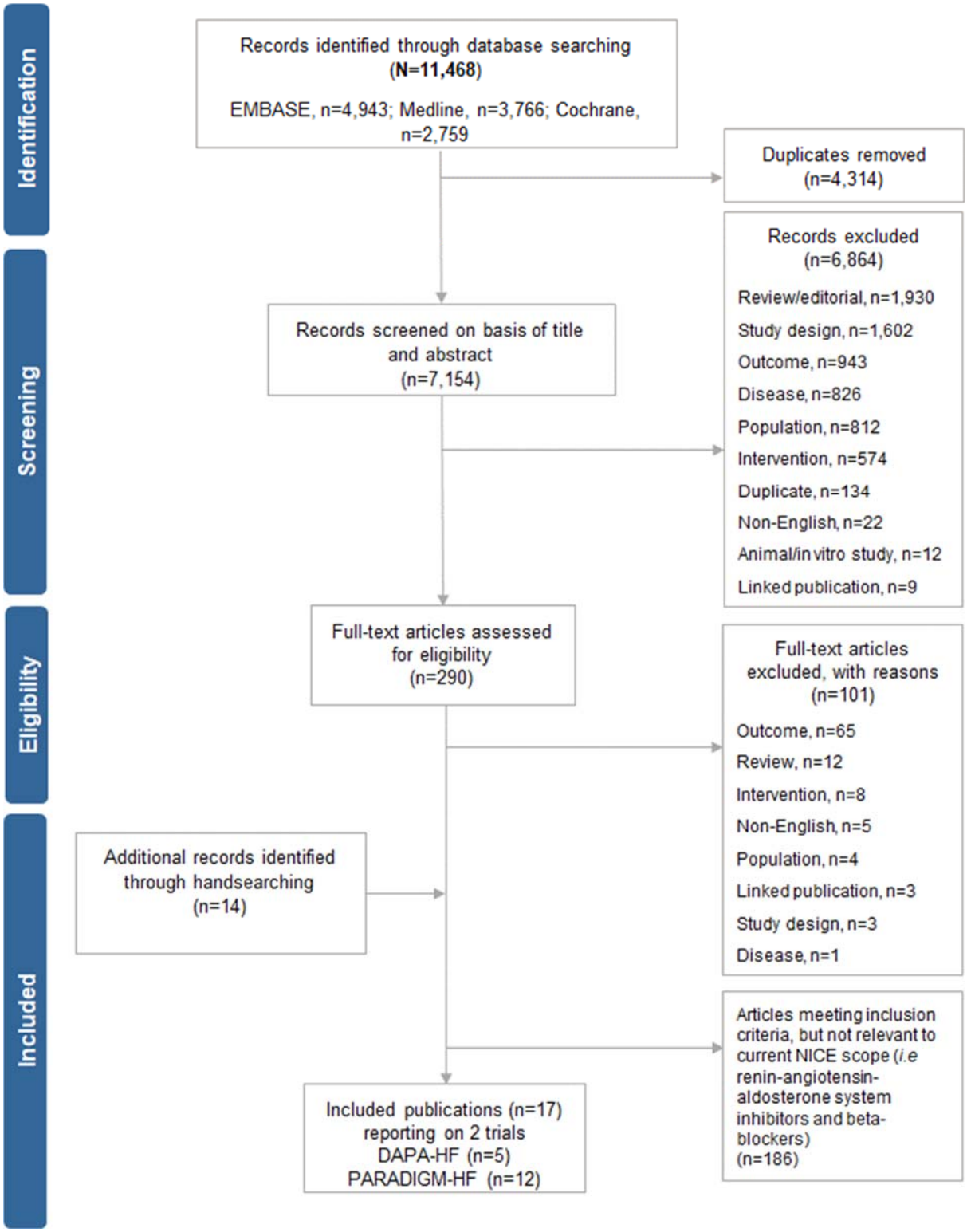
Searches of Embase, Medline, and Cochrane databases using Ovid were conducted on 11th November 2019. Supplementary hand searching of recent relevant congresses and health technology assessment (HTA) agency websites was conducted between 27 November 2019 and the 13th December 2019.

Studies of interest included RCTs investigating relevant treatments for HF and which enrolled adult patients (≥18 years) with HFrEF (NYHA stage II-IV and EF ≤40%). The search strategy was kept broad to include interventions for HFrEF currently used as standard care which included renin-angiotensin aldosterone system inhibitors (RAASi) and beta-blockers (see eligibility criteria listed in Appendix D, Table 57). The DAPA-HF trial included standard care as defined in the NICE scope and was therefore considered the primary source of data in economic modelling; only dapagliflozin and interventions considered likely to be compared with dapagliflozin were therefore included in the SLR and extracted in full (*i.e.* SGLT2i and sacubitril valsartan [an angiotensin receptor-neprilysin inhibitor, ARNI]).

The search identified a total of five citations reporting on one unique trial (45, 49-51) that reported the use of dapagliflozin in HFrEF for the endpoints of interest, DAPA-HF (pivotal trial publication (45)).

A Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram detailing studies that were included and excluded at each stage of screening is provided in Figure 4. Full lists of included and excluded studies are provided in Appendix D.

Figure 4: PRISMA diagram – clinical treatments for HFrEF



Abbreviations: HFrEF, heart failure with reduced ejection fraction; NICE, National Institute for Health and Care Excellence; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; SLR, systematic literature review

B.2.2 List of relevant clinical effectiveness evidence

The clinical trial programme relevant to the current submission consists of one Phase III trial, DAPA-HF (Table 6), which is described in full in the following sections. One other trial, DECLARE-TIMI 58, examined the effect of dapagliflozin in a small sub-group of patients with HFrEF; however, this trial was conducted exclusively in patients with type 2 diabetes and only 3.9% of patients had HFrEF at baseline (52). This sub-group analysis from DECLARE-TIMI 58 is consistent with DAPA-HF (53) and is presented in Appendix L as supporting data.

Table 6: Clinical effectiveness evidence

<table>
<tr><td>Study</td><td colspan="5">DAPA-HF</td></tr>
<tr><td>Primary sources</td><td colspan="5">McMurray et al 2019 (45, 51)</td></tr>
<tr><td>Additional sources</td><td colspan="5">CSR (54)</td></tr>
<tr><td>Study design</td><td colspan="5">Randomised, double-blind, placebo-controlled, international, multicentre Phase III trial</td></tr>
<tr><td>Population</td><td colspan="5">Patients aged ≥18 years with NYHA functional class ≥II with LVEF ≤40% who are currently optimally treated for HFrEF</td></tr>
<tr><td>Intervention(s)</td><td colspan="5">Dapagliflozin 10 mg once daily</td></tr>
<tr><td>Comparator(s)</td><td colspan="5">Placebo</td></tr>
<tr><td rowspan="2">Indicate if trial supports application for marketing authorisation</td><td>Yes</td><td>X</td><td rowspan="2">Indicate if trial used in the economic model</td><td>Yes</td><td>X</td></tr>
<tr><td>No</td><td></td><td>No</td><td></td></tr>
<tr><td>Rationale for use/non-use in the model</td><td colspan="5">Pivotal clinical efficacy and safety trial reporting outcomes relevant to the model</td></tr>
<tr><td>Reported outcomes specified in the decision problem</td><td colspan="5">• Hospitalisation for heart failure
• All-cause hospitalisation
• Mortality
• Cardiovascular mortality
• Adverse effects of treatment (including diabetic ketoacidosis, amputations and fractures)
• Symptoms, functioning and health-related quality of life (KCCQ).</td></tr>
<tr><td>All other reported outcomes</td><td colspan="5">Composite of worsening renal function (sustained decline in eGFR ≥50%), end-stage renal disease (sustained [≥28 days] eGFR <15 mL/min/1.73 m^2, sustained dialysis, or renal transplantation), or renal death</td></tr>
</table>

Abbreviations: CSR, clinical study report; eGFR, estimated glomerular filtration rate; HF, heart failure; IV, intravenous; KCCQ, Kansas City Cardiomyopathy Questionnaire; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association.

B.2.3 Summary of methodology of the relevant clinical effectiveness evidence

B.2.3.1 Summary of trial methodology

DAPA-HF was a large, multi-national, double-blind RCT with 1:1 randomisation stratified by type 2 diabetes status (established diabetes or glycated haemoglobin level ≥6.5% at both screening and randomisation) at baseline. It was an event-driven trial with a median follow-up of 18.2 months. The methodology of DAPA-HF is summarised in Table 7 and Figure 5. Definitions for the components of the composite primary end point, CV death, hHF and urgent HF visit are provided in Table 8.

Table 7: Summary of trial methodology: DAPA-HF

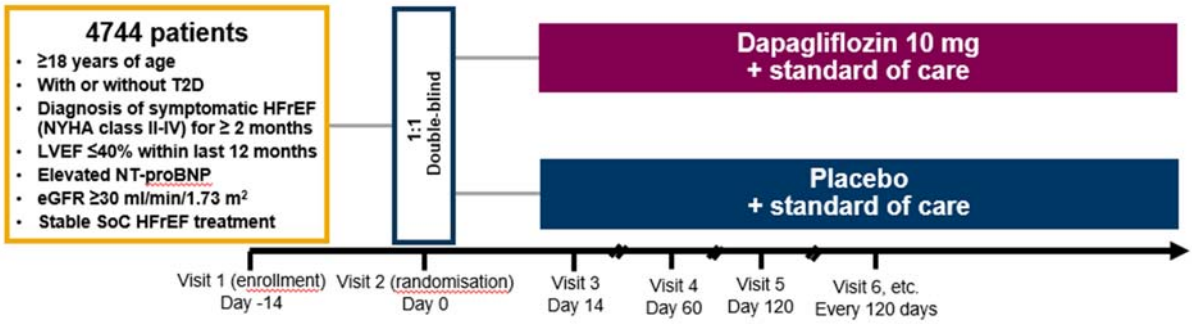
Parameter	Description
Study objective	To determine whether dapagliflozin is superior to placebo, when added to SC, in reducing the incidence of a worsening HF episode (hospitalisation or the equivalent, i.e. an urgent HF visit) or CV death, analysed as time-to-first event.
Trial design	Randomised, double-blind, placebo-controlled, international, multicentre Phase III trial.
Duration of study	This was an event driven trial; median follow-up 18.2 months (range 0 to 27.8).
Method of randomisation	Fixed-randomisation schedule using balanced blocks and interactive voice- or web-response system.
Method of blinding (care provider, patient and outcome assessor)-	Patients, investigators, and adjudication committee were blind to the assignment of treatment.
Eligibility criteria for participants	Inclusion criteria • Men and women ≥18 years of age, with or without T2D • Documented diagnosis of symptomatic HFrEF for ≥2 months (NYHA class II-IV) • LVEF ≤40% within the last 12 months • Elevated NT-proBNP (≥600 pg/mL or ≥400 pg/mL if hHF within 12 months or ≥900 pg/mL if atrial fibrillation/flutter irrespective of hHF history) • Optimal and stable (≥4 weeks) background standard care for HFrEF as per local guidelines including (unless contraindicated or not tolerated): ACEI, ARB, or sacubitril valsartan; beta-blocker; and if appropriate an MRA • eGFR ≥30 mL/min/1.73 m^2 Key exclusion criteria • T1D • Recent treatment with or unacceptable side effects associated with an SGLT2i, or concomitant use of open-label SGLT2i • Symptomatic hypotension or SBP <95 mmHg

Parameter	Description
	• Current acute decompensated HF or hospitalisation within last 4 weeks due to decompensated HF • Coronary revascularisation (PCI or CABG), valve repair/replacement, or CRT device implantation within last 12 weeks or planned after randomisation • HF due to restrictive cardiomyopathy, active myocarditis, constrictive pericarditis, hypertrophic cardiomyopathy, or uncorrected primary valvular disease
Settings and locations where the data were collected	410 centres across 20 countries in Asia Pacific, Europe, Latin America, North America, and Russia. Ten UK sites were included with 62 patients.
Trial drugs	• Dapagliflozin 10 mg oral OD plus standard care (N=2,373) • Placebo plus standard care (N=2,371)
Permitted and disallowed concomitant medications	Disallowed medications: SGLT2 inhibitors other than dapagliflozin as study medication. Permitted medications: HF medications in accordance with local guidelines, including ACEi, ARB, sacubitril valsartan, beta-blocker; and MRA. Antidiabetic medications other than SGLT2 inhibitors in accordance with the American Diabetes Association and European Association for the Study of Diabetes joint Position Statement (47).
Primary outcomes	• Time to first occurrence of any of the components of the composite: CV death or hHF or an urgent HF visit.
Other outcomes used in the economic model/specified in the scope	• Time to first occurrence of either of the components of the composite: CV death or hHF • Total number of (first and recurrent) hHF and CV death • Change from baseline measured at 8 months in the total symptom score of the KCCQ • Time to first occurrence of any of the components of the composite: ≥50% sustained decline in eGFR or reaching ESRD or renal death • Time to death from any cause
Safety	Safety data were collected for all SAEs, AEs leading to discontinuation, interruption, or dose reduction of study drug, and AEs of special interest: • Volume depletion • Renal AEs • Diabetic ketoacidosis • Major hypoglycaemic events • Fractures • AEs leading to amputation • AEs leading to a risk of lower limb amputation Data on other AEs were not routinely collected due to the extensive safety data which already exist for dapagliflozin in other indications.
Pre-planned subgroups	Pre-specified

Parameter	Description
	• T2D status at baseline (established diabetes or glycated haemoglobin level ≥6.5% at both visit 1 and visit 2) (yes/no) • Baseline eGFR (≥60 mL/min/1.73 m^2 / <60 mL/min/1.73 m^2) • MRA at baseline (yes/no) • NYHA class (II/III or IV) • LVEF (≤median/>median) • NT-proBNP (≤median/>median) • Atrial fibrillation or flutter at enrolment ECG (yes/no) • Age (≤65 years/>65 years) • Sex (male/female) • Race (white/black/Asian/other) • Geographic region (Asia/Europe [including Russia]/North America/South America) • Prior hospitalisation for HF (yes/no) • Main aetiology of HF (ischaemic/non-ischaemic or unknown) • BMI (<30 kg/m^2/≥30 kg/m^2) Post-hoc • KCCQ-TSS (≤median/>median) • NO use of MRA and NO use sacubitril valsartan at baseline (yes/no) • Use of MRA but NO use of sacubitril valsartan at baseline (yes/no) • Use of sacubitril valsartan at baseline (yes/no)

Source: McMurray et al 2019 (45).
Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blocker; BMI, body mass index; CABG, coronary artery bypass grafting; CV, cardiovascular; ECG, electrocardiogram; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; hHF, hospitalisation for heart failure; KCCQ, Kansas City Cardiomyopathy Questionnaire; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid-receptor antagonist; NT-proBNP, N-terminal pro B-type natriuretic peptide; NYHA, New York Heart Association; OD, once daily; PCI, percutaneous coronary intervention; SBP, systolic blood pressure; SGLT2i ; sodium-glucose transport protein 2 inhibitor; T1D, type 1 diabetes;T2D, type 2 diabetes.

Figure 5: DAPA-HF trial design



Source: Adapted from McMurray et al 2019 (45).
Abbreviations: eGFR, estimated glomerular filtration rate; HFrEF, heart failure with reduced ejection fraction; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; NT-proBNP, N-terminal pro B-type natriuretic peptide.

Table 8: Definitions for the components of the composite primary endpoint in DAPA-HF

Endpoint†	Description
Hospitalisation for heart failure (hHF)	hHF is defined as an event that meets all of the following criteria: • Admitted to the hospital with a primary diagnosis of HF • Length-of-stay in hospital extends for ≥24 hours • Exhibits documented new or worsening symptoms due to HF on presentation, including at least one of the following: o Dyspnoea (dyspnoea with exertion, dyspnoea at rest, orthopnoea, paroxysmal nocturnal dyspnoea); decreased exercise tolerance; fatigue • Objective evidence of new or worsening HF, consisting of ≥2 physical examination findings or 1 physical examination finding and ≥1 laboratory criterion: Physical examination finding considered to be due to HF, including new or worsened: o Peripheral oedema o Increasing abdominal distension or ascites (in absence of primary hepatic disease) o Pulmonary rales/crackles/crepitations o Increased jugular venous pressure and/or hepatojugular reflux o S3 gallop o Clinically significant or rapid weight gain thought to be related to fluid retention • Laboratory evidence of new or worsening HF, if obtained within 24 hours of presentation, including: o Increased BNP/NT-proBNP concentrations consistent with decompensation of HF (such as BNP > 500 pg/mL or NT-proBNP > 2,000 pg/mL) o Radiological evidence of pulmonary congestion o Non-invasive diagnostic evidence of clinically significant elevated left- or right-sided ventricular filling pressure or low cardiac output. OR

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Endpoint†	Description
	○ Invasive diagnostic evidence with right heart catheterisation showing a pulmonary capillary wedge pressure (pulmonary artery occlusion pressure) ≥18 mm Hg, central venous pressure ≥ 12 mm Hg, or a cardiac index < 2.2 L/min/m2 • Receives initiation or intensification of treatment specifically for HF, including at least 1 of the following: ○ Augmentation in oral diuretic therapy ○ Intravenous diuretic ○ Mechanical or surgical intervention, including: ▪ Mechanical circulatory support (e.g., intra-aortic balloon pump, ventricular assist device) ▪ Mechanical fluid removal (e.g., ultrafiltration, hemofiltration, dialysis)
Urgent HF visit	Urgent HF visit is defined as an event that meets all of the following: • Patient has an urgent, unscheduled office/practice, or emergency department visit for a primary diagnosis of HF, that does not meet the criteria for a HF hospitalisation. • All signs and symptoms for HF hospitalisation, as listed below, are met. ○ Documented new or worsening symptoms due to HF, including at least 1 of the following: dyspnoea (dyspnoea with exertion, dyspnoea at rest, orthopnoea, paroxysmal nocturnal dyspnoea), decreased exercise tolerance, or fatigue. ○ Objective evidence of new/worsening HF, consisting of at least 2 physical examination findings OR 1 physical examination finding and at least 1 laboratory criterion. • Patient receives initiation or intensification of treatment specifically for HF with the exception of oral diuretic therapy, which would not be considered sufficient.
CV death	• Death due to MI, heart failure, cardiogenic shock, stroke, cardiovascular procedures, cardiovascular haemorrhage, or other cardiovascular causes • Sudden cardiac death ○ Death witnessed and instantaneous without new or worsening symptoms ○ Death witnessed within 60 minutes of the onset of new or worsening cardiac symptoms ○ Death witnessed and attributed to an identified arrhythmia (e.g., captured on an ECG recording or witnessed on a monitor by either a medic or paramedic, or unwitnessed but found on implantable cardioverter-defibrillator review ○ Death after unsuccessful resuscitation from cardiac arrest or successfully resuscitated from cardiac arrest but who die within 24 hours without identification of a non-cardiac aetiology ○ Death > 24hrs after a patient has been successfully resuscitated from cardiac arrest and without identification of a non-cardiovascular aetiology ○ Unwitnessed death in a subject seen alive and clinically stable ≤ 24 hours prior to being found dead without any evidence supporting a specific non-cardiovascular cause of death

†All events were adjudicated in line with guidelines for trials with CV endpoints (55).
Abbreviations: BNP, B-type natriuretic peptide; ECG, electrocardiogram; CV, cardiovascular; hHF, hospitalisation for heart failure; HF, heart failure; NT-proBNP, N-terminal pro B-type natriuretic peptide.

B.2.3.2 Baseline characteristics and demographics

Patient characteristics at baseline are summarised in Table 9; in general, baseline characteristics were balanced between groups. Most patients in the dapagliflozin and placebo groups, respectively, were white (70.0% and 70.5%) males (76.2% and 77.0%), with Europe constituting the largest geographic region (46.1% and 44.7%). NYHA II (67.7% and 67.4%) was the most common functional classification in the dapagliflozin and placebo groups, respectively, the majority of patients had an ischaemic aetiology (55.5% and 57.3%), and 41.8% of patients had comorbid type 2 diabetes in both groups. Most patients were receiving diuretics (figures include MRA: 93.4%) or beta-blockers (96.1%) at baseline, with 10.7% of patients receiving sacubitril-valsartan.

There were no major differences in disease characteristics at baseline for patients in the EU or >65 years subgroups, compared with the overall population (Table 10).

Table 9: Characteristics of participants in DAPA-HF across treatment groups

Baseline characteristics	Dapagliflozin (N=2,373)	Placebo (N=2,371)
Age, years, mean±SD	66.2±11.0	66.5±10.8
Female sex, n (%)	564 (23.8)	545 (23.0)
BMI, kg/m^2, mean±SD	28.2±6.0	28.1±5.9
Race, n (%)		
White	1,662 (70.0)	1,671 (70.5)
Black	122 (5.1)	104 (4.4)
Asian	552 (23.3)	564 (23.8)
Other	37 (1.6)	32 (1.3)
Region, n (%)		
North America	335 (14.1)	342 (14.4)
South America	401 (16.9)	416 (17.5)
Europe	1,094 (46.1)	1,060 (44.7)
Asia-Pacific	543 (22.9)	553 (23.3)
NYHA functional classification, n (%)		
II	1,606 (67.7)	1,597 (67.4)
III	747 (31.5)	751 (31.7)
IV	20 (0.8)	23 (1.0)
Heart rate, beats per min, mean±SD	71.5±11.6	71.5±11.8
Systolic blood pressure, mm Hg, mean ±SD	122.0±16.3	121.6±16.3
LVEF, %, mean±SD	31.2±6.7	30.9±6.9
Median NT-proBNP, pg/mL (IQR)	1,428 (857, 2,655)	1,446 (857, 2,641)
Principal cause of HF, n (%)		
Ischaemic	1,316 (55.5)	1,358 (57.3)
Non-ischaemic	857 (36.1)	830 (35.0)

Baseline characteristics	Dapagliflozin (N=2,373)	Placebo (N=2,371)
Unknown	200 (8.4)	183 (7.7)
Medical history, n (%)		
Hospitalisation for HF	1,124 (47.4)	1,127 (47.5)
Atrial fibrillation	916 (38.6)	902 (38.0)
Type 2 diabetes mellitus†	993 (41.8)	990 (41.8)
eGFR		
Mean±SD, mL/min/1.73 m^2	66.0±19.6	65.5±19.3
<60 mL/min/1.73 m^2, n (%)	962/2,372 (40.6)	964 (40.7)
Heart failure medication, n (%)		
Diuretic	2,216 (93.4)	2,217 (93.5)
ACEI	1,332 (56.1)	1,329 (56.1)
ARB	675 (28.4)	632 (26.7)
Sacubitril-valsartan	250 (10.5)	258 (10.9)
Beta-blocker	2,278 (96.0)	2,280 (96.2)
MRA	1,696 (71.5)	1,674 (70.6)
Digitalis	445 (18.8)	442 (18.6)
Glucose-lowering medication, n/N (%)§		
Biguanide	504/993 (50.8)	512/990 (51.7)
Sulfonylurea	228/993 (23.0)	210/990 (21.2)
DPP-4 inhibitor	161/993 (16.2)	149/990 (15.1)
GLP-1 receptor agonist	11/993 (1.1)	10/990 (1.0)
Insulin	274/993 (27.6)	266/990 (26.9)

Source: McMurray et al 2019 (45).
Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blocker; DPP-4, dipeptidyl peptidase 4; eGFR, estimated glomerular filtration rate; GLP-1, glucagon-like peptide-1; HF, heart failure; IQR, interquartile range; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid-receptor antagonist; NT-proBNP, N-terminal pro B-type natriuretic peptide; NYHA, New York Heart Association; SD, standard deviation.
†An additional 82 patients in the dapagliflozin group and 74 in the placebo group had previously undiagnosed diabetes at screening (HbA1c ≥49 mmol/mol). ‡Includes either an implantable cardioverter-defibrillator or cardiac resynchronisation therapy with a defibrillator. ¶Includes cardiac resynchronisation therapy with or without a defibrillator. §Glucose-lowering medications are only provided for patients with a history of diabetes at baseline.

Table 10: Baseline characteristics by subgroup

Baseline characteristics	EU subgroup (N=2,154)	>65 years subgroup (N=2,714)	Overall population (N=4,744)
Age, years, mean±SD	[redacted]	73.9±5.6	66.3±10.9
Female sex, n (%)	[redacted]	690 (25.4)	1,109 (23.4)
BMI, kg/m^2, mean±SD	[redacted]	27.6±5.4	28.2±6.0
Race, n (%)			

Baseline characteristics	EU subgroup (N=2,154)	>65 years subgroup (N=2,714)	Overall population (N=4,744)
White	[redacted]	2,056 (75.8)	3,333 (70.3)
Black	[redacted]	91 (3.4)	226 (4.8)
Asian	[redacted]	539 (19.9)	1,116 (23.5)
Other	[redacted]	28 (1.0)	67 (1.4)
Region, n (%)			
North America	[redacted]	418 (15.4)	677 (14.3)
South America	[redacted]	409 (15.1)	817 (17.2)
Europe	[redacted]	1,363 (50.2)	2,154 (45.4)
Asia-Pacific	[redacted]	524 (19.3)	1,096 (23.1)
NYHA functional classification, n (%)			
II	[redacted]	1,808 (66.6)	3,203 (67.5)
III	[redacted]	888 (32.7)	1,498 (31.6)
IV	[redacted]	18 (0.7)	43 (0.9)
Heart rate, beats per min, mean±SD	[redacted]	70.4±11.2	71.5±11.7
Systolic blood pressure, mm Hg, mean ±SD	[redacted]	123.2±16.2	121.8±16.3
LVEF, %, mean±SD	[redacted]	31.7±6.6	31.1±6.8
Median NT-proBNP, pg/mL (IQR)	[redacted]	1,583 (955, 2,816)	1,437 (857, 2,650)
Principal cause of HF, n (%)			
Ischaemic	[redacted]	1,670 (61.5)	2,674 (56.4)
Non-ischaemic	[redacted]	840 (31.0)	1,687 (35.6)
Unknown	[redacted]	204 (7.5)	383 (8.1)
Medical history, n (%)			
Hospitalisation for HF	[redacted]	1,263 (46.5)	2,251 (47.4)
Atrial fibrillation	[redacted]	1,244 (45.8)	1,818 (38.3)
Type 2 diabetes mellitus[†]	[redacted]	1,131 (41.7)	1,983 (41.8)
eGFR			
Mean±SD, mL/min/1.73 m^2	[redacted]	59.0±16.0	65.8±19.4
<60 mL/min/1.73 m^2, n (%)	[redacted]	1,444 (53.2)	1,926 (40.6)
Heart failure medication, n (%)			
Diuretic	[redacted]	2,497 (92.0)	4,433 (93.4)
ACEi	[redacted]	1,457 (53.7)	2,661 (56.1)
ARB	[redacted]	799 (29.4)	1,307 (27.6)
Sacubitril-valsartan	[redacted]	285 (10.5)	508 (10.7)

Baseline characteristics	EU subgroup (N=2,154)	>65 years subgroup (N=2,714)	Overall population (N=4,744)
Beta-blocker	[redacted]	2,580 (95.1)	4,558 (96.1)
MRA	[redacted]	1,789 (65.9)	3,370 (71.0)
Digitalis	[redacted]	457 (16.8)	887 (18.7)
Glucose-lowering medication, n/N (%)§			
Biguanide	[redacted]	548 (48.5)	1,016 (51.2)
Sulfonylurea	[redacted]	235 (20.8)	438 (22.1)
DPP-4 inhibitor	[redacted]	209 (18.5)	310 (15.6)
GLP-1 receptor agonist	[redacted]	14 (1.2)	21 (1.1)
Insulin	[redacted]	301 (26.6)	540 (27.2)

Source: DAPA-HF CSR, data on file (IEMT5227) and data on file (IEMT5203). Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blocker; HF, heart failure; IQR, interquartile range; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid-receptor antagonist; NT-proBNP, N-terminal pro B-type natriuretic peptide; NYHA, New York Heart Association; SD, standard deviation.

B.2.4 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

B.2.4.1 Definitions of patient population analysis sets

Full analysis set: All patients who were randomised to study treatment were included in the full analysis set (FAS) irrespective of their protocol adherence and continued participation in the study. Patients were analysed according to their randomised study drug assignment, irrespective of the treatment received. The FAS was considered the primary analysis set for the primary and secondary variables, as well as for the exploratory efficacy variables.

Safety analysis set: All randomised patients who received at least 1 dose of randomised treatment were included in the safety population.

B.2.4.2 Statistical analysis

A summary of the statistical analysis in DAPA-HF is provided in Table 11.

Table 11: Summary of statistical analyses in DAPA-HF

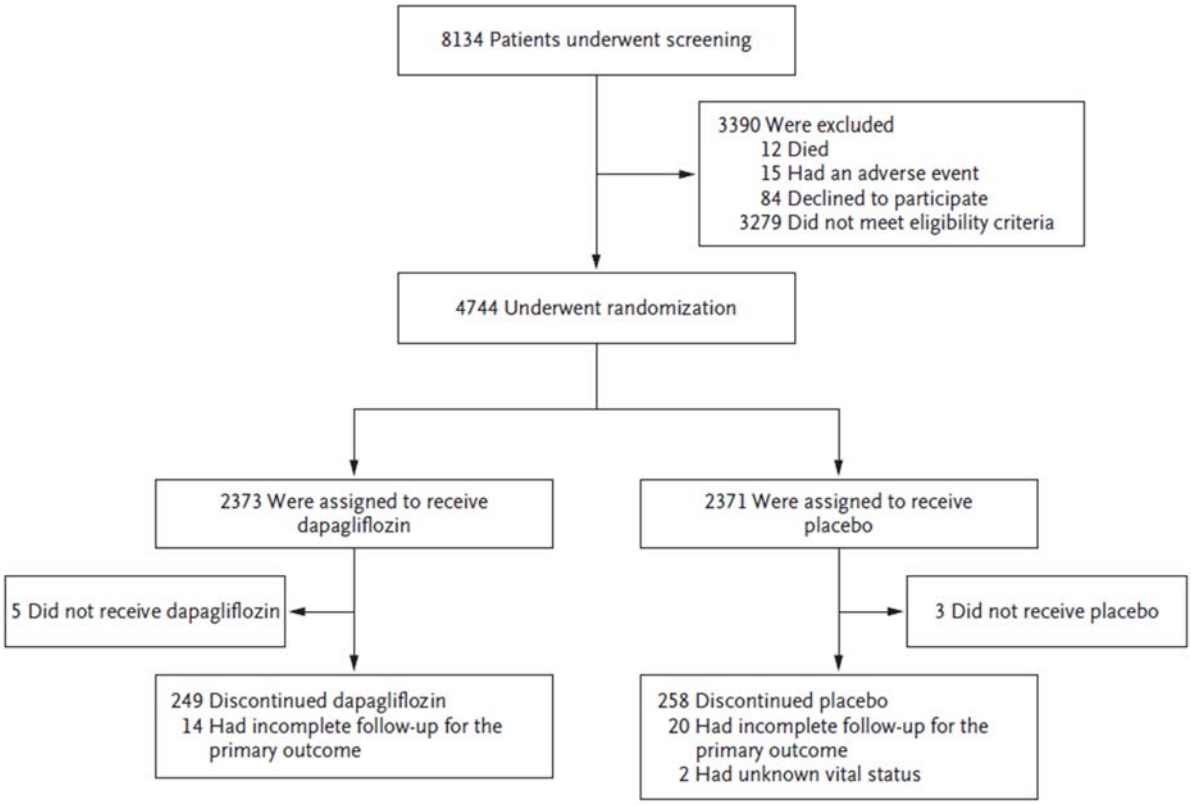
DAPA-HF	Description
Hypothesis objective	That dapagliflozin is superior to placebo, when added to SC, in reducing the incidence of a worsening HF episode (hospitalisation or the equivalent, i.e. an urgent HF visit) or CV death, analysed as time-to-first event.
Statistical analysis	A closed testing procedure was used with pre-specified hierarchical testing of the primary and secondary outcomes. Type I error was controlled at a two-sided α level of 0.0499 for multiple comparisons across primary and secondary outcomes, with one interim efficacy analysis taken into account. Time-to-event data were evaluated using Kaplan-Meier estimates and Cox proportional hazards models, stratified according to diabetes status, with history of hHF and treatment-group assignment as fixed-effect factors; for the renal outcome, baseline eGFR was included instead of history of hHF. Cox models were used to calculate HRs, 95% CIs, and two-sided p values. A semiparametric proportional-rates model was used to calculate total number of (first and recurrent) hHF and CV death events. Total symptom score on the KCCQ was analysed as a composite, rank-based outcome, incorporating patient vital status at 8 months along with change in score from baseline to 8 months in surviving patients, using the rank analysis of covariance method with a corresponding win ratio used to estimate the magnitude of treatment effect.
Sample size, power calculation	It was calculated that 844 primary outcome events would provide 90% power to detect an HR of 0.80 for dapagliflozin vs placebo with a two-sided α level of 0.05. The expected annual event incidence for primary outcome events was expected to be 11%, resulting in an estimate of approximately 4,500 patients based on an anticipated recruitment period of 18 months and an average follow-up period of approximately 24 months.
Data management, patient withdrawals	All patients who underwent randomisation were included in the analyses of the primary and secondary outcomes

Source: McMurray et al 2019 (45).
Abbreviations: CV, cardiovascular; eGFR, estimated glomerular filtration rate; HF, heart failure; hHF, hospitalisation for heart failure; HR, hazard ratio; KCCQ, Kansas City Cardiomyopathy Questionnaire.

B.2.4.3 Participant flow in the relevant randomised controlled trials

Participant flow in DAPA-HF is summarised in Figure 6.

Figure 6: Patient disposition in DAPA-HF



Source: McMurray et al 2019 (45).

B.2.5 Quality assessment of the relevant clinical effectiveness evidence

A summary of quality assessment results for DAPA-HF is provided in Table 12.

Table 12: Quality assessment results for parallel group RCTs

Trial number (acronym)	Trial 1
Was randomisation carried out appropriately?	Yes. Patients were randomised in a 1:1 ratio stratified by diabetes status at baseline based on a computer-generated randomisation schedule prepared before the study by or under the supervision of the sponsor.
Was the concealment of treatment allocation adequate?	Yes. An interactive voice/web-response system was used to determine treatment assignment and matching placebo was used.
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes. Demographics and disease characteristics were balanced between the groups and patients were stratified according to baseline diabetes status.
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes. This was a double-blind study. The interactive voice/web-response system was used to manage study agent inventory while ensuring that no one at the sites had to be unblinded. The investigator was not provided with the treatment randomisation codes. The investigators and the site personnel were blinded to the treatment assignment.
Were there any unexpected imbalances in drop-outs between groups?	No. Discontinuations of study medication were low and well-balanced between treatment arms.
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No. Based on the clinical study report all outcomes are reported in detail.
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes. Efficacy analyses were performed on the full analysis set.

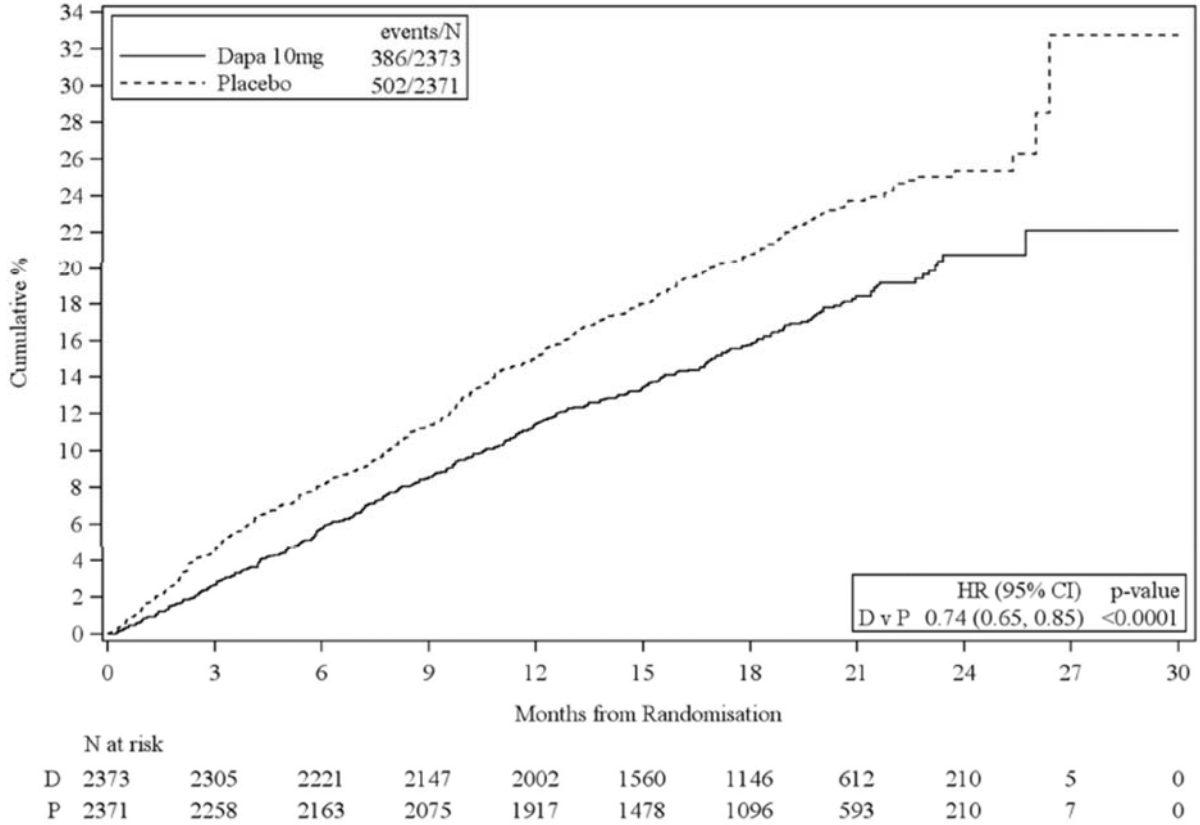
B.2.6 Clinical effectiveness results of the relevant trials: DAPA-HF

B.2.6.1 Primary efficacy outcome: Composite of CV death, hHF or uHFv

Dapagliflozin significantly reduced the proportion of patients experiencing the primary composite outcome of CV death, hHF or uHFv (urgent visit resulting in intravenous therapy for HF); 386 (16.3%) patients vs 502 (21.2%) patients, HR 0.74, 95% CI 0.65, 0.85; p<0.001 (Figure 7). It should be noted that the effect of dapagliflozin was rapid and evident from early-on in treatment, as shown by the early separation of the KM curves for the primary endpoint. In an exploratory analysis (5), a HR corresponding to a p-value of <0.05 was observed when including data up to 28 days following randomisation, and the p-value remained below 0.05 in analysis of cumulative data at subsequent daily cut-offs. This separation continued over time demonstrating long-term benefits for treatment in addition to the short-term benefits. In addition, all individual components of the primary outcome were significantly lower with dapagliflozin, compared with placebo (Section B.2.6.4). Urgent HF

visits were infrequent with only 10 and 23 events in the dapagliflozin and standard care arms, respectively.

Figure 7: Primary composite endpoint CV death, hHF or uHFv



Source: AZ data on file (54).
Abbreviations: CI, confidence interval.

B.2.6.2 Sensitivity analysis of primary outcome

A sensitivity analysis of the primary efficacy outcome where deaths adjudicated as 'undetermined' were not included as endpoint events but were treated as censoring events, was consistent with the primary analysis (14.4% vs 19.2%, HR 0.72 [95% CI 0.63, 0.83]; p<0.0001). A "worst case scenario" analysis was performed in which patients in the dapagliflozin treatment group, censored before primary analysis censoring date (PACD), including those censored due to non-CV death, were considered having experienced the composite endpoint, using their censoring time as the time of the imputed event. Patients in the placebo group, censored before PACD, were considered censored and event free. This constitutes the most unfavourable scenario for dapagliflozin with regard to outcome in the censored patients. The resulting treatment effect estimate remained statistically significant (HR 0.85 [95% CI 0.74, 0.96], p=0.0103).

Table 13: Sensitivity analysis of the primary efficacy outcome in DAPA-HF

	Dapagliflozin (N=2,373)	Placebo (N=2,371)
Worsening HF (composite of CV death or hHF or an urgent HF visit), n (%)	440 (18.5)	502 (21.2)
HR (95% CI; p) vs placebo	0.85 (0.74, 0.96; p=0.0103)	-

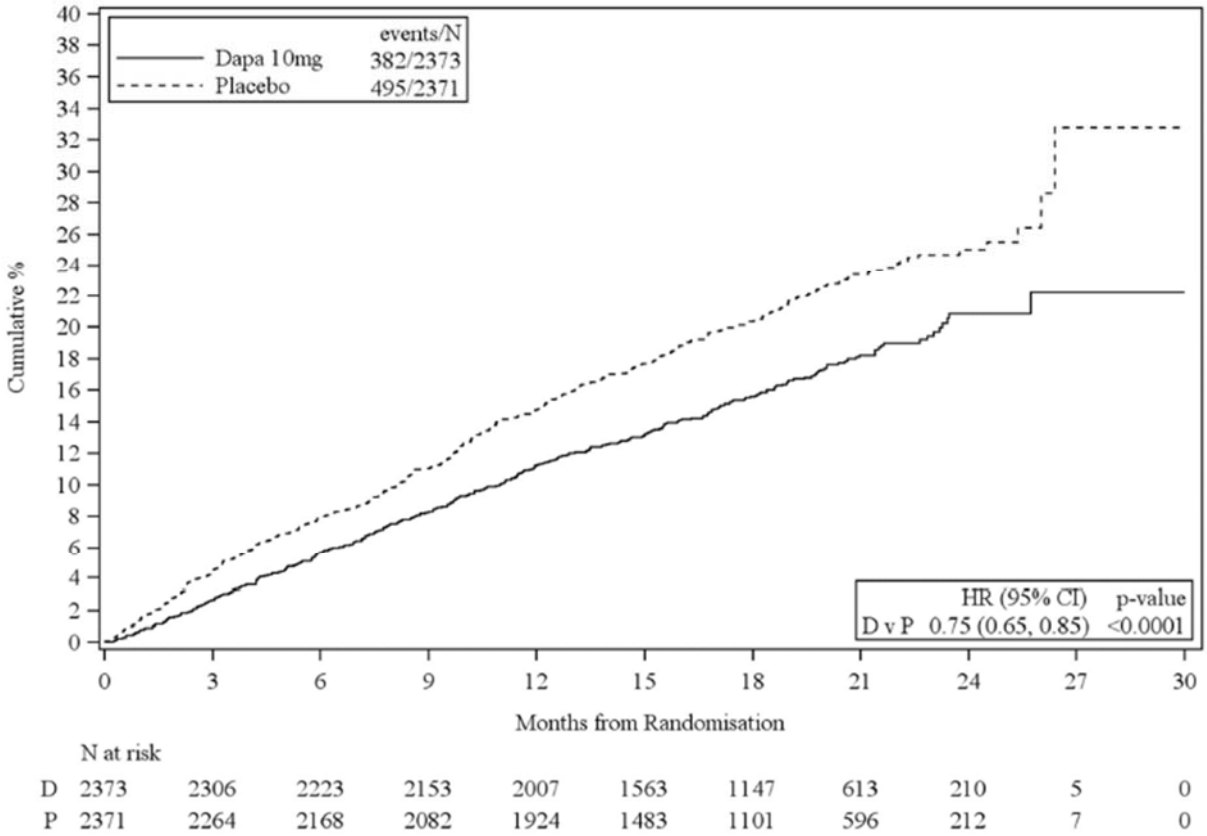
Source: AZ data on file (54).
Abbreviations: CI, confidence interval; CV, cardiovascular; hHF, hospitalisation for heart failure; HF, heart failure; HR, hazard ratio.

B.2.6.3 Secondary efficacy outcomes

B.2.6.3.1 Composite of CV death or hHF

Dapagliflozin significantly reduced time to CV death or hHF compared with placebo (HR 0.75 [95% CI 0.65, 0.85]; p<0.001]) (Figure 8). The proportion of patients experiencing CV death or hHF was 16.1% vs 20.9%, respectively. This outcome was very similar to the primary endpoint due to the low number of urgent HF visits (10 and 23 events in the dapagliflozin and placebo arms, respectively) in the primary endpoint composite.

Figure 8: Secondary efficacy endpoint for DAPA-HF: Composite of CV death or hHF



Source: AZ data on file (54).
Abbreviations: CI, confidence interval; HR, hazard ratio.

B.2.6.3.2 Total number for (first and recurrent) hospitalisations for HF and CV death

B.2.6.3.3 Dapagliflozin significantly reduced the total number of hospitalisations for HF (first and repeat admissions) and CV deaths compared with placebo (567 vs 742, respectively, rate ratio 0.75 [95% CI 0.65, 0.88]; p<0.001).[redacted]KCCQ-TSS

Dapagliflozin patients had a greater mean increase in KCCQ-TSS at 8 months, compared with placebo (6.1±18.6 vs 3.3±19.2; p<0.001), while more dapagliflozin patients had a ≥5-point (58.3% vs 50.9%; OR 1.15 95% CI 1.08, 1.23; p<0.001), ≥10 point (54.5% vs 47.6%; OR 1.15 95% CI 1.08, 1.22; p<0.0001), or ≥15-point (54.0% vs 48.2%; OR 1.14 95% CI 1.07, 1.22;p<0.0001) increase and fewer had a ≥5-point reduction (25.3% vs 32.9%; OR 0.84 95% CI 0.78, 0.90; p<0.001) in KCCQ-TSS, compared with placebo (Table 14). Higher KCCQ-TSS indicates a lower symptom burden.

Table 14: Secondary efficacy outcome in DAPA-HF: KCCQ-TSS

Outcome	Dapagliflozin (N=2,373)	Placebo (N=2,371)
Change in KCCQ-TSS at 8 months, mean±SD	6.1±18.6	3.3±19.2
Win ratio vs placebo (95% CI)[†]	1.18 (1.11, 1.26; p<0.001)	-
Increases in KCCQ-TSS at 8 months		
≥5-point increase %	58.3%	50.9%
OR[‡] (95% CI) vs placebo	1.15 (1.08, 1.23; p<0.0001)	-
≥10-point increase %	54.5%	47.6%
OR[‡] (95% CI) vs placebo	1.15 (1.08, 1.22; p<0.0001)	
≥15-point increase %	54.0%	48.2%
OR[‡] (95% CI) vs placebo	1.14 (1.07, 1.22;p<0.0001)	
Reductions in KCCQ-TSS at 8 months		
≥5-point reduction, n (%)	25.3%	32.9%
OR[§] (95% CI) vs placebo	0.84 (0.78, 0.90; p<0.001)	-

Source: Kosiborod et al 2019 (56).
Abbreviations: CI, confidence interval; KCCQ, Kansas City Cardiomyopathy Questionnaire; OR, odds ratio; SD, standard deviation; TSS, Total Symptom Score.
[†]Win ratio >1 indicates superiority of dapagliflozin over placebo. [‡] OR >1 for ≥5-point increase in KCCQ-TSS indicates superiority of dapagliflozin over placebo. [§] OR <1 for ≥5-point reduction in KCCQ-TSS indicates superiority of dapagliflozin over placebo.

B.2.6.3.4 Composite of worsening renal function (sustained decline in eGFR ≥50%), end-stage renal disease (sustained [≥28 days] eGFR <15 mL/min/1.73 m2, sustained dialysis, or renal transplantation), or renal death

There was a numerical trend towards a reduction in the proportion of patients experiencing worsening renal function with dapagliflozin, compared with placebo, but this did not reach statistical significance (1.2% vs 1.6%, HR 0.71 [95% CI 0.44, 1.16]) (Figure 9).

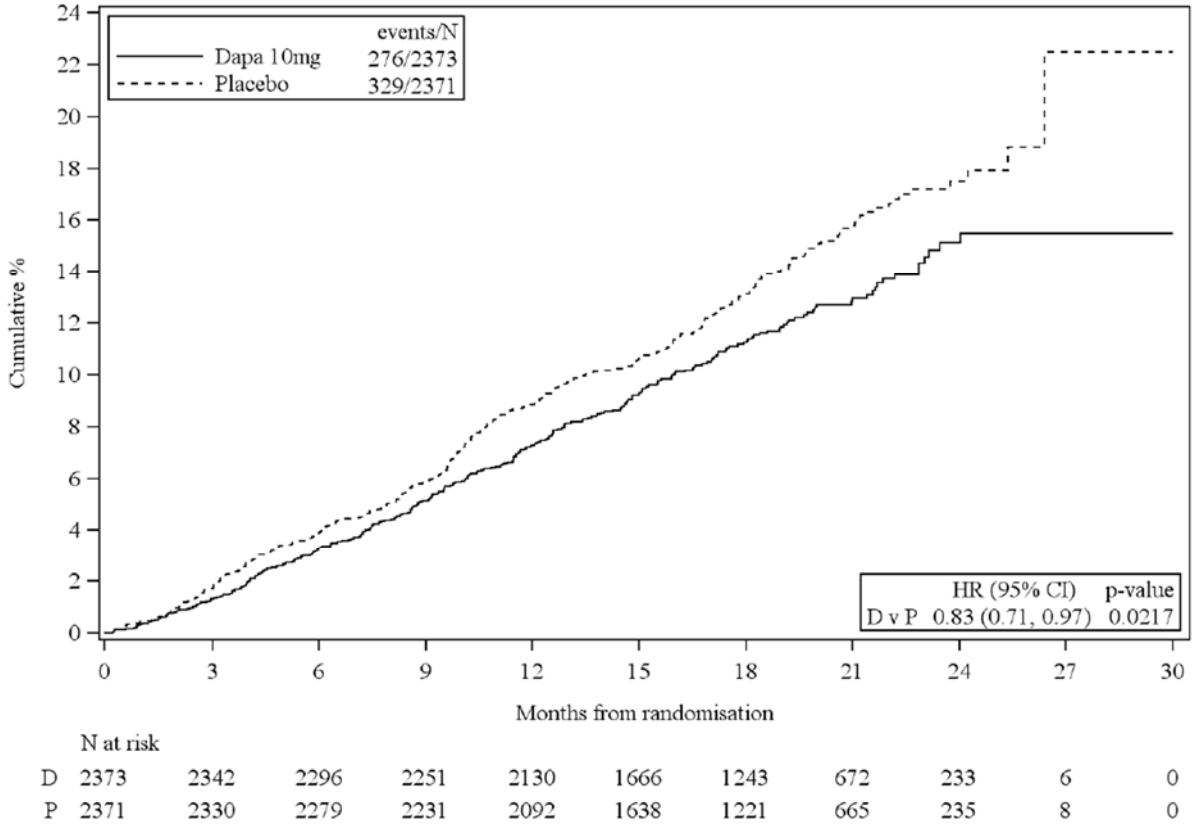
Figure 9: Secondary efficacy endpoint in DAPA-HF: Composite of worsening renal function

Source: AZ data on file (54).
Abbreviations: CI, confidence interval; HR, hazard ratio.

B.2.6.3.5 All-cause death

Dapagliflozin significantly reduced the proportion of patients experiencing all-cause death compared with placebo (11.6% vs 13.9%, respectively, HR 0.83 [95% CI 0.71, 0.97; nominal p=0.022]) (Figure 10).

Figure 10: Secondary efficacy outcome for DAPA-HF: All-cause death



Source: AZ data on file (54).
Abbreviations: CI, confidence interval.

B.2.6.4 Individual components of composite primary outcome

Dapagliflozin reduced the proportion of patients experiencing each of the individual components of the primary efficacy outcome, compared with placebo (Table 15).

Table 15: Secondary efficacy outcome in DAPA-HF: Components of primary composite outcome

Outcome	Dapagliflozin (N=2,373)	Placebo (N=2,371)	HR (95% CI) dapagliflozin vs placebo*
hHF or an urgent visit for HF	237 (10.0)	326 (13.7)	0.70 (95% CI 0.59, 0.83) p<0.0001
hHF	231 (9.7)	318 (13.4)	0.70 (95% CI 0.59, 0.83) p<0.0001
Urgent heart failure visit	10 (0.4)	23 (1.0)	0.43 (95% CI 0.20, 0.90) p=0.0213
CV death	227 (9.6)	273 (11.5)	0.82 (95% CI 0.69, 0.98) p=0.0294

* Nominal p values, not included in hierarchical testing
Source: McMurray et al 2019 (45).
Abbreviations: CI, confidence interval; hHF, hospitalisation for heart failure; HF, heart failure; HR, hazard ratio.

B.2.6.5 Exploratory endpoints

B.2.6.5.1 EQ-5D-5L

There was no significant difference in change from baseline in European quality of life 5 dimensions 5 levels (EQ-5D-5L) score between dapagliflozin and placebo at 24 months (least squares mean[redacted] vs [redacted] least squares mean difference[redacted]).

B.2.6.5.2 Change in NYHA class from baseline

The proportion of patients with no worsening of NYHA class from baseline was [redacted] for dapagliflozin at 4 months[redacted] and 8 months[redacted].

B.2.7 Subgroup analysis

Pre-planned subgroup analyses of the primary efficacy outcome were performed for 14 relevant subgroups:

- T2D status at baseline (yes/no)
- Baseline eGFR (≥60 mL/min/1.73 m^2 / <60 mL/min/1.73 m^2)
- MRA at baseline (yes/no)
- NYHA class (II or III / IV)
- LVEF (≤median/>median)
- NT-proBNP (≤median/>median)

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- Atrial fibrillation or flutter at enrolment ECG (yes/no)
- Age (≤65 years/>65 years)
- Sex (male/female)
- Race (white/black/Asian/other)
- Geographic region (Asia/Europe/North America/South America)
- Prior hospitalisation for HF (yes/no)
- Main aetiology of HF (ischaemic/non-ischaemic or unknown)
- BMI (<30 kg/m2/≥30 kg/m2)

Post-hoc subgroup analyses were also conducted for:

- KCCQ-TSS (≤median/>median)
- NO use of MRA and NO use sacubitril valsartan at baseline (yes/no) – this analysis explores the subgroup of patients who have not yet intensified their treatment with MRA and sacubitril valsartan, or who cannot tolerate intensification with MRA and sacubitril valsartan
- Use of MRA but NO use of sacubitril valsartan at baseline (yes/no) – this analysis explores the subgroup of patients who have not yet intensified their treatment with sacubitril valsartan, or who cannot tolerate intensification with sacubitril valsartan
- Use of sacubitril valsartan at baseline (yes/no) – this analysis explores the subgroup of patients who have already intensified their treatment with sacubitril valsartan

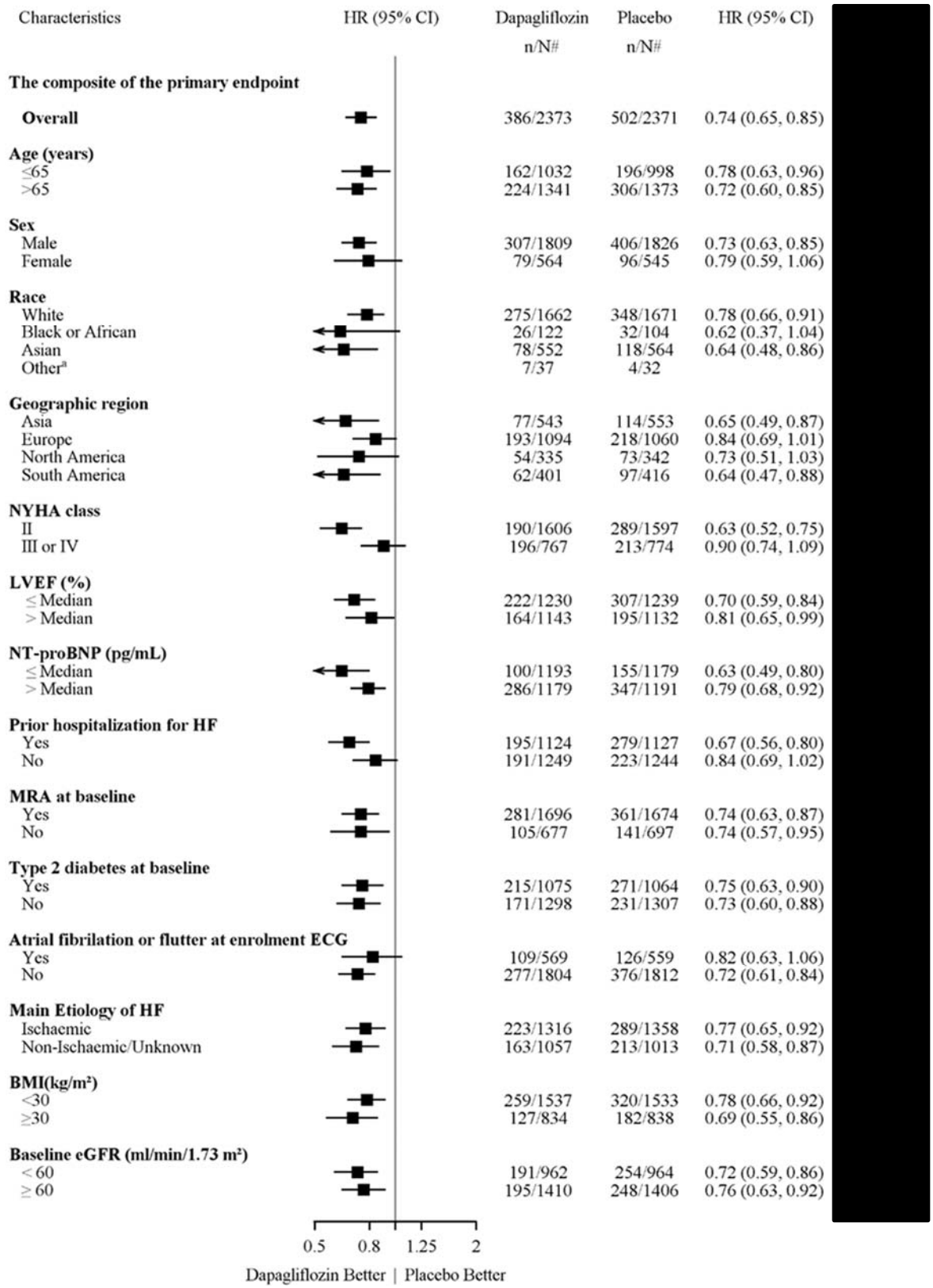
Baseline characteristics of patients are described in Section B.2.3.2 with statistical methods summarised in Section B.2.4.2.

Overall the effect seen for the primary endpoint of CV death or HF events was consistent across prespecified sub-groups (Figure 11). Subgroup analyses were considered exploratory and were not under type 1 error control. Thus, the results from analyses of subgroups should be interpreted with caution. The large number of analysed subgroups of limited size without multiplicity control results in a large risk of chance findings.

In the 14 pre-specified subgroups, [redacted] While the direction of the effect was the same, there was a difference in the magnitude of treatment effect suggesting a larger effect in patients with NYHA class II compared to those with class III/IV. Subgroup analyses by other measures of disease severity at baseline (LVEF, NT-proBNP, KCCQ-TSS) did not support interaction between treatment effect and disease severity, and additionally the directionality of trends in treatment effect with disease severity are not consistent across disease severity measures, [redacted].

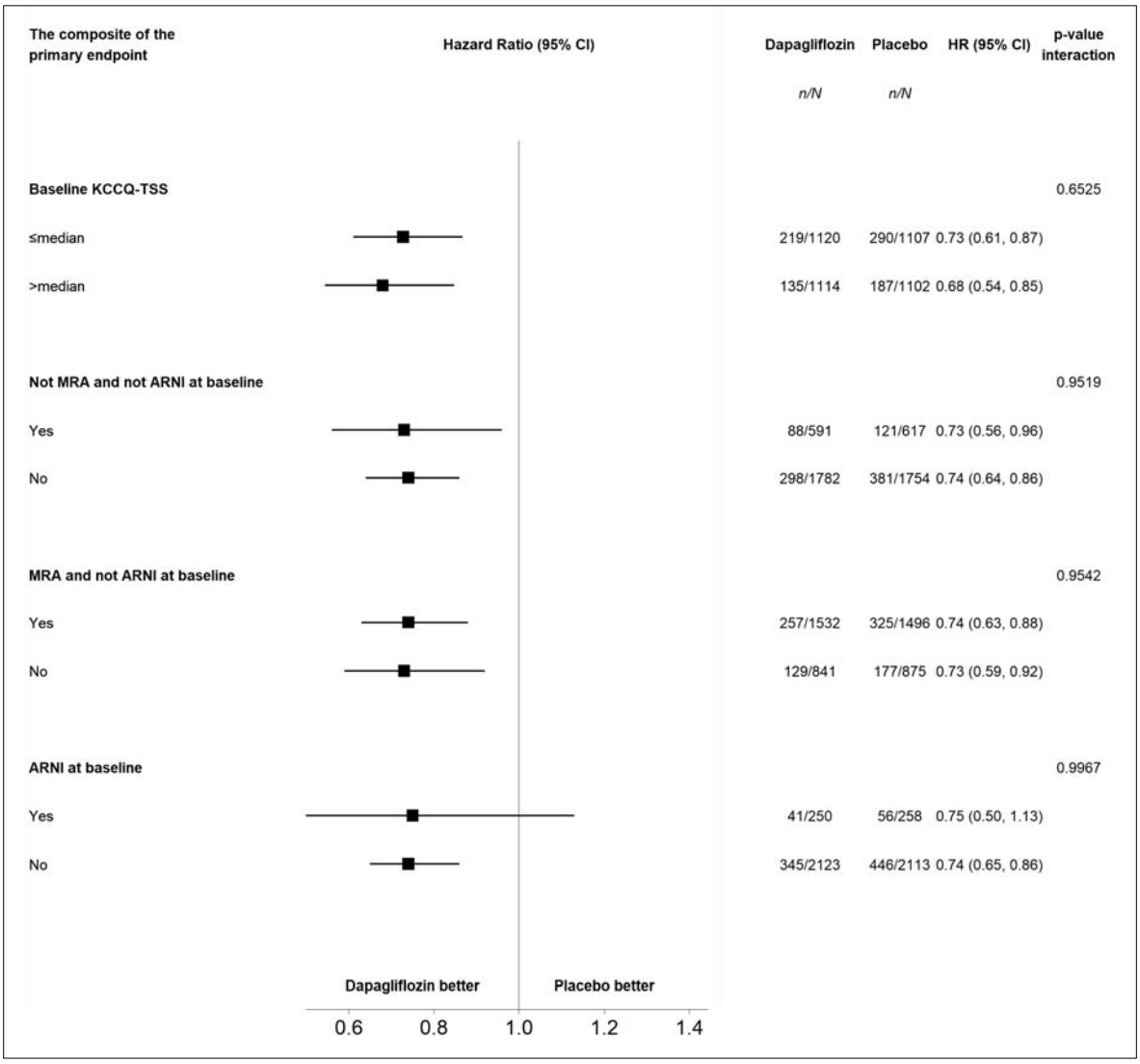
There was no difference in the efficacy of dapagliflozin across subgroups based on baseline treatment, including patients treated with or without MRA and/or sacubitril valsartan (Figure 11, Figure 12). This shows that dapagliflozin offers benefits to all patients with HFrEF, regardless of their current treatment regimen.

Figure 11: Pre-specified subgroup analyses, the primary efficacy outcome (DAPA- HF)



[a] Hazard ratio estimates are not presented for subgroups with less than 15 events in total, both arms combined
Source: McMurray et al 2019 (45) and DAPA-HF CSR (54).
Abbreviations: CI, confidence interval; ECG, electrocardiogram; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro B-type natriuretic peptide; NYHA, New York Heart Association.

Figure 12: Post-hoc subgroup analyses of the primary efficacy outcome for DAPA-HF



Source: AZ data on file (IEMT5213) (57).
Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitor; CI, confidence interval; eGFR, estimated glomerular filtration rate; HF, heart failure; HR, hazard ratio; LVEF, left ventricular ejection fraction; KCCQ-TSS, Kansas City Cardiomyopathy – total symptom score; MRA, mineralocorticoid-receptor antagonist.

B.2.8 Meta-analysis

Meta-analysis was not conducted as a matching-adjusted indirect comparison was considered the most appropriate methodology.

B.2.9 Indirect and mixed treatment comparisons

Rationale

- A MAIC was conducted to compare dapagliflozin with sacubitril valsartan
- Comparisons against beta-blockers, ACEis, ARBs, and MRAs were not conducted as dapagliflozin is most likely to be used as an add-on therapy to these treatments; data on the dapagliflozin as an add-on therapy is provided directly by DAPA-HF

Results

- While dapagliflozin was numerically favoured vs sacubitril valsartan for all outcomes, no statistically significant difference in efficacy was found for:
    - Time to first of hHF CV death
    - Time to CV death
    - Time to hHF
    - Time to death by any cause
- The analyses were not substantially affected by patient-level adjustment for differences in treatment effect modifying covariates
- There was no evidence of any difference in safety for SAE outcomes

B.2.9.1 Methodology

A summary of the objectives, comparators and endpoints of the MAIC are provided below, with details of the MAIC methodology provided in Appendix F.

B.2.9.1.1 Objectives of the MAIC

In the absence of direct evidence of dapagliflozin versus sacubitril valsartan, a MAIC was carried out to compare the investigational treatment arms of the DAPA-HF and PARADIGM-HF trials. This MAIC therefore addresses the comparison between dapagliflozin versus sacubitril valsartan specified in the decision problem (see Table 1).

MAICs have been widely adopted to estimate comparative efficacy in the absence of evidence from head-to-head trials (58). A MAIC was performed to reweight individual patient data in the index trial (DAPA-HF) in order to indirectly compare the outcomes in the DAPA-HF dapagliflozin plus standard care arm to those experienced in the PARADIGM-HF sacubitril valsartan plus standard care arm. This method, as described by Signorovitch et al. (59) and in accordance with the NICE DSU TSD18 (58), involves reweighting of individual patient data in the index trial, ensuring that the weighted baseline characteristic summary statistics match the cohort in the comparator trial. Patient-level outcomes are similarly weighted by these values and provide an estimate of the outcomes that would have been observed should patients, equivalent to those in the comparator trial, have been randomised to the arms of the index trial.

B.2.9.1.2 Comparators

DAPA-HF and PARADIGM-HF have similar, but not identical control arms. In DAPA-HF, patients randomised to the intervention arm were treated with dapagliflozin and patients randomised to the control arm were treated with placebo in combination with standard care. Standard care within the DAPA-HF trial varied between patients and consisted of combinations of ACEi/ARB, beta-blocker, MRA and/or sacubitril valsartan. As such, the DAPA-HF trial population consists of several sub-populations of patients with different standard care therapies. In the PARADIGM-HF trial, patients were first treated with enalapril followed by sacubitril valsartan during the 5–10-week run-in phase, before randomisation to the sacubitril valsartan intervention arm, or the enalapril active control arm.

For the purposes of the MAIC, a subgroup of the control arm of DAPA-HF and the enalapril active control arm of PARADIGM-HF were used as the anchor for the comparison of dapagliflozin versus sacubitril valsartan. Since enalapril is an ACEi, the subgroup of patients in the DAPA-HF control arm treated with placebo in combination with ACEi, was considered to be most similar to the enalapril control arm in PARADIGM-HF, and therefore this sub-group was selected as the anchor from the DAPA-HF trial.

The intervention arm of DAPA-HF was split into subgroups by standard care, to compare the following treatment regimens in the MAIC via the MAIC anchor described above:

- Dapagliflozin in combination with an ACEi as part of standard care versus sacubitril valsartan in combination with standard care; this subgroup was selected for the primary analysis, as this subgroup is most comparable to PARADIGM-HF patients given all patients in this subgroup were known to be tolerant of ACEi (PARADIGM-HF eligibility criteria)
- Dapagliflozin in combination with an ARB as part of standard care versus sacubitril valsartan in combination with standard care
- Dapagliflozin in combination with an ACEi or an ARB as part of standard care versus sacubitril valsartan in combination with standard care
- Dapagliflozin in combination with sacubitril valsartan as part of standard care versus sacubitril valsartan in combination with standard care

B.2.9.1.3 Endpoints

The following study endpoints were selected for comparison as they are clinically important, overlap across the DAPA-HF and PARADGM-HF studies and are considered by the cost-effectiveness model:

- Time to the earliest of CV death or first hHF
- Time to CV death
- Time to first hHF
- Time to all-cause death
- Incidence during study of AEs of special interest
- Incidence during study of SAEs

B.2.9.2 Results

B.2.9.2.1 Baseline characteristics

Baseline characteristics before and after matching on the primary adjustment set are summarised in Table 16. The sacubitril valsartan subgroup (subgroup 4) had too few patients (250 receiving dapagliflozin) to achieve matching to the primary matching set, and so analysis was not performed using this matching set on that subpopulation. Otherwise, matching was complete to the expected level of precision, and even those covariates not adjusted for (BMI, serum creatinine) did not substantially differ prior to or after adjustment.

Effective sample size was reduced to less than half of the original sample, but more than one third remained in all cases. Histograms (Figure 13, Figure 14) show a continuous distribution of patient weights, without a strong concentration of high-weight patients with similar covariates. Table 17 shows that the proportion of the effective sample size concentrated in patients with effective sample size (ESS) normalised weights > 5 is less than [redacted] for all subgroups, therefore they have a small and acceptable influence on the outcome. However, it should be noted that all high weight individuals had the covariate “Race = Other”. This is scrutinised further in the discussion (Section B.2.9.3).

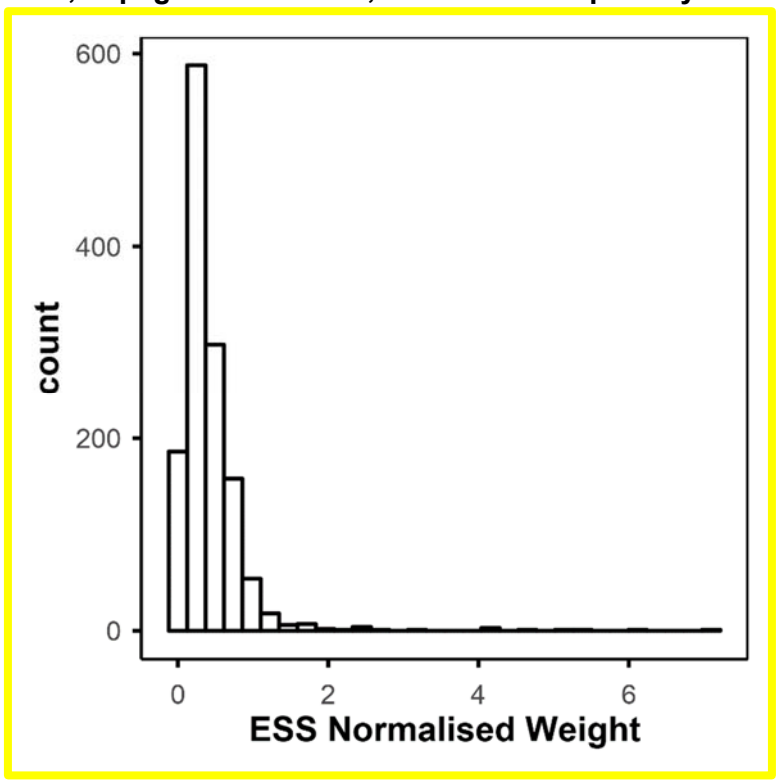
Table 16: Baseline covariates prior and post matching; primary matching set‡

Variable	PARADIGM-HF enalapril	DAPA-HF placebo + ACEi (anchor)		DAPA-HF dapagliflozin + ACEi (subgroup 1)		DAPA-HF dapagliflozin + ARB (subgroup 2)		DAPA-HF dapagliflozin + ACEi or ARB (subgroup 3)	
		Raw	Adjusted	Raw	Adjusted	Raw	Adjusted	Raw	Adjusted
N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sex (female)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Race (white)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Race (black)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Race (Asian)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Region (NA)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Region (SA)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Region (AP)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SBP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Heart rate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BMI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Creatinine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ischaemic HF	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LVEF	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
NT-proBNP†	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
NYHA Class III	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
NYHA Class IV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hx HTN	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Variable	PARADIGM-HF enalapril	DAPA-HF placebo + ACEi (anchor)		DAPA-HF dapagliflozin + ACEi (subgroup 1)		DAPA-HF dapagliflozin + ARB (subgroup 2)		DAPA-HF dapagliflozin + ACEi or ARB (subgroup 3)	
		Raw	Adjusted	Raw	Adjusted	Raw	Adjusted	Raw	Adjusted
Hx DM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hx AF	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hx hHF	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hx MI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hx stroke	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

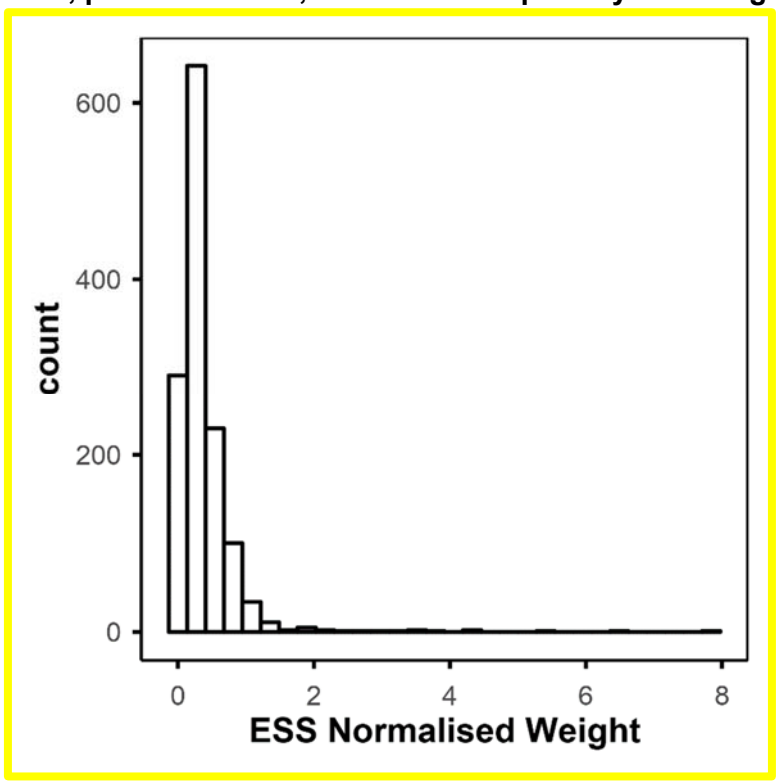
† Median (lower quartile, upper quartile). ‡The sacubitril valsartan subgroup had too few patients (250 receiving dapagliflozin) to achieve matching to the primary matching set, and so analysis was not performed using this matching set on that subpopulation.
Abbreviations: ACM, all-cause mortality; AF, atrial fibrillation; AP, Asia or Pacific; CVD, cardiovascular death; DM, diabetes mellitus; HF, heart failure; hHF, hospitalisation for heart failure; HTN, hypertension; HR, heart rate; Hx, history of; IQR, inter-quartile range; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NA, North America; NT-proBNP, N-terminal pro B-type natriuretic peptide; NYHA, New York Heart Association; SA, South America; SBP, systolic blood pressure; SD, standard deviation

Figure 13: DAPA-HF, dapagliflozin + ACEi, distribution of primary matching weights



Abbreviations: ACEi, angiotensin converting enzyme inhibitor; ESS, effective sample size.

Figure 14: DAPA-HF, placebo + ACEi, distribution of primary matching weights



Abbreviations: ACEi, angiotensin converting enzyme inhibitor; ESS, effective sample size.

Table 17: Extreme patient weights within the primary matching set

	DAPA-HF placebo + ACEi (anchor)	DAPA-HF dapagliflozin + ACEi (subgroup 1)	DAPA-HF dapagliflozin + ARB (subgroup 2)	DAPA-HF dapagliflozin + ACEi or ARB (subgroup 3)
ESS	[redacted]	[redacted]	[redacted]	[redacted]
Patients with weight > 5	[redacted]	[redacted]	[redacted]	[redacted]
% of ESS concentrated in these patients	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; ESS, effective sample size.

B.2.9.2.2 Outcomes

B.2.9.2.2.1 Time to event

Subgroup 1: DAPA-HF dapagliflozin + ACEi

The effect of matching-adjustment in this population is shown in Figure 15. Differences in the mean treatment effects due to matching were [redacted]. Numerically, outcomes of dapagliflozin plus ACEi versus placebo plus ACEi were [redacted] after matching-adjustment to the PARADIGM-HF control arm, for all outcomes [redacted]. For all outcomes [redacted] the decrease in effective sample size associated with matching-adjustment of the two arms of DAPA-HF led to [redacted] in the differences in outcomes at the [redacted] level.

In Figure 16, the final comparisons of outcomes for patients receiving dapagliflozin plus ACEi versus sacubitril valsartan are displayed.
[redacted] in the adjusted analysis versus the naïve analysis, with the exception of [redacted], and all relative treatment effects in both the adjusted and naïve analyses were [redacted]. There was no statistically detectable difference in outcomes between dapagliflozin and sacubitril valsartan in either the adjusted or naïve comparisons, but this was expected given that neither study was powered to detect such a difference.

The results from the primary analysis in subgroup 1 of the MAIC, showed that there is no statistically significant difference in outcomes between patients treated with sacubitril valsartan plus standard care and dapagliflozin plus ACEi, in a population adjusted to match the patients in PARADIGM-HF.

Figure 15: Effect of adjustment on DAPA-HF time to event outcomes, dapagliflozin + ACEi subgroup. PARADIGM-HF outcome for reference only

Grey, unadjusted; purple, matching-adjusted
Abbreviations: con., control; CV, cardiovascular; ACEi, angiotensin converting enzyme inhibitor; HHF, heart failure hospitalisation; inv, intervention.

Figure 16: Final comparison of dapagliflozin + ACEi vs sacubitril valsartan + standard care time to event outcomes

Grey, unadjusted; purple, matching-adjusted
Abbreviations: con., control; CV, cardiovascular; ACEi, angiotensin converting enzyme inhibitor; HHF, heart failure hospitalisation; inv, intervention.

Subgroup 2: DAPA-HF dapagliflozin + ARB

The effect of matching-adjustment in this population is shown in Figure 17. Differences in the mean treatment effects due to matching were . Numerically, outcomes versus placebo plus ACEi were for dapagliflozin plus ARB after matching-adjustment to the PARADIGM-HF control arm, for all outcomes . For all outcomes , the decrease in effective sample size associated with matching-adjustment of the two arms of DAPA-HF led to in the differences in outcomes at the level.

In Figure 18, the final comparisons of outcomes for patients receiving dapagliflozin plus ARB versus sacubitril valsartan are displayed. Numerically, most outcomes were in the adjusted analysis versus the naïve analysis, with the exception of , and all relative treatment effects both in the adjusted and naïve analyses were . The relative treatment effect of dapagliflozin versus sacubitril valsartan was in this subgroup than the subgroup selected for concomitant use of ACEi. There was no statistically detectable difference in outcomes between the dapagliflozin and sacubitril valsartan in either the adjusted or naïve comparisons, but this was expected given that neither study was powered to detect such a difference.

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The results from the analysis in subgroup 2 of the MAIC, showed that there is no statistically significant difference in outcomes between patients treated with sacubitril valsartan plus standard care and dapagliflozin plus ARB, in a population adjusted to match the patients in PARADIGM-HF.

Figure 17: Effect of adjustment on DAPA-HF time to event outcomes, dapagliflozin + ARB subgroup. PARADIGM-HF outcome for reference only

Grey, unadjusted; purple, matching-adjusted
Abbreviations: con., control; CV, cardiovascular; ACEi, angiotensin converting enzyme inhibitor; HHF, heart failure hospitalisation; inv, intervention.

Figure 18: Final comparison of dapagliflozin + ARB vs sacubitril valsartan + standard care time to event outcomes

Grey, unadjusted; purple, matching-adjusted
Abbreviations: con., control; CV, cardiovascular; ACEi, angiotensin converting enzyme inhibitor; HHF, heart failure hospitalisation; inv, intervention.

Subgroup 3: DAPA-HF dapagliflozin + ACEi and/or ARB

The effect of matching-adjustment in this population is shown in Figure 19. Differences in the mean treatment effects due to matching were . Numerically, outcomes versus placebo plus ACEi were for dapagliflozin plus ACEi and/or ARB after matching-adjustment to the PARADIGM-HF control arm, for all outcomes. For all except , the decrease in effective sample size associated with matching-adjustment of the two arms of DAPA-HF led to in the differences in outcomes at the level.

In Figure 20, the final comparisons of outcomes for patients receiving dapagliflozin plus ACEi and/or ARB versus sacubitril valsartan are displayed. Numerically, all outcomes were in the adjusted analysis versus the naïve analysis, but all relative effects were in both the adjusted and naïve analyses. The relative treatment effect of dapagliflozin over sacubitril valsartan was to the subgroup selected for concomitant use of ACEi. There was no statistically detectable difference in outcomes between dapagliflozin and sacubitril valsartan in either the adjusted or naïve comparisons, but this was expected given that neither study was powered to detect such a difference.

The results from the analysis in subgroup 3 of the MAIC showed that there is no statistically significant difference in outcomes between patients treated with sacubitril valsartan plus standard care and dapagliflozin plus ACEi or ARB, in a population adjusted to match the patients in PARADIGM-HF.

Figure 19: Effect of adjustment on DAPA-HF time to event outcomes, dapagliflozin + ACEi and/or ARB subgroup. PARADIGM-HF outcome for reference only

Grey, unadjusted; purple, matching-adjusted
Abbreviations: con., control; CV, cardiovascular; ACEi, angiotensin converting enzyme inhibitor; HHF, heart failure hospitalisation; inv, intervention.

Figure 20: Final comparison of dapagliflozin + ACEi and/or ARB vs sacubitril valsartan + standard care time to event outcomes

Grey, unadjusted; purple, matching-adjusted
Abbreviations: con., control; CV, cardiovascular; ACEi, angiotensin converting enzyme inhibitor; HHF, heart failure hospitalisation; inv, intervention.

B.2.9.2.2.2 Safety outcomes

Safety outcomes for PARADIGM-HF were obtained from the supplementary appendix of McMurray 2014 (60), with adverse events with an incidence of >5% in either trial arm included for comparison. These adverse events were compared with the adverse events recorded in DAPA-HF. Incidence of AEs of any seriousness prior to adjustment for baseline characteristics are shown in Table 18. As expected, given the differences in trial protocols of DAPA-HF and PARADIGM-HF, there was a clear difference in the incidence of AE events captured in these studies. In DAPA-HF, the only AE events recorded were those that qualified as:

- SAEs
- AE as reason for permanent discontinuation from investigational product (IP)
- AE as reason for IP interruption or dose reduction
- An AE of interest
    - Volume depletion
    - Renal events
    - Major hypoglycaemic events
    - Fractures
    - Diabetic ketoacidosis (DKA)
    - AEs leading to amputation
- AE leading to a potential endpoint:

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- All deaths
- All HF events
- eGFR declines ≥50% from baseline
- eGFR values <15 mL/min/1.73 m^2
- Dialysis
- Kidney transplantations
- Doubling of serum creatinine (since the most recent central laboratory measurement)
- Cardiac ischaemic events (MI and unstable angina)
- Cerebrovascular events (stroke and transient ischaemic attack)
- New diagnosis of T2D
- New diagnosis of atrial fibrillation

PARADIGM-HF did not have these criteria for recording AEs. These criteria for recording AEs in DAPA-HF are likely to have led to the incidences of AE of any seriousness to be incomparable between the DAPA-HF and PARADIGM. However, as all SAEs were recorded in both studies during the study period, it was deemed reasonable to compare the SAEs in DAPA-HF and PARADGM-HF. Patient characteristics that were prognostic of AE endpoint incidence were not removed from the primary matching set. The inclusion of variables not strongly correlated with treatment outcome are anticipated to provide no net biasing effect.

Table 18: Incidence of adverse events of any seriousness in PARADIGM-HF and DAPA-HF

Study	Arm	N	Incidence – n (%)									
			Hypotension	Cardiac Failure	Hyperkalaemia	Renal Impairment	Dizziness	Atrial Fibrillation	Pneumonia	Oedema (peripheral)	Dyspnoea	Bronchitis
PARADIGM-HF	Enalapril	4229	506 (12.0%)	832 (19.7%)	592 (14.0%)	487 (11.5%)	236 (5.6%)	236 (5.6%)	237 (5.6%)	213 (5.0%)	306 (7.2%)	224 (5.3%)
	Sacubitril/ valsartan	4203	740 (17.6%)	730 (17.4%)	488 (11.6%)	426 (10.1%)	251 (6.0%)	251 (6.0%)	227 (5.4%)	215 (5.1%)	213 (5.1%)	183 (4.4%)
DAPA-HF	Placebo	2368	[redacted]									
	Dapagliflozin	2368	[redacted]									

Subgroup 1: DAPA-HF dapagliflozin + ACEi

Table 19: Incidence of SAEs in PARADIGM-HF and DAPA-HF subgroup 1, before and after matching-adjustment

		PARADIGM-HF		DAPA-HF unadjusted		DAPA-HF primary adjustment	
		Enalapril	Sacubitril/ valsartan	Placebo + ACEi	Dapagliflozin + ACEi	Placebo + ACEi	Dapagliflozin + ACEi
N/ESS (Safety)		4229	4203	[redacted]	[redacted]	[redacted]	[redacted]
SAE cardiac failure	N (%)	649 (15.3%)	588 (14.0%)	[redacted]	[redacted]	[redacted]	[redacted]
	OR	0.90 (0.80, 1.01)		[redacted]		[redacted]	
SAE pneumonia	N (%)	181 (4.3%)	155 (3.7%)	[redacted]	[redacted]	[redacted]	[redacted]
	OR	0.86 (0.69, 1.07)		[redacted]		[redacted]	
SAE cardiac failure (chronic)	N (%)	135 (3.2%)	112 (2.7%)	[redacted]	[redacted]	[redacted]	[redacted]
	OR	0.83 (0.64, 1.07)		[redacted]		[redacted]	
SAE cardiac failure (congestive)	N (%)	140 (3.3%)	112 (2.7%)	[redacted]	[redacted]	[redacted]	[redacted]
	OR	0.80 (0.62, 1.03)		[redacted]		[redacted]	
SAE atrial fibrillation	N (%)	113 (2.7%)	108 (2.6%)	[redacted]	[redacted]	[redacted]	[redacted]
	OR	0.96 (0.74, 1.25)		[redacted]		[redacted]	
SAE cardiac death	N (%)	114 (2.7%)	85 (2.0%)	[redacted]	[redacted]	[redacted]	[redacted]
	OR	0.75 (0.56, 0.99)		[redacted]		[redacted]	
SAE cardiac failure (acute)	N (%)	93 (2.2%)	67 (1.6%)	[redacted]	[redacted]	[redacted]	[redacted]
	OR	0.72 (0.52, 0.99)		[redacted]		[redacted]	
SAE ventricular tachycardia	N (%)	85 (2.0%)	66 (1.6%)	[redacted]	[redacted]	[redacted]	[redacted]
	OR	0.78 (0.56, 1.08)		[redacted]		[redacted]	

Abbreviations: ACEi, angiotensin converting enzyme inhibitor; ESS, effective sample size; OR, odds ratio; SAE, serious adverse event.

Company evidence submission template for dapagliflozin for HFrEF.

Table 19 shows the incidence of SAEs in PARADIGM-HF and the subgroup in DAPA-HF receiving dapagliflozin plus ACEi and placebo plus ACEi. Some of the SAEs, such as cardiac death, overlap with efficacy outcomes. Absolute incidence was generally lower in DAPA-HF, but there was also less follow-up in this study. The relative rates between the investigational and control arms were considered comparable in PARADIGM-HF and in the DAPA-HF subgroups in Table 19. The exception to this was [redacted], which demonstrated a marked difference in incidence between the two trials, indicating that it may have been encoded differently. Among the other SAEs, [redacted] showed a significant difference in incidence odds between the arms in either trial at [redacted] without adjusting for multiple comparisons. Matching-adjustment in most cases resulted in [redacted] with dapagliflozin versus placebo.

Table 20 shows the final odds ratios for SAE incidence in patients receiving dapagliflozin + ACEi versus patients receiving sacubitril valsartan. The only odds ratio significantly different from 1 at the α = 5% level without adjustment for multiple comparison is in [redacted], which is [redacted]. This difference is [redacted] after adjustment, and due to the number of comparisons and the presence of differences in treatment effect modifiers on the unadjusted comparison, observation of such a difference should [redacted]. Matching-adjustment [redacted] for SAE incidence for the majority of SAEs compared to pre-adjustment odds ratios. Nevertheless, there is insufficient evidence to conclude that there is any difference in incidence of SAE between patients receiving dapagliflozin + ACEi and patients receiving sacubitril valsartan.

Table 20: Odds ratios of incidence of SAEs in patients receiving dapagliflozin + ACEi versus in patients receiving sacubitril valsartan; before and after matching-adjustment

	Odds ratio: Dapagliflozin + ACEi vs sacubitril valsartan	
	Unadjusted	**Primary**
SAE cardiac failure	[redacted]	[redacted]
SAE pneumonia	[redacted]	[redacted]
SAE cardiac failure (chronic)	[redacted]	[redacted]
SAE cardiac failure (congestive)	[redacted]	[redacted]
SAE atrial fibrillation	[redacted]	[redacted]
SAE cardiac death	[redacted]	[redacted]
SAE cardiac failure (acute)	[redacted]	[redacted]
SAE ventricular tachycardia	[redacted]	[redacted]

Abbreviations: ACEi, angiotensin converting enzyme inhibitor; SAE, serious adverse event.

Subgroup 2: DAPA-HF dapagliflozin + ARB

Table 21: Incidence of SAEs in PARADIGM-HF and DAPA-HF subgroup 2, before and after matching-adjustment

		PARADIGM-HF		DAPA-HF unadjusted		DAPA-HF primary adjustment	
		Enalapril	Sacubitril/ valsartan	Placebo + ACEi	Dapagliflozin + ARB	Placebo + ACEi	Dapagliflozin + ARB
N/ESS (Safety)		4229	4203	[redacted]	[redacted]	[redacted]	[redacted]
SAE cardiac failure	N (%)	649 (15.3%)	588 (14.0%)	[redacted]	[redacted]	[redacted]	[redacted]
	OR	0.90 (0.80, 1.01)		[redacted]		[redacted]	
SAE pneumonia	N (%)	181 (4.3%)	155 (3.7%)	[redacted]	[redacted]	[redacted]	[redacted]
	OR	0.86 (0.69, 1.07)		[redacted]		[redacted]	
SAE cardiac failure (chronic)	N (%)	135 (3.2%)	112 (2.7%)	[redacted]	[redacted]	[redacted]	[redacted]
	OR	0.83 (0.64, 1.07)		[redacted]		[redacted]	
SAE cardiac failure (congestive)	N (%)	140 (3.3%)	112 (2.7%)	[redacted]	[redacted]	[redacted]	[redacted]
	OR	0.80 (0.62, 1.03)		[redacted]		[redacted]	
SAE atrial fibrillation	N (%)	113 (2.7%)	108 (2.6%)	[redacted]	[redacted]	[redacted]	[redacted]
	OR	0.96 (0.74, 1.25)		[redacted]		[redacted]	
SAE cardiac death	N (%)	114 (2.7%)	85 (2.0%)	[redacted]	[redacted]	[redacted]	[redacted]
	OR	0.75 (0.56, 0.99)		[redacted]		[redacted]	
SAE cardiac failure (acute)	N (%)	93 (2.2%)	67 (1.6%)	[redacted]	[redacted]	[redacted]	[redacted]
	OR	0.72 (0.52, 0.99)		[redacted]		[redacted]	
SAE ventricular tachycardia	N (%)	85 (2.0%)	66 (1.6%)	[redacted]	[redacted]	[redacted]	[redacted]
	OR	0.78 (0.56, 1.08)		[redacted]		[redacted]	

Abbreviations: ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; ESS, effective sample size; OR, odds ratio; SAE, serious adverse event.

Table 21 shows the incidence of SAEs in PARADIGM-HF and the subgroup in DAPA-HF receiving dapagliflozin plus ARB and placebo plus ACEi. Some of the SAEs, such as cardiac death, overlap with efficacy outcomes [redacted] showed a significant difference in incidence odds between the arms in either trial [redacted] Table 22 shows the final odds ratios for SAE incidence in patients receiving dapagliflozin + ARB versus patients receiving sacubitril valsartan [redacted] There is insufficient evidence to conclude that there is any difference in incidence of SAE between patients receiving dapagliflozin + ARB and patients receiving sacubitril valsartan.

Table 22: Odds ratios of incidence of SAEs in patients receiving dapagliflozin + ARB versus in patients receiving sacubitril valsartan; before and after matching-adjustment

	Odds ratio: Dapagliflozin + ARB vs sacubitril valsartan	
	Unadjusted	**Primary**
SAE cardiac failure	[redacted]	[redacted]
SAE pneumonia	[redacted]	[redacted]
SAE cardiac failure (chronic)	[redacted]	[redacted]
SAE cardiac failure (congestive)	[redacted]	[redacted]
SAE atrial fibrillation	[redacted]	[redacted]
SAE cardiac death	[redacted]	[redacted]
SAE cardiac failure (acute)	[redacted]	[redacted]
SAE ventricular tachycardia	[redacted]	[redacted]

Abbreviations: ARB, angiotensin II receptor blocker; SAE, serious adverse event.

Subgroup 3: DAPA-HF dapagliflozin + ACEi and/or ARB

Table 23: Incidence of SAEs in PARADIGM-HF and DAPA-HF subgroup 3, before and after matching-adjustment

		PARADIGM-HF		DAPA-HF unadjusted		DAPA-HF primary adjustment	
		Enalapril	Sacubitril/ valsartan	Placebo + ACEi	Dapagliflozin + ACEi and/or ARB	Placebo + ACEi	Dapagliflozin + ACEI and/or ARB
N/ESS (Safety)		4229	4203	[redacted]	[redacted]	[redacted]	[redacted]
SAE cardiac failure	N (%)	649 (15.3%)	588 (14.0%)	[redacted]	[redacted]	[redacted]	[redacted]
	OR	0.90 (0.80, 1.01)		[redacted]		[redacted]	
SAE pneumonia	N (%)	181 (4.3%)	155 (3.7%)	[redacted]	[redacted]	[redacted]	[redacted]
	OR	0.86 (0.69, 1.07)		[redacted]		[redacted]	
SAE cardiac failure (chronic)	N (%)	135 (3.2%)	112 (2.7%)	[redacted]	[redacted]	[redacted]	[redacted]
	OR	0.83 (0.64, 1.07)		[redacted]		[redacted]	
SAE cardiac failure (congestive)	N (%)	140 (3.3%)	112 (2.7%)	[redacted]	[redacted]	[redacted]	[redacted]
	OR	0.80 (0.62, 1.03)		[redacted]		[redacted]	
SAE atrial fibrillation	N (%)	113 (2.7%)	108 (2.6%)	[redacted]	[redacted]	[redacted]	[redacted]
	OR	0.96 (0.74, 1.25)		[redacted]		[redacted]	
SAE cardiac death	N (%)	114 (2.7%)	85 (2.0%)	[redacted]	[redacted]	[redacted]	[redacted]
	OR	0.75 (0.56, 0.99)		[redacted]			
SAE cardiac failure (acute)	N (%)	93 (2.2%)	67 (1.6%)	[redacted]	[redacted]	[redacted]	[redacted]
	OR	0.72 (0.52, 0.99)		[redacted]		[redacted]	

		PARADIGM-HF		DAPA-HF unadjusted		DAPA-HF primary adjustment	
		Enalapril	Sacubitril/ valsartan	Placebo + ACEi	Dapagliflozin + ACEi and/or ARB	Placebo + ACEi	Dapagliflozin + ACEI and/or ARB
SAE ventricular tachycardia	N (%)	85 (2.0%)	66 (1.6%)	[redacted]	[redacted]	[redacted]	[redacted]
	OR	0.78 (0.56, 1.08)		[redacted]		[redacted]	

Abbreviations: ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; ESS: effective sample size; OR: odds ratio; SAE: serious adverse event.

Table 23 shows the incidence of SAEs in PARADIGM-HF and subgroup in DAPA-HF receiving dapagliflozin plus ACEi and/or ARB, and placebo plus ACEi. Some of the SAEs, such as cardiac death, overlap with efficacy outcomes. [redacted] showed a significant difference in incidence odds between the arms in either trial [redacted] The significance of this observation was [redacted] For most SAEs, matching-adjustment [redacted] Table 24 shows the final odds ratios for SAE incidence in patients receiving dapagliflozin + ACEi and/or ARB versus patients receiving sacubitril valsartan [redacted] There is no evidence to conclude that there is any difference in SAE incidence between patients receiving dapagliflozin + ACEi and/or ARB and patients receiving sacubitril valsartan.

Table 24: Odds ratios of incidence of SAEs in patients receiving dapagliflozin + ACEi and/or ARB versus in patients receiving sacubitril valsartan; before and after matching-adjustment

	Odds ratio: Dapagliflozin + ACEi and/or ARB vs sacubitril valsartan	
	Unadjusted	Primary
SAE cardiac failure	[redacted]	[redacted]
SAE pneumonia	[redacted]	[redacted]
SAE cardiac failure (chronic)	[redacted]	[redacted]
SAE cardiac failure (congestive)	[redacted]	[redacted]
SAE atrial fibrillation	[redacted]	[redacted]
SAE cardiac death	[redacted]	[redacted]
SAE cardiac failure (acute)	[redacted]	[redacted]
SAE ventricular tachycardia	[redacted]	[redacted]

Abbreviations: ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; SAE, serious adverse event.

B.2.9.3 Uncertainties in the indirect and mixed treatment comparisons

There were irreconcilable differences between the indirectly compared treatment arms, due to differences in trial protocols for capturing AEs, amongst other reasons, which are likely to have contributed to in residual confounding.

The 5–10-weeks pre-randomisation run-in period in PARADIGM-HF was associated with study discontinuation in a large number of patients who could not tolerate enalapril or sacubitril valsartan. These patients were therefore not included in the intent-to-treat analysis for PARADIGM-HF. DAPA-HF did not have such a run-in period, and as such any patients who became intolerant of dapagliflozin would have discontinued treatment after randomisation. This is likely to have reduced the treatment effect in DAPA-HF, compared to a hypothetical scenario where enrolled patients are pre-tested for tolerance of dapagliflozin during a run-in period.

The geographic and racial diversity of PARADIGM-HF was greater than that in DAPA-HF. One of the greatest imbalances between the two trials was the proportion of patients reporting “Race = Other”; race was selected as a predictive treatment effect modifier for the outcome of hHF/CV death. Most patients with “Race = Other” in the ITT population of DAPA-HF were resident in Brazil (51/63 patients), with most describing themselves as “mixed races”. The diversity of South and Latin American countries represented in PARADIGM-HF is far greater than in DAPA-HF, and it is notable that in the prespecified subgroup analyses of PARADIGM-HF, the HR of sacubitril valsartan versus enalapril for the primary outcome observationally decreased for this subgroup, whereas the corresponding HR in DAPA-HF observationally reduced. However, it should be noted that there were only 11 events for “Race = Other” in DAPA-HF, and as such it is not possible to draw any conclusions from these observations. It is possible that there is heterogeneity among patients classified as “Race = Other”, which leads to uncaptured variation in patient characteristics.

Given the large number of variables that have been adjusted for, the odds of partial adjustment for the any potentially unadjusted covariables by adjusting for correlated variables is expected to be high. The lack of sensitivity of the outcomes to the adjustment set used is indicative that the results would be robust to the inclusion of any additional potential covariables.

Due to the concentration of population samples in small centres globally, there may be populations of heterogenous outcomes with correlated baseline covariates that are not generally informative of outcome in the global super-population – i.e. there may be correlated “noise” terms within the DAPA-HF data. This risk is alleviated by the solicitation of expert advice to select the range of potential treatment effect modifiers, and by the large number of sites involved in the DAPA-HF trial.

B.2.10 Adverse reactions

Dapagliflozin is well-tolerated in patients with HFrEF:

- SAEs were numerically less frequent with dapagliflozin (35.7%) than with placebo (40.2%)
- No difference in AEs leading to discontinuation between dapagliflozin (4.7%) and placebo (4.9%)
- No SAEs occurring in ≥1% of patients occurred more frequently with dapagliflozin than with placebo
- AEs with an outcome of death were numerically lower in the dapagliflozin arm (9.6%) than the placebo arm (10.6%)
- AEs of special interest (hypoglycaemia, volume depletion, fractures, and renal AEs) were generally balanced between treatment groups or less frequent with dapagliflozin than with placebo. Diabetic ketoacidosis occurred only in the dapagliflozin group; however, it occurred in only 0.1% of patients

B.2.10.1 Studies identified in Section 2.2

Safety data were collected for all SAEs, AEs leading to discontinuation, interruption, or dose reduction of study drug, and AEs of special interest:

- Volume depletion
- Renal AEs
- Diabetic ketoacidosis
- Major hypoglycaemic events
- Fractures
- AEs leading to amputation
- AEs leading to a risk of lower limb amputation

Data on other AEs were not routinely collected due to the extensive safety data which already exist for dapagliflozin in other indications. A summary of common and uncommon adverse drug reactions which have been experienced in these indications is therefore provided in Table 28 based on the Summary of Product Characteristics for dapagliflozin.

A summary of AEs specified as of interest in DAPA-HF is provided in Table 25 (on and off treatment) with SAEs occurring in ≥1% of patients (on and off treatment) and SAEs in ≥0.5% of patients (on treatment) in Table 26 and Table 27, respectively. Safety outcomes were generally balanced between dapagliflozin and placebo; SAEs occurred in 35.7% and 40.2% of patients, respectively, with AEs leading to discontinuation occurring in 4.7% and 4.9% of patients, respectively. No AEs of special interest occurred with a notably higher frequency in the dapagliflozin arm than in the placebo arm. While symptoms of volume depletion occurred in 7.2% of dapagliflozin patients and 6.5% of placebo patients, SAEs related to volume depletion occurred in 1.2% of dapagliflozin patients and 1.7% of placebo patients. Serious renal AEs occurred in 1.6% of dapagliflozin patients and 2.7% of placebo patients. There was no SAE which occurred more frequently with dapagliflozin than with placebo.

Table 25: AEs specified as of interest in DAPA-HF

AE, n (%)	Dapagliflozin (N=2,368)	Placebo (N=2,368)
On treatment†		
AE with an outcome of death	227 (9.6)	250 (10.6)
SAE	846 (35.7)	951 (40.2)
AE leading to discontinuation	111 (4.7)	116 (4.9)
AE leading to dose interruption	284 (12.0)	349 (14.7)
AE leading to dose reduction	43 (1.8)	25 (1.1)
AE possibly related to investigational product	244 (10.3)	198 (8.4)
Definite or probable diabetic ketoacidosis	3 (0.1)	0
Major hypoglycaemic event	4 (0.2)	4 (0.2)
Symptoms of volume depletion	170 (7.2)	153 (6.5)
Fracture AE	48 (2.0)	47 (2.0)
Renal AE	141 (6.0)	158 (6.7)
Amputation	11 (0.5)	11 (0.5)
On and off treatment‡		
AE with an outcome of death	286 (12.1)	333 (14.1)
SAE	895 (37.8)	994 (42.0)
AE leading to discontinuation	111 (4.7)	116 (4.9)
AE leading to dose interruption	284 (12.0)	349 (14.7)
AE leading to dose reduction	43 (1.8)	25 (1.1)
AE possibly related to investigational product	244 (10.3)	198 (8.4)
Definite or probable diabetic ketoacidosis	3 (0.1)	0
Major hypoglycaemic event	4 (0.2)	4 (0.2)
Symptoms of volume depletion	178 (7.5)	162 (6.8)
Fracture AE	49 (2.1)	50 (2.1)
Renal AE	153 (6.5)	170 (7.2)
Amputation	13 (0.5)	12 (0.5)

†On treatment includes AEs with an onset date on or after date of first dose and up to and including 30 days following last dose of study drug.
‡On and off treatment includes AEs with an onset date on or after date of first dose of study drug.
Source: McMurray et al 2019 (supplementary appendix) (45).
Abbreviations: AE, adverse event; SAE, serious adverse event.

Table 26: Serious adverse events occurring in ≥1% of patients in any treatment arm (on and off treatment)

AE, n (%)	Dapagliflozin (N=2,368)	Placebo (N=2,368)
Cardiac failure	262 (11.1)	351 (14.8)
Pneumonia	76 (3.2)	82 (3.5)
Cardiac failure congestive	65 (2.7)	70 (3.0)
Death	48 (2.0)	48 (2.0)
Acute myocardial infarction	37 (1.6)	38 (1.6)
Ventricular tachycardia	34 (1.4)	54 (2.3)
Cardiac failure chronic	27 (1.1)	33 (1.4)
Atrial fibrillation	26 (1.1)	39 (1.6)
Ischaemic stroke	24 (1.0)	26 (1.1)
Acute kidney injury	23 (1.0)	46 (1.9)
Angina unstable	21 (0.9)	30 (1.3)
Sudden cardiac death	18 (0.8)	27 (1.1)

Source: McMurray et al 2019 (supplementary appendix) (45).
Abbreviations: AE, adverse event.

Table 27: Serious adverse events occurring in ≥0.5% of patients in any treatment arm (on treatment)

SAE, n (%)	Dapagliflozin (N=2,368)	Placebo (N=2,368)
Cardiac failure	239 (10.1)	325 (13.7)
Pneumonia	70 (3.0)	73 (3.1)
Cardiac failure congestive	57 (2.4)	65 (2.7)
Cardiac failure acute	36 (1.5)	51 (2.2)
Death	33 (1.4)	38 (1.6)
Acute myocardial infarction	32 (1.4)	32 (1.4)
Ventricular tachycardia	32 (1.4)	53 (2.2)
Cardiac failure chronic	24 (1.0)	26 (1.1)
Ischaemic stroke	24 (1.0)	24 (1.0)
Atrial fibrillation	23 (1.0)	37 (1.6)
Angina unstable	21 (0.9)	29 (1.2)
Acute kidney injury	20 (0.8)	41 (1.7)
Sudden cardiac death	17 (0.7)	27 (1.1)
Sudden death	17 (0.7)	7 (0.3)
Chronic obstructive pulmonary disease	14 (0.6)	22 (0.9)
Myocardial infarction	14 (0.6)	17 (0.7)
Transient ischaemic attack	13 (0.5)	7 (0.3)
Angina pectoris	12 (0.5)	12 (0.5)
Bronchitis	11 (0.5)	6 (0.3)
Peripheral arterial occlusive disease	11 (0.5)	9 (0.4)
Sepsis	10 (0.4)	11 (0.5)
Urinary tract infection	10 (0.4)	16 (0.7)
Cardiogenic shock	9 (0.4)	12 (0.5)
Acute respiratory failure	7 (0.3)	13 (0.5)
Cerebral infarction	7 (0.3)	11 (0.5)
Pulmonary embolism	7 (0.3)	13 (0.5)
Syncope	7 (0.3)	12 (0.5)
Non-cardiac chest pain	6 (0.3)	14 (0.6)

Source: DAPA-HF CSR (54).
Abbreviations: SAE, serious adverse event.

Table 28: Adverse drug reactions reported in the Summary of Product Characteristics for dapagliflozin in T1DM and T2DM

System organ class	Very common	Common	Uncommon	Rare	Very rare
Infections and infestations	-	Vulvo-vaginitis, balanitis, and related genital infections Urinary tract infection	Fungal infection	-	Necrotising fasciitis of the perineum (Fourier's gangrene)
Metabolism and nutrition disorders	Hypo-glycaemia†	Diabetic ketoacidosis (T1DM)	Volume depletion Thirst	Diabetic ketoacidosis (T2DM)	-
Nervous system disorders	-	Dizziness	-	-	-
Gastrointestinal disorders	-	-	Constipation Dry mouth	-	-
Skin and subcutaneous tissue disorders	-	Rash	-	-	-
Musculoskeletal and connective tissue disorders	-	Back pain	-	-	-
Renal and urinary disorders	-	Dysuria Polyuria	Nocturia	-	-
Reproductive system and breast disorders	-	-	Vulvovaginal pruritis Pruritis genital	-	-
Investigations	-	Haematocrit increased Creatinine renal clearance decreased during initial treatment Dyslipidaemia	Blood creatinine increased during initial treatment Blood urea increased Weight decreased	-	-

†When used with sulfonylurea or insulin.
Source: Dapagliflozin SPC (61); please consult the SPC for further details.
Abbreviations: SPC, Summary of Product Characteristics; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus.

B.2.10.2 Additional studies

DECLARE-TIMI 58 examined the effect of dapagliflozin in patients with type 2 diabetes and included a small sub-group of patients with HFrEF (3.9% of patients) (52). The sub-group

analysis from DECLARE-TIMI 58 is consistent with DAPA-HF (53) and is presented in Appendix L as supporting data.

B.2.11 Ongoing studies

DETERMINE-reduced is an ongoing international, multicentre, parallel-group, randomised, double-blind, placebo-controlled, Phase III study evaluating the effect of dapagliflozin on exercise capacity, HF symptoms and physical limitation in patients with HFrEF. Patient inclusion criteria are broadly the same as in DAPA HF trial (≥18 years of age with symptomatic HFrEF [NYHA functional Class II–IV] present ≥8 weeks, LVEF ≤40%, elevated NT-proBNP levels, eGFR ≥25 mL/min/1.73 m^2, and stable standard care HFrEF treatment ≥4 weeks) with the added requirement of 6-minute walk distance (6MWD) ≥100 metres and ≤425 metres. The primary endpoints are change from baseline in 6MWD, KCCQ-TSS, and KCCQ physical limitation score at Week 16.

DETERMINE-reduced is expected to report in Q4 2020; however, it includes outcomes which have either already been examined in DAPA-HF (KCCQ-TSS) or are unlikely to be relevant to the current decision problem (6-MWD, time spent in light to vigorous physical activity).

B.2.12 Innovation

One in five people over 40 years old will develop HF in their lifetime (1), and patients with HFrEF have historical mortality rates five years post-diagnosis of 54.5% (2). It is anticipated that the burden of HF will rise in future due to a growing and ageing population, and hospital admissions related to HF are projected to rise by 50% over the next 25 years (4). Currently, standard pharmacological therapy for patients with HFrEF consists of either ACEi/ARB and beta-blocker, ACEi/ARB and beta-blocker and MRA, or beta-blocker and sacubitril valsartan ±MRA (with or without MRA, according to patient's tolerance of MRA) (4). However, these treatments can present challenges for patients:

- Dose titration is required with beta-blockers, ACEis/ARBs and MRAs, which delays reaching guideline-recommended doses and achieving potential efficacy benefits. Patients require multiple appointments with their healthcare team to achieve this and up-titration often occurs only in specialist care, with these teams frequently facing capacity issues as identified in interviews with heart failure specialists (36)
- Hypotension can occur with beta-blockers, ACEis/ARBs and MRAs (39, 40), which can result in dose reduction or discontinuation
- Hyperkalaemia can occur with ACEis, and MRAs (39, 40), which again may result in dose reduction or discontinuation

While prescribing rates for these treatments is considered a key performance indicator in the National Heart Failure Audit, many hospitals consequently fall short of these targets (26).

Dapagliflozin is an innovative treatment for HFrEF; while the exact mechanism of action remains unknown, dapagliflozin represents the first treatment for HFrEF in over 20 years with a non-neurohumoral mechanism of action. In addition, dapagliflozin reduces mortality and hospitalisations compared with current standard care and has a favourable safety Company evidence submission template for dapagliflozin for HFrEF.

profile. In addition to its efficacy benefits, dapagliflozin represents innovation in heart failure care through the simplicity in administration, as it does not require dose titration, and can be initiated at the recommended dose with statistically significant benefits observed from day 28 of treatment onwards as shown by the early separation of the KM curves for the primary endpoint, with the HR corresponding to a p-value of <0.05 from day 28 onwards (exploratory analysis) (5). Dapagliflozin is also not associated with hypotension and hyperkalaemia AEs which can limit use of current standard care. Dapagliflozin is available as a single-dose, once-daily treatment, making it easy to initiate and for patients to adhere to.

In particular, the beneficial effect of dapagliflozin is present both in patients receiving treatment with ACEi/ARB and beta-blockers ±MRA (with or without MRA, according to patient's suitability for MRA) and in patients receiving sacubitril valsartan and beta-blockers ±MRA (according to patient's suitability for MRA); the latter group of patients represents those receiving the most extensive range of pharmacological therapies recommended by NICE guidance (Section B.1.3.6). Dapagliflozin consequently offers clinical benefits for patients with HFrEF regardless of their current treatment for HFrEF, indicating that it is an important and innovative treatment which can help ease the burden of HFrEF to the NHS.

The effect of dapagliflozin in HFrEF appears to be independent of the glucose-lowering properties of SGLT2is, as shown by the early separation of the KM curves for the primary endpoint. The exact mechanism of action of dapagliflozin in HFrEF is currently unknown and is therefore likely to be a new and innovative mechanism of action. Mechanisms of action which have been postulated include effects on myocardial metabolism, ion transporters, fibrosis, adipokines, and vascular function (62).

B.2.13 Interpretation of clinical effectiveness and safety evidence

B.2.13.1 Principal findings from the clinical evidence highlighting the clinical benefits and harms of the technology

Dapagliflozin plus standard care significantly reduces worsening of HF in patients with HFrEF compared with placebo plus standard care. In a double-blind RCT (N=4,744) with a median duration of 18.2 months, the HR vs placebo for the primary composite endpoint of CV death, hHF, or urgent HF visit was 0.74 (95% CI 0.65, 0.85; p<0.001). The risk of each of the individual components was also significantly lower with dapagliflozin compared with placebo (hHF HR 0.70 [95% CI 0.59, 0.83]; urgent HF visit HR 0.43 [95% CI 0.20, 0.90]; CV death HR 0.82 [95% CI 0.69, 0.98]), and the efficacy of dapagliflozin was evident from the very early stages of treatment, as shown by the early separation of the KM curves for the primary endpoint, with the HR corresponding to a p-value of <0.05 from day 28 onwards (exploratory analysis) (5). The effect of dapagliflozin was generally consistent across subgroups, including patients receiving or not receiving sacubitril valsartan background therapy.

Dapagliflozin showed a favourable tolerability profile; SAEs were numerically less frequent with dapagliflozin (35.7%) than with placebo (40.2%) and there was no difference in AEs leading to discontinuation between dapagliflozin (4.7%) and placebo (4.9%). AEs of special interest (hypoglycaemia, volume depletion, fractures, and renal AEs) were generally

balanced between treatment groups or less frequent with dapagliflozin than with placebo. While diabetic ketoacidosis occurred only in the dapagliflozin group, it occurred in only 0.1% of patients.

These results demonstrate that dapagliflozin is an effective and well tolerated treatment across the full patient spectrum which can help ease the burden of HFrEF to the NHS. The early efficacy of dapagliflozin, along with its favourable tolerability profile, make it a highly appropriate treatment for early initiation prior to sacubitril valsartan, as well as initiation as an add-on therapy in patients already receiving sacubitril valsartan.

B.2.13.2 Strengths and limitations of the clinical evidence base for the technology

Internal validity

DAPA-HF was a large (N=4,744), Phase III, multinational, double-blind, high quality RCT. Inclusion criteria, outcomes, and comparator were aligned with recent trials in HFrEF (60). Concomitant treatment with current standard care was allowed in both arms in line with local guidelines; dapagliflozin was therefore used in addition to existing therapies and compared against current standard care.

Treatment groups were well balanced at baseline for demographics, disease history, and background therapy. The outcome measures selected were those most relevant to HFrEF, hHF, uHFv and CV death, with a composite of these outcomes as the primary efficacy measure.

External validity

The evidence base for dapagliflozin reflects the expected licensed indication and anticipated use in clinical practice in the UK, adults with HFrEF.

Treatment groups were well balanced at baseline for demographics, disease history, and background therapy and broadly reflective of UK clinical practice. While the Asian population in DAPA-HF was larger (23.3–23.8%) than would be expected in UK clinical practice due to the locations the trial was conducted in, subgroup analyses by race demonstrated a consistent treatment effect for dapagliflozin.

The inclusion criteria for DAPA-HF were generally in line with guidelines for HFrEF in clinical practice in the UK. A LVEF cut-off of ≤40% was used in DAPA-HF, in line with the definitions of HFrEF in NICE NG106 and the ESC clinical guidelines for HF diagnosis and management.

Standard care was provided in both treatment arms in line with NICE guidance, with 83.3%, 96.1% and 71.0% of patients receiving ACEis or ARBs, beta-blockers, or MRAs at baseline, respectively. Sacubitril valsartan was used by 10.7% of patients, reflecting its positioning as a later-line therapy in NICE guidance (43). In comparison, data from the 2017/18 UK National Heart Failure Audit show that ACEi and/or ARB are used by ~85% of patients, beta-blockers by 89% of patients, and MRA by ~55% of patients (26). This demonstrates that patients in DAPA-HF were well-treated, and that dapagliflozin can provide a benefit as an add-on to standard care treatments.
Company evidence submission template for dapagliflozin for HFrEF.

The DAPA-HF population is reflective of the likely population which would be eligible for dapagliflozin in clinical practice. As there may have been some variation between regions in standard care, regional subgroup analyses were conducted which showed a generally consistent trend across regions. In common with other recent submissions in HFrEF (43) the effect size in the European subgroup was slightly less than in the overall population, although there was no indication of interaction (p=0.38). It should be noted that subgroup analyses were not powered to detect statistically significant differences between treatment groups, and geographic location was not identified as a treatment effect modifier in the subgroup analysis.

Dapagliflozin is an SGLT2i which has previously been used as an anti-diabetic medication due to its glucose-lowering properties, and the effect on CV death and hHF of dapagliflozin has been established in patients with diabetes (52). DAPA-HF enrolled patients with (45.1%) and without (54.9%) diabetes (medical history of T2DM or HbA1c ≥ 6.5% at both screening and randomisation), and subgroup analysis of DAPA-HF demonstrated that the effect of dapagliflozin was consistent across both populations.

Dapagliflozin is most likely to be used following optimisation of ACEi/ARB, beta-blocker, ±MRA (according to patient's suitability for MRA), and therefore it is likely that dapagliflozin in some instances will be used as an alternative to sacubitril valsartan in clinical practice. A MAIC was therefore conducted to evaluate the relative efficacy of dapagliflozin versus sacubitril valsartan. The MAIC results demonstrated that there were no statistically significant differences in outcomes between dapagliflozin and sacubitril valsartan, with numerical differences favouring dapagliflozin for the key endpoints that drive cost-effectiveness (CV death and hHF). The results from the MAIC inform the cost-minimisation analysis versus sacubitril valsartan in Section B.3 and the results from the DAPA-HF trial inform the cost-effectiveness analyses of dapagliflozin as add-on therapy to ACEi/ARB, beta-blocker, ±MRA and as add-on therapy to sacubitril valsartan, beta-blocker, ±MRA.

B.2.13.3 End of life

The population of interest in this appraisal face a high 5-year mortality rate of 54.5% and there is evidence to show that dapagliflozin reduces CV mortality and all-cause mortality (2). However, the median survival in the population of interest exceeds 3 years, and therefore end-of-life does not apply to this appraisal.

B.3 Cost-effectiveness

- A Markov model based on KCCQ-TSS quartile health states and data from the DAPA-HF trial was used to evaluate the cost-effectiveness of dapagliflozin for patients with HFrEF
- A cost-minimisation analysis was conducted for base case analysis #1 to compare dapagliflozin versus sacubitril valsartan; this analysis assumed equivalent efficacy based on the results from the MAIC (see Section B.2.9). The results showed dapagliflozin to be dominant over sacubitril valsartan
- In base case analyses #2 and #3, evaluating dapagliflozin as an add-on to standard care and as an add-on to sacubitril valsartan, respectively, dapagliflozin was highly cost-effective versus placebo, with ICERs of £5,830 and £5,866 per QALY, respectively
- Deterministic sensitivity analyses demonstrated that the cost-effectiveness results were robust to changes in model parameters, with all scenarios of base case analysis #1 remaining cost-saving, and all ICERs remaining <£7,500 per QALY (range £4,379–7,311 per QALY) for scenarios of base case analyses #2 and #3
- In probabilistic sensitivity analysis there was a 94.5% probability of dapagliflozin being cost-effective versus placebo at a willingness-to-pay threshold of £20,000 per QALY, and a 96.4% probability of dapagliflozin being cost-effective versus placebo at a willingness-to-pay threshold of £30,000 per QALY
- Dapagliflozin remained cost-effective in scenario analyses which varied key model parameters, with all scenario analyses resulting in ICERs <£7,500 per QALY
- Dapagliflozin is consequently likely to be a highly cost-effective use of NHS resources for the treatment of HFrEF

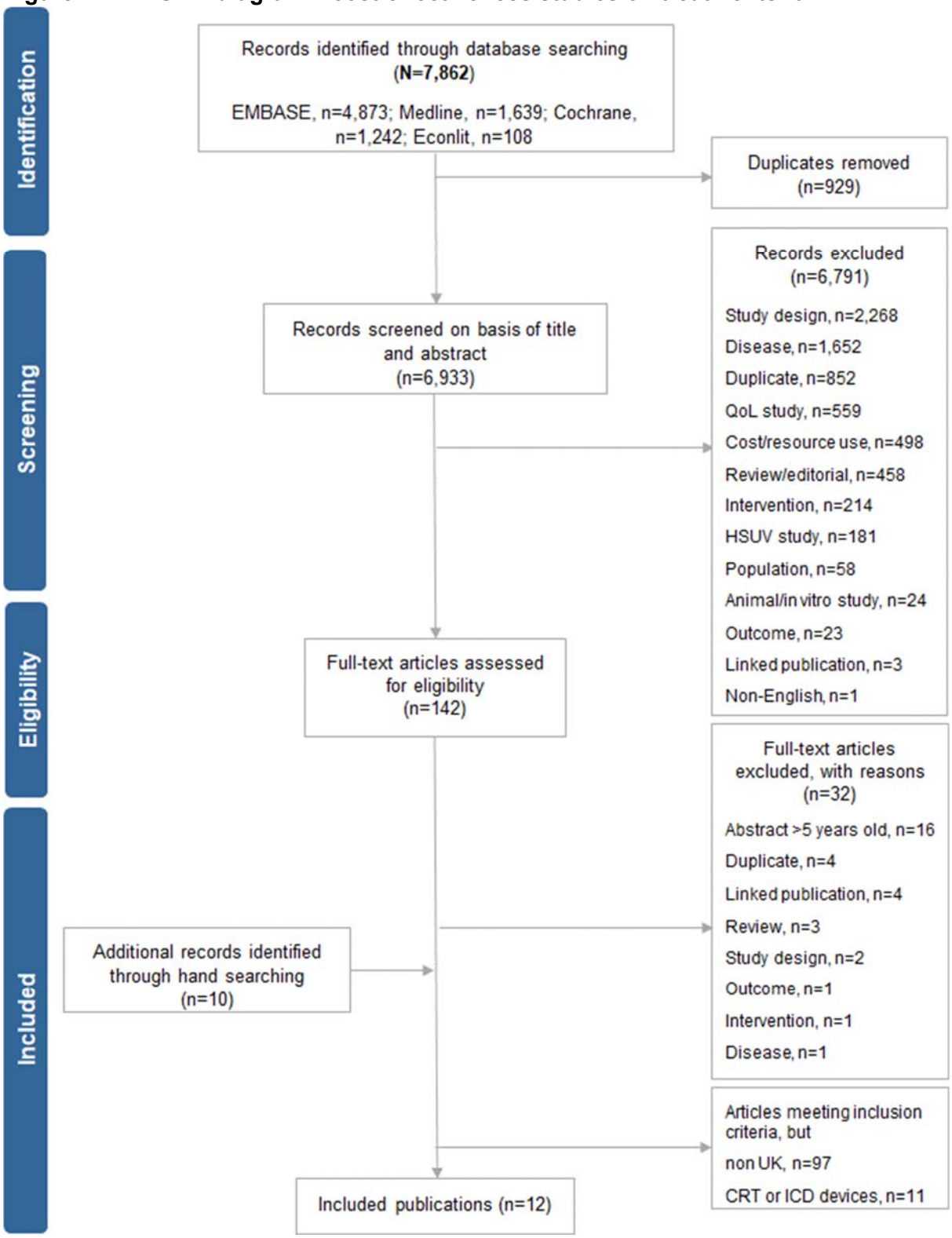
B.3.1 Published cost-effectiveness studies

An SLR was conducted to identify economic evaluations of relevant interventions for the management of HF. The search used to identify cost-effectiveness evidence was also designed to identify studies reporting health state utility values (HSUVs) and cost and resource data. Full details of the SLR methodology are presented in Appendix G. PRISMA flow diagrams detailing studies that were included and excluded at each stage of the SLR are provided in Figure 21.

The prespecified inclusion and exclusion criteria are detailed in Appendix G (Table 71). After completion of the SLR, due to the high number of eligible publications identified, it was deemed appropriate that only publications reporting data relevant to UK clinical practice would undergo data extraction (i.e. drug-based interventions with a UK perspective).

A total of 120 economic evaluations were identified for inclusion in the SLR. Twelve publications (63-74) reporting on drug-based interventions from a UK perspective were extracted into Table 72 (study characteristics) and Table 73 (principal results). Of the 12 publications, 10 were published economic evaluations and two were prior HTA submissions in a HF population.

Figure 21: PRISMA diagram – cost-effectiveness studies on treatments for HFrEF



Abbreviations: CRT, cardiac resynchronisation therapy; HFrEF, heart failure with reduced ejection fraction; HSUV, health state utility value; ICD, Implantable cardioverter defibrillator; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; QoL, quality of life.

B.3.1.1 Summary of the cost-effectiveness studies relevant to UK clinical practice

All 12 drug-based, UK publications utilised a model to estimate the cost-effectiveness of treatments for HF (63-74). The majority of studies (n=9) reported cost/QALY as an outcome (64-67, 69, 70, 72-74). One study reported both cost/QALY and incremental net monetary benefit (63), and a further two reported QALY/life-year (LY) (68, 71) (Table 29).

The majority of the included economic evaluations were published as full texts, however two were abstract-only publications (67, 70) and two were NICE HTA submissions (43, 44). All studies investigated patients with HF, with two studies investigating HF post-MI (66, 69) and another as a comorbidity in patients with type 2 diabetes (67).

Five studies used Markov models to assess cost-effectiveness with a two-state model being the most common structure employed (64, 73, 74); a further study used a five-state model (69) and one used a Markov model but did not report details of model structure (72). Other cost-effectiveness models included: a patient-level, fixed-time increment stochastic simulation model (63), discrete-event simulation models (65, 67), a probabilistic decision model (66), and deterministic and stochastic analyses (68). Details of the model structure were limited in two studies (70, 71).

The majority of studies adopted a UK healthcare payer perspective (n=11) (63-69, 71-74), with one study not reporting the perspective of the analysis (70). The annual discount rate applied to costs and health outcomes ranged from 2% (68) to 6% (68, 71). The majority of studies, however, applied an annual rate of 3.5% to costs and health outcomes (n=8) (63-66, 69, 72-74). Time horizons ranged from 1.3 years (71) to a lifetime (63-67, 72-74). The treatments for HF that were assessed for cost-effectiveness included ACEis (68, 70, 74), ARBs (69, 70, 74), MRAs (65, 66, 75), beta-blockers (71, 72), ivabradine (64, 73), SGLT2is (67), and potassium management (63).

Two studies investigated the cost-effectiveness of sacubitril valsartan (70, 74). The first was the single technology appraisal (STA) submission to NICE (TA388) investigating sacubitril valsartan versus enalapril in adult patients with HFrEF (43). A two-state Markov model was used with the health states of ‘dead’ or ‘alive’. In the base case, the model included all-cause mortality, all-cause-hospitalisation rates, EQ-5D, and AE rates and employed patient-level data from PARADIGM-HF. Individual patients' outcomes were averaged to determine model outcomes. Patients not compliant with ACEi treatment were added to a secondary base case model which compared sacubitril valsartan versus treatment with ARB. In the submission, the base case deterministic ICER for sacubitril valsartan was £18,187 and £16,753 per QALY versus ACEis and ARBs respectively. However, under the advice of the evidence review group (ERG), the appraisal committee agreed that an estimated ICER of £26,000–£30,000 per QALY gained for sacubitril /valsartan compared with ACEi was more appropriate but was still deemed cost-effective.

Trueman et al. (2016) compared the cost-effectiveness of sacubitril valsartan versus enalapril in the PARADIGM-HF population (70), by using data from real-world national datasets to attempt to enhance generalisability to a UK population. A cost-utility model was used based on regression models of all-cause mortality, all-cause hospitalisations, and EQ-

5D from the PARADIGM-HF trial and a method called “raking” was used to employ weights so that selected characteristics (age and gender) of the weighted PARADIGM-HF population matched those of the UK HF population. Weighted analysis showed that sacubitril valsartan was cost-effective with ICERs of £18,142 and £18,436 per QALY versus enalapril using English and Scottish cost data, respectively.

None of the economic evaluations identified by the SLR evaluated the cost-effectiveness of dapagliflozin in patients with HF and therefore were not directly generalisable to the NICE decision problem.

Table 29: Summary list of published cost-effectiveness studies

Study	Year	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
Bakhai (63)	2018	Patient-level, fixed-time increment stochastic simulation model	Patients with HF (73 years)	Total QALYs: • Ongoing RAASi treatment: 3.72 • Control: 3.19 Total LYs • Ongoing RAASi treatment: 6.79 • Control: 5.81	Total costs: • Ongoing RAASi treatment: £5,734[5] • Control: £5,843[3]	• At a WTP threshold of £20,000 per QALY gained: incremental NMB was £10,679[3] • At a WTP threshold of £30,000 per QALY gained: incremental NMB was £15,964[3]
Griffiths (64)	2014	Two-state Markov model	Patients with systolic HF (aligned with SHIfT study (76)): • NYHA functional class II-IV • LVEF ≤35% • Sinus rhythm • Prior hospitalisation for HF within 12 months • Baseline resting heart rate ≥70bpm (Average age NR)	Patients with HR ≥70bpm: Total QALYs: • Ivabradine plus SC: 4.41 • SC alone: 4.23 Total LYs: • Ivabradine plus SC: 6.03 • SC alone: 5.89 Patients with HR ≥75bpm: Total QALYs: • Ivabradine plus SC: 4.27 • SC alone: 3.99 Total LYs: • Ivabradine plus SC: 5.86 SC alone: 5.61	Patients with HR ≥70bpm: Total costs: • Ivabradine plus SC: £11,796 • SC alone: £9,312 Patients with HR ≥75bpm: Total costs: • Ivabradine plus SC: £11,822 • SC alone: £9,446	Patients with HR ≥70bpm: Ivabradine plus SC vs SC alone: • ICER incremental QALY: £13,764 • ICER incremental LYs: £17,875 Patients with HR ≥75bpm: Ivabradine plus SC vs SC alone: • ICER incremental QALY: £8,498 • ICER incremental LYs: £9,363
Lee (65)	2014	Discrete-event simulation	Patients with HF (aligned with EMPHASIS-HF study (77)): • NYHA functional class II • LVEF ≤30% • QRS duration of >130 ms on ECG	Total QALYs: • Eplerenone plus SC: 6.19 • SC alone: 4.98 Total LYs: • Eplerenone: 7.74 • SC alone: 6.23	Total costs: • Eplerenone plus SC: £18,559 • SC alone: £14,275	Eplerenone plus SC vs SC alone: • ICER: £3,520 • Cost per LYG: £2825

[5]Discounted at 3.5% annually. Undiscounted values also reported.

Study	Year	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
			• Recent hospitalisation for a CV reason • Elevated BNP or N-terminal pro-BNP (Mean (SD) age: • Eplerenone: 68.7 (7.7) • SC alone: 68.6 (7.6))			
McKenna (66)	2012	Probabilistic decision analytic model	Patients with post-MI HF (65 years)	Lifetime treatment: Mean QALYs: • Eplerenone: 5.11 • Spironolactone: 4.62 • SC: 4.60 2-year treatment: Mean QALYs: • Eplerenone: 4.85 • Spironolactone: 4.56 • SC: 4.60	Lifetime treatment: Mean costs: • Eplerenone: £8,177 • Spironolactone: £4,446 • SC: £4,130 2-year treatment Mean costs: • Eplerenone: £5,249 • Spironolactone: £4,191 • SC: £4,129	Lifetime treatment: Eplerenone vs SC alone: • ICER: £7,893 • Eplerenone has a lower ICER than Spironolactone 2-year treatment: Eplerenone vs SC alone: • ICER: £4,457
Reifsnider, (67)	2018	Discrete event simulation economic model	Patients with T2DM and HF (Average age NR)	Total QALYs: • Empagliflozin: 0.65 Total LYs: • Empagliflozin: 1.22	NR	Empagliflozin vs SC alone: • ICER: £434 per QALY
Sculpher, (68)	2000	Deterministic and stochastic analyses (Bayesian approach)	Patients with HF (aligned with the ATLAS study (78)): • NYHA functional class II-IV • LVEF ≤30% • No MI, unstable angina or revascularisation procedure in the preceding 2 months	Mean LYs: • High dose lisinopril: 2.98 • Low dose lisinopril: 2.90	Mean cost per patient: • High dose lisinopril: £6,867 • Low dose lisinopril: £7,264	NR

Study	Year	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
			• No symptomatic ventricular tachycardia or unstable congestive HF • No use of various negatively or positively isotropic drugs (Mean (SD) age: • High dose lisinopril: 63.6 (10.5) • Low dose lisinopril: 63.6 (10.3))			
Taylor (69)	2009	Five-state Markov model: • No complication (after first MI) • Post-HF • Post-stroke • Post-subsequent MI • Death	Post MI patients • with left ventricular systolic dysfunction, HF, or both. • Not suitable for treatment with ACEi. (Average age NR)	QALYs: • Valsartan: 5.02 • Placebo: 4.52 LYs: • Valsartan: 5.80 • Placebo: 5.23	Costs: • Valsartan: £8,878 • Placebo: £6,198	Valsartan vs placebo: • Incremental cost per QALY: £5,338 • Incremental cost per LY: £4,672
Trueman (70)	2016	Cost-utility model based on models of regression	Patients with HFrEF (Average age: • CPRD dataset, 75 • SMR dataset, 76)	NR	NR	Sacubitril vValsartan vs Enalapril: • Unweighted analysis: ICERs of £17,939 and £18,348 per QALY using English and Scottish cost data, respectively • Weighted analysis: ICERs of £18,142 and £18,436 per QALY using the CPRD and SMR datasets, respectively

Study	Year	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
Varney (71)	2001	Cost-effectiveness model	Patients with HF (Mean (range) age: • Bisoprolol: 61 (26-80) • Placebo: 61 (22–80))	Discounted LYG: • Bisoprolol: 0.228 under limited benefits scenario† • Bisoprolol: 0.368 under extended benefits scenario‡	NR	Cost-effective ratios for Bisoprolol (result over 5 years): • Extended benefits, shared care§: £1917/LYG • Extended benefits, community care¶: £2043/LYG • Limited benefits, shared care: £2557/LYG Limited benefits, community care: £2761/LYG
Yao (72)	2008	Individual simulation model based on a Markov modelling framework¥	Elderly patients (≥70 years old) with chronic HF: • Documented hospital admission within previous 12 months • LVEF ≤35% within previous 6 months (70 years)	QALYs: • Nebivolol: 5.84 • SC: 5.20 LY: • Nebivolol: 8.38 • SC: 7.55	Costs: • Nebivolol: €9,288 • SC: €6,740	Nebivolol vs SC ICER: • €3,926 per LYG • €3,066 per QALY
NICE TA388 (43)	2016	Two-state Markov model: • Alive • Dead	Patients with chronic HFrEF (aligned with PARADIGM-HF study): • Age ≥18 years • NYHA functional class II-IV • LVEF ≤35% • Plasma BNP ≥150 pg/mL • No history of severe pulmonary disease (63.8 years)	Total QALYs: • Sacubitril valsartan: 4.87 • ACEi: 4.46 • ARB: 4.37	Total costs: • Sacubitril valsartan: £20,734 • ACEi: £13,286 • ARB: £12,281	ICER/QALY, sacubitril valsartan vs • ACEi: £18,187 • ARB: £16,753

Study	Year	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
NICE TA267 (44)	2012	Two-state Markov model: • Alive • Dead	Patients with HF: • LVEF ≤35% • in sinus rhythm • heart rate ≥70bpm (Mean (SD) age: • Ivabradine: 60.7 (11.2) • Placebo: 60.1 (11.5))	NR	NR	Ivabradine vs SC: • Incremental QALY: 0.28 • Incremental cost: £2,376 • ICER: £8,498 per QALY

†Limited benefits scenario assumed no additional benefits from bisoprolol after the end of the trial. ‡Extended benefits scenario assumed benefits would extend on after the trial period. §Shared care by outpatients' clinics and GP. ¶Nurse working in the community. ¥Health states were defined by NYHA class and death.
Abbreviations: ACEi, angiotensin converting enzyme inhibitor; AE, adverse event; AIRE, Acute Infarction Ramipril Efficacy; ARB, angiotensin II receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitor; ATLAS, Assessment of Treatment with Lisinopril and Survival; BNF, British National Formulary; BNP, brain natriuretic peptide; BPM, beats per minute; CPRD, Clinical Practice Research Datalink; CRT, cardiac resynchronisation therapy; CV, cardiovascular; ECG, electrocardiography; EMPHASIS-HF, Eplerenone in Mild Patients Hospitalization and Survival in Heart Failure; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; HTA, health technology assessment; LVEF, left ventricular ejection fraction; LY, life-years; LYG, life-years gained; MI, myocardial infarction; NICE, National Institute for Health and Care Excellence; NR, not reported; NYHA, New York Heart Association; PARADIGM-HF, Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure Trial; QALY, quality-adjusted life year; QOL, quality of life; RAASi, Renin-angiotensin-aldosterone system; SHIfT, Systolic HF Treatment with the If Inhibitor Ivabradine Trial; SC, standard care; T2DM, type 2 diabetes mellitus.

B.3.2 Economic analysis

A de novo economic model was created for this submission, as no previous models were available for the evaluation of the cost-effectiveness of dapagliflozin versus sacubitril valsartan, and of dapagliflozin versus placebo in adult HFrEF patients. The modelling approach adopted by previous models in HF, in particular the model in evaluating sacubitril valsartan as part of TA388, were considered when conceptualising the de novo model. The cost-effectiveness model of dapagliflozin versus placebo as an add-on therapy to standard care has been accepted as an oral presentation as part of the Heart Failure Association Discoveries 2020 program on 15th June 2020 (originally accepted for oral presentation at the European Society of Cardiology – Heart Failure [ESC-HF] 2020 Conference, which has now been cancelled) (79) and, more recently, published in the European Journal of Heart Failure (80).

B.3.2.1 Patient population

In line with the expected licensed indication and the decision problem for the current submission, the cost-effectiveness analysis evaluated adult patients with symptomatic HFrEF. Base case analysis #1 and base case analysis #2 modelled a cohort of patients who are already treated with ACEi or ARB, in combination with beta-blocker, ±MRA (according to patient's suitability for MRA). Base case analysis #3 modelled a cohort of patients who are already treated with sacubitril valsartan, in combination with beta-blocker, ±MRA (according to patient's suitability for MRA).

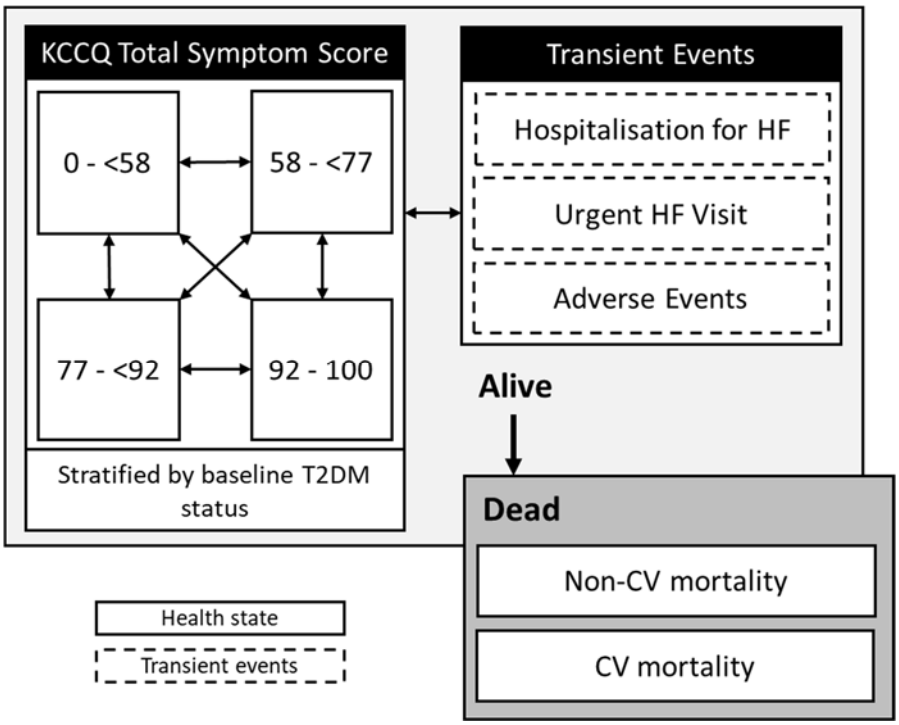
B.3.2.2 Model structure

The dapagliflozin cost-effectiveness model is a Markov state-transition model. Disease progression was modelled through transitions between discrete health states characterised by KCCQ-TSS quartiles (scores of 0–<58, 58–<77, 77–<92, 92–100, where higher scores represent better health status), with health state-specific costs and utility values. These health states were further stratified by the presence of T2DM. Additionally, the model captured the incidence of first and recurrent hHF and urgent heart failure visit (uHFv) as transient events. Patient mortality (i.e. transition to the absorbing dead state) was modelled through the application of parametric survival equations describing CV mortality and all-cause mortality.

At each cycle transition, the proportion of patients who die from CV mortality was estimated, but without removing the patients from the alive health states, in order to calculate the costs associated with CV mortality. Subsequently, the proportion of patients who die from all-cause mortality was calculated to remove these patients from the alive health states to the dead health state. The difference between the all-cause mortality rate and the CV mortality rate represented the non-CV mortality rate. The transition probability matrix for transitions between the different KCCQ-TSS quartiles was then applied to the remaining number of patients in the alive health states, to calculate the health state distribution in the next cycle.

Patients had a per cycle probability of discontinuing treatment with dapagliflozin due to tolerability or other reasons. Patients discontinuing treatment with dapagliflozin experienced the same event rates as patients receiving placebo.

Figure 22: Markov state-transition model structure, health states, and possible transitions



Abbreviations: CV, cardiovascular; HF, heart failure; KCCQ, Kansas City Cardiomyopathy Questionnaire; T2DM, type 2 diabetes mellitus.

The implementation of a Markov state-transition model was appropriate as the heterogeneity between HFrEF patients and important disease characteristics can be captured by a tractable number of mutually exclusive and exhaustive health states, and therefore it was considered unnecessary to conduct a patient level analysis. Additionally, Markov models have the advantage of being simpler and consequently have more manageable runtimes in comparison to individual patient level models. There is historical precedent for modelling HF progression in a Markov framework (43, 44), as HF patients can be appropriately described by a small set of health states.

KCCQ-TSS is an extensively validated and established self-administered instrument for quantifying HF-related symptoms, function, and quality of life in patients with HF. The KCCQ-TSS is a specifically designed patient-reported measure of HF health status, reflective of patient utility, and therefore KCCQ-TSS quartiles are appropriate for defining health states in the cost-effectiveness model. Stratification of patients by baseline KCCQ-TSS score shows KCCQ-TSS to be prognostic for the primary endpoint of DAPA-HF, where patients with lower baseline KCCQ-TSS (worse health status) experienced higher rates of CV death or worsening HF (25.0%, 17.3%, and 13.6% of patients in the dapagliflozin and placebo trial arms with KCCQ-TSS tertiles of ≤65.6, 65.7–87.5, and >87.5 experienced worsening HF, respectively; P<0.001) (35). The inclusion of KCCQ-TSS health states in the cohort Markov model is an improvement to the 2-state Markov modelling approach previously used in NICE appraisals for HFrEF (TA267, TA388), as the KCCQ-TSS health states enable the impact of disease severity to be captured in the health state utility values and in the risk of events, and therefore allow the impact of disease severity to be more accurately modelled.

Heart failure is a chronic and progressive disease associated with increased risk of mortality. As such, the model incorporated a lifetime horizon in line with technology assessment guidelines (81, 82). Consistent with population life tables, it was assumed that all patients died upon reaching 100

years old. The cycle length was 1 month, and a half-cycle correction was applied, in line with previous cost-effectiveness analyses in adult HFrEF patients.

Table 30: Features of the economic analysis

Factor	Previous appraisals		Current appraisal	
	TA267 (ivabradine)	TA388 (sacubitril valsartan)	Chosen values	Justification
Model structure	2-state cohort Markov model	Individual patient simulation model and 2-state cohort Markov model	Cohort Markov model, with health states by KCCQ-TSS quartiles	The KCCQ-TSS health states enable disease severity to be a covariate in the survival/risk/utility equations, allowing the impact of disease severity to be more accurately modelled compared to a 2-state model. Cohort Markov models sufficiently capture the heterogeneity between HFrEF patients and additionally have the advantage of having quicker runtimes in comparison to individual patient level models (issue discussed in TA388).
Time horizon	Lifetime	Lifetime	Lifetime	Heart failure is a chronic disease, for which treatments have an impact on costs and outcomes over a patient's lifetime
Treatment waning effect?	No	No	No	No treatment waning effect was identified in the DAPA-HF trial and no treatment waning was modelled in previous appraisals of interventions for the treatment of HF
Source of utilities	SHIFT trial	Baseline utility: Berg et al. 2015(83) Disutilities and disease progression: PARADIGM-HF	DAPA-HF trial	As per NICE Methods Guide

Factor	Previous appraisals		Current appraisal	
	TA267 (ivabradine)	TA388 (sacubitril valsartan)	Chosen values	Justification
Source of costs	Costs related to NHS and PSS resources were valued using prices relevant to the NHS and PSS; other cost inputs were sourced from the literature	Costs related to NHS and PSS resources were valued using prices relevant to the NHS and PSS; other cost inputs were sourced from the literature	Costs related to NHS and PSS resources were valued using prices relevant to the NHS and PSS; other cost inputs were informed by systematic and targeted literature reviews	As per NICE Methods Guide
Discounting	3.5% per annum for costs, QALYs and life years	3.5% per annum for costs, QALYs and life years	3.5% per annum for costs, QALYs and life years	As per NICE Methods Guide
Perspective on outcomes	All direct health effects	All direct health effects	All direct health effects	As per NICE Methods Guide
Perspective on costs	NHS and PSS	NHS and PSS	NHS and PSS	As per NICE Methods Guide

Abbreviations: KCCQ-TSS, Kansas City Cardiomyopathy Questionnaire – total symptom score; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; PSS, personal social services; QALY, quality-adjusted life year.

B.3.2.3 Intervention technology and comparators

This submission covers the use of dapagliflozin in adults with symptomatic HFrEF, in line with the marketing authorisation and decision problem.

In line with the proposed positioning for dapagliflozin in the HF treatment pathway, as described in Section B.1.3.8, base case analysis #1 is a cost-minimisation analysis of dapagliflozin versus sacubitril valsartan in patients who are already treated with ACEi or ARB, in combination with beta-blocker, ±MRA. This analysis assumes dapagliflozin and sacubitril valsartan to have equal efficacy and equal event rates, based on the results of the MAIC which showed that there was not statistically significant difference in efficacy for key clinical outcomes (see Section B.2.9). Base case analysis #2 evaluates the cost-effectiveness of dapagliflozin versus placebo as an add-on therapy in patients who are already treated with ACEi or ARB, in combination with beta-blocker, ±MRA. Base case analysis #3 evaluates the cost-effectiveness of dapagliflozin versus placebo as an add-on therapy in patients who are already treated with sacubitril valsartan, in combination with beta-blocker, ±MRA.

For completeness, a scenario analysis was conducted to show the overall cost-effectiveness of dapagliflozin when used as an add-on therapy in the DAPA-HF cohort treated with different combinations of background therapies, including the use of ACEi/ARB, beta-blocker, MRA, sacubitril valsartan, ivabradine, hydralazine and digoxin (Scenarios #6 and #7, Section B.3.8.3).

B.3.3 Clinical parameters and variables

B.3.3.1 Incorporation of clinical data into the model

Results from the DAPA-HF trial and statistical analyses of data from the DAPA-HF trial were incorporated into the dapagliflozin cost-effectiveness model relating to: patient baseline characteristics, KCCQ-TSS quartile health state transition probabilities, time-variant transition probabilities for death, incidence of hHF and uHFv, incidence of AEs and incidence of treatment discontinuation. Additionally, health state utility values were also derived directly from the DAPA-HF trial (see Section B.3.4.1).

The treatment effect of dapagliflozin was incorporated into the cost-effectiveness model as coefficients for the survival equations and risk equations for all-cause mortality, CV mortality, hHF and uHFv. Additionally, the statistically significant treatment effect with respect to change in KCCQ-TSS from baseline in DAPA-HF was incorporated in the cost-effectiveness model as treatment-specific KCCQ-TSS quartile transition probabilities.

B.3.3.1.1 Baseline characteristics

For base case analysis #1, the baseline characteristics were derived from the DAPA-HF cohort weighted to match PARADIGM-HF in the MAIC (see Section B.2.9.2.1). These baseline characteristics were selected for base case analysis #1 as the efficacy results from the MAIC informing this cost-minimisation analysis were generated for a population of patients matched to correspond to patients in the PARADIGM-HF trial. For base case analysis #2, the baseline characteristics were taken from the subgroup of patients who were not treated with sacubitril valsartan at baseline in DAPA-HF (Table 31). These baseline characteristics were selected for base case analysis #2 to reflect the patient population of interest, i.e. patients who are already treated with ACEi or ARB, in combination with beta-blocker, ±MRA. For base case analysis #3, the baseline characteristics were taken from the subgroup of patients treated with sacubitril valsartan at baseline in DAPA-HF (Table 31). These baseline characteristics were selected for base case analysis #3 to reflect the patient population of interest, i.e. patients who are already treated with ACEi or ARB, in combination with beta-blocker, ±MRA. The patient baseline characteristics determined the cohort's initial distribution across the alive health states and influenced the rates of all-cause mortality, CV mortality, and hHF estimated by the covariate-adjusted survival equations and covariate-adjusted risk equations.

Table 31: Patient baseline characteristics (base case)

Characteristic	PARADIGM-HF matched population (base case analysis #1)		ACEi/ARB, beta-blocker, ±MRA subgroup† (base case analysis #2)		Sacubitril valsartan, beta-blocker, ±MRA subgroup‡ (base case analysis #3)	
	Mean	SE	Mean	SE	Mean	SE
Age (years)	63.80	0.12	66.32	0.16	66.66	0.61
Female	0.22	0.01	0.240	0.01	0.190	0.02
BMI (kg/m2)	28.15	0.12	28.02	0.09	29.850	0.35
KCCQ-TSS Q1: 0-<58	0.23	0.01	0.230	0.01	0.270	0.02
KCCQ-TSS Q2: 58-<77	0.25	0.01	0.250	0.01	0.240	0.02
KCCQ-TSS Q3: 77-<92	0.28	0.01	0.280	0.01	0.250	0.02
KCCQ-TSS Q4: 92-100	0.24	0.01	0.240	0.01	0.240	0.02
NT-proBNP (pg/mL)	2342.53	43.52	2345.94	43.94	2298.05	212.23
Ischaemic HF	0.60	0.01	0.57	0.01	0.500	0.03
Duration of HF >2 years	0.62	0.01	0.61	0.01	0.730	0.02
Prior hHF	0.63	0.01	0.48	0.01	0.400	0.03
LVEF	0.30	0.12	0.31	0.00	0.285	0.00
Creatinine (µmol/L)	99.89	0.29	104.07	0.46	109.33	1.64
T2DM	0.35	0.01	0.45	0.01	0.44	0.03

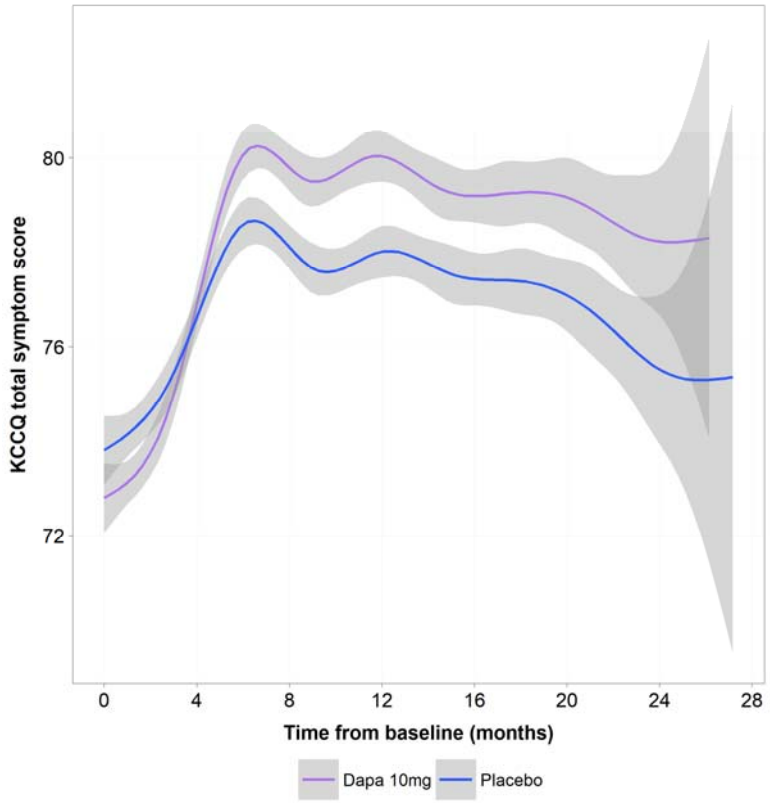
† Subgroup defined as patients who are not treated with sacubitril valsartan at baseline
‡ subgroup defined as patients who are treated with sacubitril valsartan at baseline
Abbreviations: BMI, body mass index, HF, heart failure; hHF, hospitalisation for heart failure; ITT, intention to treat; KCCQ; Kansas City Cardiomyopathy Questionnaire; LVEF, left ventricular ejection fraction; Q, quartile; SE, standard error; T2DM, type 2 diabetes mellitus; TSS, Total Symptom Score.

B.3.3.1.2 Health state transitions

Transition probabilities between health states defined by KCCQ-TSS quartiles were derived using monthly transition count data assuming last observation carried forward (i.e. patients were assumed to remain in a KCCQ-TSS quartile until an observation indicating that they had moved). Independent transition matrices were derived based on the first four months of the DAPA-HF trial, after which an inflection point was observed, and a second transition matrix was applied for months five onwards (Figure 23). Transition counts have a multinomial likelihood, which was combined with a flat Dirichlet prior distribution using Gibbs sampling to obtain the posterior probability distribution of the KCCQ-TSS transition matrix (84).

A statistically significant treatment effect was observed with respect to change in KCCQ-TSS from baseline in DAPA-HF (win ratio at 8 months: 1.18, 95% confidence interval: 1.11 to 1.26), and as such, treatment specific transition matrices were derived from DAPA-HF clinical trial data.

Figure 23: Mean KCCQ-TSS over time in DAPA-HF, stratified by treatment arm



Abbreviations: KCCQ-TSS, Kansas City Cardiomyopathy Questionnaire – total symptom score.

The monthly probably of transition between health states defined by KCCQ-TSS quartiles is shown in Table 32. In base case analysis #1, the treatment effect of sacubitril valsartan was assumed to be the same as dapagliflozin. Therefore, in line with this assumption, the dapagliflozin plus standard care transition probabilities were also used for the sacubitril valsartan arm in base case analysis #1.

Table 32: Monthly KCCQ-TSS transition matrix

KCCQ-TSS quartile transitions [From, To]	Dapagliflozin† + SC				Placebo + SC			
	Month 0–4		Month 5+		Month 0–4		Month 5+	
	Mean	SE	Mean	SE	Mean	SE	Mean	SE
KCCQ[1,1]	0.86240	0.00015	0.94360	0.00007	0.88180	0.00015	0.94140	0.00007
KCCQ[1,2]	0.08042	0.00012	0.03682	0.00006	0.07071	0.00012	0.03876	0.00006
KCCQ[1,3]	0.03679	0.00008	0.01409	0.00004	0.03164	0.00008	0.01212	0.00003
KCCQ[1,4]	0.02043	0.00006	0.00551	0.00002	0.01582	0.00006	0.00776	0.00003
KCCQ[2,1]	0.03126	0.00007	0.02629	0.00004	0.03870	0.00008	0.03220	0.00005
KCCQ[2,2]	0.85790	0.00015	0.92200	0.00007	0.85300	0.00015	0.91550	0.00007
KCCQ[2,3]	0.07122	0.00011	0.03781	0.00005	0.06635	0.00010	0.03708	0.00005
KCCQ[2,4]	0.03959	0.00008	0.01392	0.00003	0.04194	0.00008	0.01519	0.00003
KCCQ[3,1]	0.00903	0.00004	0.00820	0.00002	0.01665	0.00006	0.00747	0.00002
KCCQ[3,2]	0.03829	0.00008	0.02750	0.00004	0.04910	0.00009	0.03459	0.00004
KCCQ[3,3]	0.86130	0.00015	0.92090	0.00006	0.85680	0.00015	0.91960	0.00006
KCCQ[3,4]	0.09133	0.00012	0.04339	0.00005	0.07747	0.00012	0.03833	0.00005
KCCQ[4,1]	0.00713	0.00004	0.00259	0.00001	0.00513	0.00003	0.00426	0.00002
KCCQ[4,2]	0.01519	0.00005	0.01024	0.00002	0.01676	0.00006	0.01359	0.00003
KCCQ[4,3]	0.04547	0.00009	0.03300	0.00004	0.05305	0.00010	0.03852	0.00004
KCCQ[4,4]	0.93220	0.00011	0.95420	0.00004	0.92510	0.00012	0.94360	0.00005

† In base case analysis #1, the same transition probabilities are applied to the dapagliflozin + SC arm and the sacubitril valsartan + SC arm.
Abbreviations: KCCQ, Kansas City Cardiomyopathy Questionnaire; SE, standard error; SC, standard care; TTS, total symptom score.

B.3.3.1.3 CV mortality and all-cause mortality

CV mortality and all-cause mortality were modelled based on methods advocated by NICE for the analysis of survival data alongside clinical trials (85, 86) and the survival equation fitting and selection was carried out in line with published guidelines (86-88). The Weibull, log-logistic, log-normal, and Gompertz distributions were explored. More flexible parametric forms such as generalised gamma and generalised F distributions were not considered, in order to reduce the risk of overfitting within trial data. The exponential distribution was not considered for patient mortality as it would not capture increasing risk of mortality over time.

Pre-defined subgroups of DAPA-HF were selected as candidate covariables and tested in univariable analysis to identify covariables that were likely to be predictive of CV mortality and all-cause mortality in the ITT population. Multivariable analysis was then carried out using all covariables to assess which covariables were still influential after multivariable adjustment, the effect size of each covariable, and the clinical face validity of the directionality of the effects. Following these assessments, stepwise backward elimination based on Akaike information criterion (AIC) and p-values was used to remove covariables from the fully-adjusted model that did not improve model fit.

The survival curves based on the Weibull distribution had the most plausible estimates of long-term survival based on clinical expert opinion and when compared with previously published estimates (89), and these curves were therefore used in the base case (Figure 24 and Figure 25). The parameters for these survival equations are shown in Table 33 for the overall DAPA-HF trial population. Survival curves based on the Gompertz, lognormal, and log-logistic distributions were also evaluated (Table 34): clinical expert opinion suggested that predictions made using the Gompertz equations were likely to underestimate patient survival, and conversely, lognormal and log-logistic distributions were likely to overestimate patient survival (Figure 26 and Figure 27). The AIC and Bayesian information criterion (BIC) for the survival curves evaluated also supported the use of the Weibull distribution as the distributions with the best goodness of fit for CV mortality, and the Weibull distribution as a distribution with one of the best goodness of fit for all-cause mortality (Table 35).

The impact of applying the Gompertz, log-logistic, and log-normal survival curve distributions in the cost-effectiveness model was tested in scenario analyses (see Section B.3.8.3).

There was no statistically significant interaction between treatment effect and baseline therapy (see Section B.2.7), and therefore baseline therapy was not a variable in the parametric survival equations for CV mortality and all-cause mortality. To maximise use of available data, the survival equations used in the base cases of the economic analysis were derived from data from the DAPA-HF ITT population. To test the sensitivity of the model to the numerical differences in the treatment effect in patient subgroups with different background therapies, unadjusted survival equations were derived from patient subgroup with different background therapies and applied to the cost-effectiveness model in scenario analyses (see Section B.3.8.3).

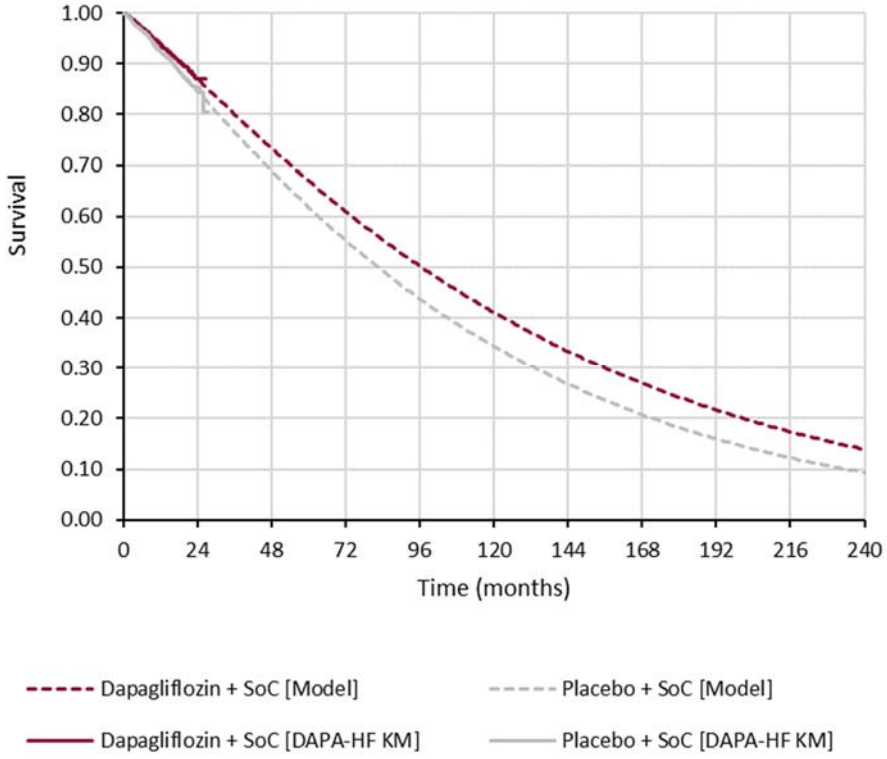
Prior hHF was also tested as a candidate covariable for the all-cause mortality and CV mortality survival equations. However, prior hHF was not an independent predictor of mortality, and therefore this candidate covariable was not included in the final survival equations.

Table 33: Parameterisations of adjusted all-cause and CV mortality parametric (Weibull) survival equations (base case)

Parameter	CV mortality			All-cause mortality		
	Coefficient	SE	p-value	Coefficient	SE	p-value
Shape	1.222	0.052	<0.001	1.245	0.048	<0.001
Scale	209901.536	89817.275	0.019	139304.051	51809.337	0.007
Dapagliflozin	0.144	0.077	0.060	0.133	0.068	0.051
Female	0.381	0.103	<0.001	0.383	0.091	<0.001
LVEF (centred)	0.017	0.005	0.002	-	-	-
NT-proBNP (log)	-0.571	0.047	<0.001	-0.545	0.041	<0.001
Type 2 diabetes	-0.208	0.077	0.007	-0.175	0.068	0.010
Ischaemic HF	-0.235	0.081	0.004	-0.217	0.072	0.002
KCCQ: 58–77	0.460	0.100	<0.001	0.436	0.089	<0.001
KCCQ: 77–92	0.809	0.110	<0.001	0.790	0.097	<0.001
KCCQ: >92	0.880	0.115	<0.001	0.902	0.104	<0.001
HF >2 years	-0.289	0.086	<0.001	-0.303	0.076	<0.001

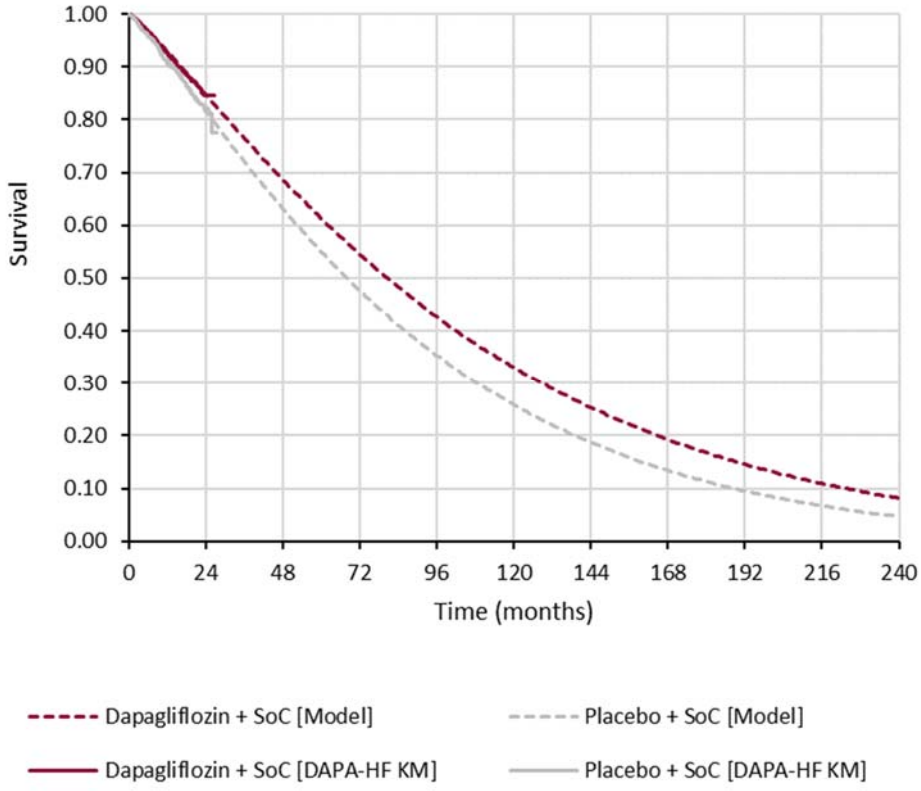
Abbreviations: ACM, all-cause mortality; CV, cardiovascular; HF, heart failure; KCCQ, Kansas City Cardiomyopathy Questionnaire; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-brain natriuretic peptide; SE, standard error; T2DM, type 2 diabetes mellitus.

Figure 24: Kaplan-Meier curve from DAPA-HF and Weibull survival curve for CV mortality



Abbreviations: CV, cardiovascular; KM, Kaplan Meier; SC, standard care.

Figure 25: Kaplan-Meier curve from DAPA-HF and Weibull survival curve for all-cause mortality



Abbreviations: CV, cardiovascular; KM, Kaplan Meier; SC, standard care.

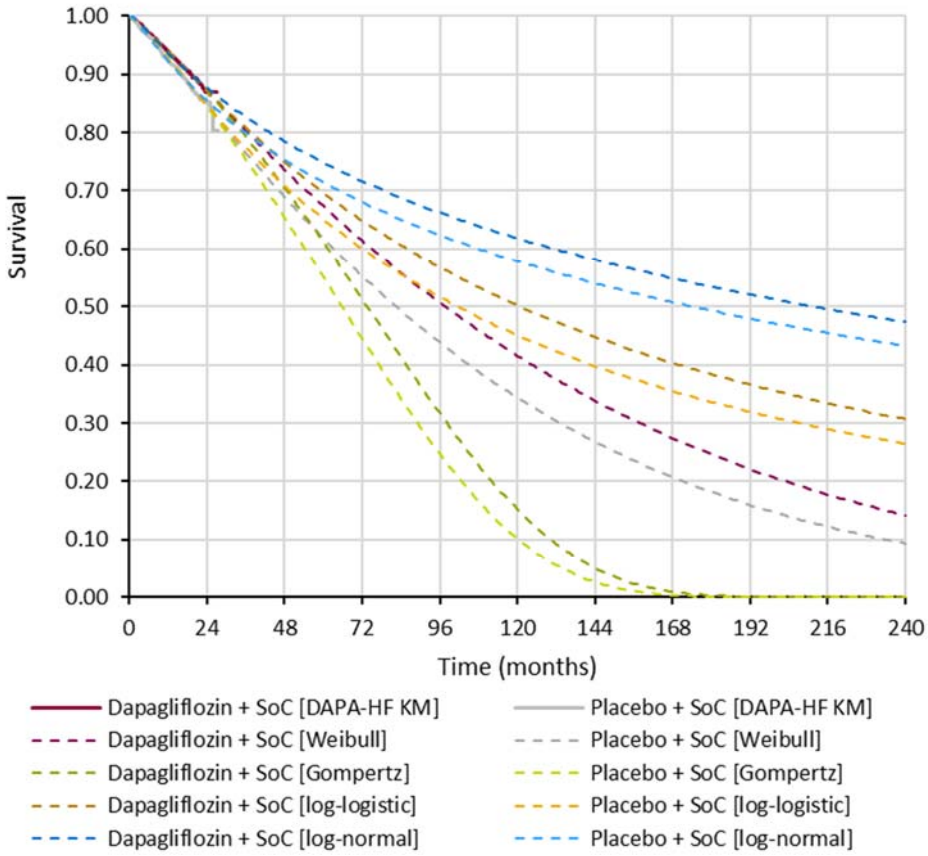
Table 34: Parameterisations of adjusted all-cause and CV mortality parametric (Gompertz, log-logistic, log-normal) survival equations (scenario analyses)

Parameter	CV mortality			All-cause mortality		
	Coefficient	SE	p-value	Coefficient	SE	p-value
Gompertz (scenario #1, see Section B.3.8.3)						
Shape	9.061E-04	2.370E-04	<0.001	0.001	2.146E-04	<0.001
Scale	9.798E-07	4.308E-07	0.023	1.393E-06	5.505E-07	0.011
Dapagliflozin	-0.180	0.093	0.054	-0.164	0.08	0.053
Female	-0.465	0.124	<0.001	-0.473	0.11	<0.001
LVEF (centred)	-0.021	0.007	0.002	-	-	-
NT-proBNP (log)	0.695	0.050	<0.001	0.677	0.04	<0.001
Type 2 diabetes	0.256	0.093	0.006	0.218	0.08	0.010
Ischaemic HF	0.285	0.098	0.004	0.270	0.09	0.002
KCCQ: 58-77	-0.557	0.121	<0.001	-0.539	0.11	<0.001
KCCQ: 77-92	-0.977	0.129	<0.001	-0.973	0.12	<0.001
KCCQ: >92	-1.058	0.136	<0.001	-1.101	0.12	<0.001
HF > 2 years	0.354	0.103	<0.001	0.377	0.09	<0.001
Log-logistic (scenario #2, see Section B.3.8.3)						
Shape	1.307	0.055	<0.001	1.345	0.051	<0.001

Parameter	CV mortality			All-cause mortality		
	Coefficient	SE	p-value	Coefficient	SE	p-value
Scale	207588.013	89968.930	0.021	143414.256	54459.256	0.008
Dapagliflozin	0.174	0.079	0.027	0.153	0.071	0.030
Female	0.390	0.104	<0.001	0.393	0.092	<0.001
LVEF (centred)	0.018	0.006	0.002	-	-	-
NT-proBNP (log)	-0.599	0.049	<0.001	-0.580	0.043	<0.001
Type 2 diabetes	-0.201	0.079	0.011	-0.170	0.071	0.016
Ischaemic HF	-0.238	0.083	0.004	-0.223	0.074	0.002
KCCQ: 58-77	0.494	0.105	<0.001	0.474	0.093	<0.001
KCCQ: 77-92	0.842	0.112	<0.001	0.830	0.099	<0.001
KCCQ: >92	0.912	0.116	<0.001	0.934	0.105	<0.001
HF > 2 years	-0.281	0.087	0.001	-0.296	0.078	<0.001
Log-normal (scenario #3, see Section B.1.1.1.1)						
Mean log	13.022	0.480	<0.001	12.540	0.418	<0.001
SD log	1.662	0.063	<0.001	1.577	0.054	<0.001
Dapagliflozin	0.231	0.088	0.008	0.204	0.078	0.009
Female	0.399	0.112	<0.001	0.393	0.099	<0.001
LVEF (centred)	0.020	0.006	0.002	-	-	-
NT-proBNP (log)	-0.654	0.054	<0.001	-0.630	0.048	<0.001
Type 2 diabetes	-0.223	0.088	0.011	-0.187	0.078	0.017
Ischaemic HF	-0.263	0.091	0.004	-0.242	0.081	0.003
KCCQ: 58-77	0.586	0.120	<0.001	0.558	0.107	<0.001
KCCQ: 77-92	0.912	0.123	<0.001	0.892	0.109	<0.001
KCCQ: >92	0.978	0.126	<0.001	0.989	0.113	<0.001
HF > 2 years	-0.310	0.095	0.001	-0.324	0.084	<0.001

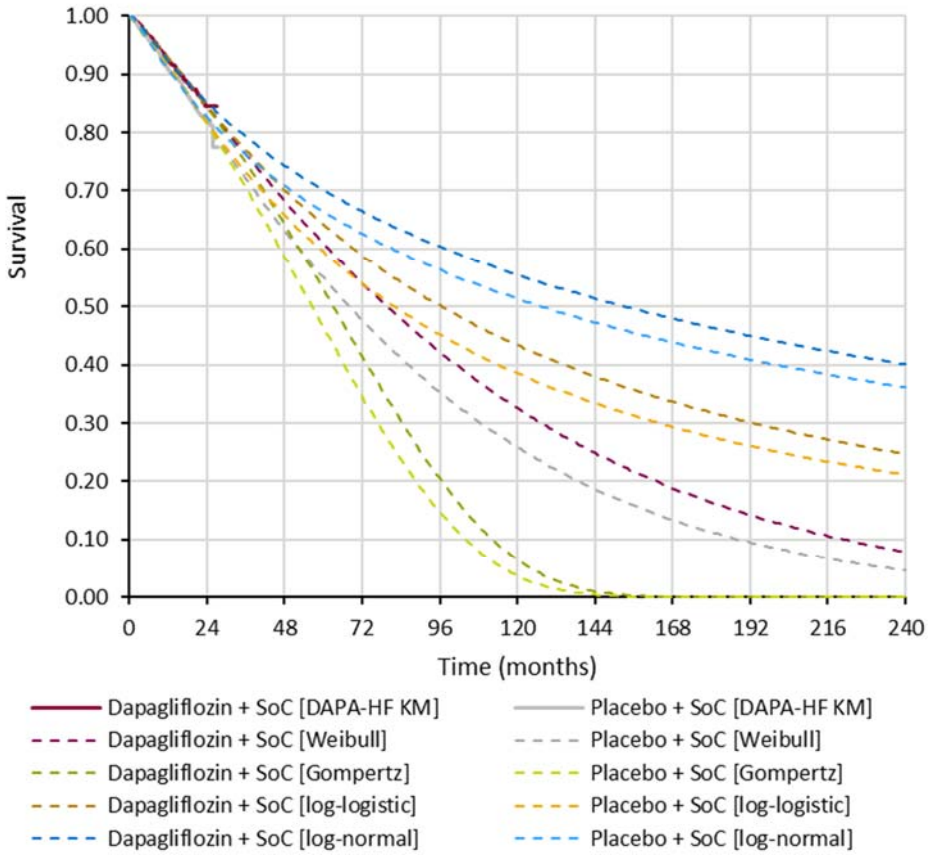
Abbreviations: CV, cardiovascular; HF, heart failure; KCCQ, Kansas City Cardiomyopathy Questionnaire; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-brain natriuretic peptide; SE, standard error; T2DM, type 2 diabetes mellitus.

Figure 26: Alternative CV mortality survival curves (scenario analyses)



Abbreviations: CV, cardiovascular; KM, Kaplan Meier; SC, standard care.

Figure 27: Alternative all-cause mortality survival curves (scenario analyses)



Abbreviations: KM, Kaplan Meier; SC, standard care.

Table 35: Survival curve goodness of fit

Distribution	CV mortality		All-cause mortality	
	AIC	BIC	AIC	BIC
Weibull	8558	8669	10196	10297
Gompertz	8565	8676	10206	10309
Log-logistic	8558	8670	10193	10296
Log-normal	8585	8697	10224	10327

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; CV, cardiovascular.

B.3.3.1.3.1 Non-CV mortality

There was no increase in non-CV mortality with increasing age in DAPA-HF. Therefore, UK life tables were used to inform the non-CV mortality in each model cycle where the non-CV mortality rate estimated from the CV mortality and all-cause mortality survival curves was lower than the non-CV mortality rate from the UK life tables. The UK life tables are displayed in Appendix O.

A scenario analysis was carried out using the CV mortality and all-cause mortality survival curves from DAPA-HF only, without applying the non-CV mortality rate from UK life tables (see Section B.3.8.3).

B.3.3.1.4 hHF and uHFv event incidence

The incidence of hHF and uHFv events were modelled using generalised estimating equations assuming that events are Poisson-distributed in order to capture first and recurrent hHF and uHFv events.

Pre-defined subgroups of DAPA-HF were selected as candidate covariables and tested in univariable analysis to identify covariables that were likely to be predictive of hHF and uHFv. Multivariable analysis was then carried out using all covariables to assess which covariables were still influential after multivariable adjustment, the effect size of each covariable, and the clinical face validity of the directionality of the effects. Following these assessments, stepwise backward elimination based on QIC and p-values was used to remove covariables from the fully-adjusted model that did not improve model fit.

There was no statistically significant interaction between treatment effect and baseline therapy (see Section B.2.7), and therefore baseline therapy was not a variable in the generalised estimating equation for hHF. To maximise use of available data, the generalised estimating equation used in the base cases of the economic analysis were derived from data from the DAPA-HF ITT population. To test the sensitivity of the model to the numerical differences in the treatment effect in patient subgroups with different background therapies, unadjusted generalised estimating equation were derived from patient subgroup with different background therapies and applied to the cost-effectiveness model in scenario analyses (see Section B.3.8.3).

The parameters of the fitted generalised estimating equations for predicting hHF are shown in Table 36.

Only 39 uHFv events were observed within DAPA-HF and therefore the incidence of uHFv events was assumed to be constant for all patients and not adjusted by covariates (Table 37).

Table 36: Adjusted generalised estimating equations predicting hHF events

Covariate	Coefficient	SE	p-value
Intercept	-9.321	0.366	<0.001
Dapagliflozin	-0.309	0.074	<0.001
KCCQ: 58–77	-0.488	0.096	<0.001
KCCQ: 77–92	-0.682	0.098	<0.001
KCCQ: >92	-1.101	0.113	<0.001
LVEF (centred)	-0.029	0.005	<0.001
NT-proBNP (log)	0.590	0.043	<0.001
Prior hHF	0.435	0.075	<0.001
Type 2 diabetes	0.387	0.076	<0.001
BMI (kg/m^2) (centred)	0.020	0.006	0.001
Creatinine (µmol/L) (centred)	0.005	0.001	<0.001
HF >2 years	0.438	0.084	<0.001
Time since baseline (days)	0.0004	0.0002	0.041

Abbreviations: BMI, body mass index; HF, heart failure; hHF, hospitalisation for heart failure; KCCQ, Kansas City Cardiomyopathy Questionnaire; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-brain natriuretic peptide; T2DM, type 2 diabetes mellitus.

Table 37: Unadjusted generalised estimating equations predicting uHFv events

Covariate	Coefficient	SE	p-value
Intercept	-7.280	0.225	<0.001
Dapagliflozin	-1.075	0.388	0.006

Abbreviations: SE, standard error; uHFv, urgent heart failure visit.

B.3.3.1.5 Adverse events

The modelled rates of adverse events were informed by the most common serious AEs reported in the DAPA-HF trial (Table 38). Genital infection and urinary tract infection (UTI) occurrences were not routinely collected in the DAPA-HF trial, as genital infections and UTIs were not an AE of special interest, given the availability of data on these AEs from the use of dapagliflozin in other indications. The incidences of genital infection and UTI were nevertheless included in the cost-effectiveness model, based on the incidences observed in the dapagliflozin and placebo arms of the cardiovascular outcomes trial of dapagliflozin in T2DM patients (DECLARE) (52).

Patients who discontinued treatment with dapagliflozin were subject to the risk of adverse events associated with the placebo arm of DAPA-HF.

Table 38: Annual probability of adverse events

Adverse events	Dapagliflozin + SC		Placebo + SC	
	Mean	SE	Mean	SE
Volume depletion	0.050	0.009	0.045	0.008
Renal events	0.041	0.008	0.047	0.009
Hypoglycaemic events	0.001	0.001	0.001	0.001
Fractures	0.014	0.005	0.014	0.005
Diabetic ketoacidosis	0.001	0.001	0.000	0.000
Amputation	0.003	0.002	0.003	0.002
Genital infections	0.009	0.001	0.001	0.000
UTI	0.016	0.002	0.015	0.002

Source: DAPA-HF (all AEs except genital infection), DECLARE (genital infections)
Abbreviations: SE, standard error; SC, standard care; UTI, urinary tract infection.

B.3.3.1.6 Treatment discontinuation

The modelled rate of treatment discontinuation was derived from the DAPA-HF clinical trial, with a constant rate of discontinuation applied to all patients receiving treatment with dapagliflozin in each modelled cycle. Following discontinuation of dapagliflozin, patients were modelled as per placebo-treated patients i.e. discontinued patients were subject to the same event risks, costs, and utility decrements as patients in the control arm. The default annual probability of treatment discontinuation was 0.07 (standard error: 0.01).

B.3.3.2 Input from clinical experts

Clinicians at a UK clinical advisory board agreed that the DAPA-HF trial was largely representative of UK clinical practice, with the exception that patients in the UK are likely to be older than patients recruited to DAPA-HF (42).

B.3.4 Measurement and valuation of health effects

B.3.4.1 Health-related quality-of-life data from clinical trials

Health state utility values and disutilities were derived from a pooled analysis of individual patient data from the DAPA-HF clinical trial. Linear mixed effects regression models were fitted to predict patient reported utility values derived from EQ-5D-5L questionnaires, which were collected at trial randomisation, day 120, day 240, day 360, and every 12 months thereafter. Mixed effects models were used to account for repeated measures and within-patient correlation adjusted for time from baseline, sex, KCCQ-TSS quartile, T2DM at baseline, body mass index, and age. EQ-5D-5L responses were mapped to EQ-5D-3L applying the mapping function developed by van Hout et al. (90), in line with NICE technology assessment guidelines (91) and assuming that reported domain scores within individual questionnaires were uncorrelated. Responses were then converted to utility index scores using published UK utility values for EQ-5D health states, derived using the time trade-off method described in Dolan (92). The utility model used to inform health state utilities and utility decrements associated with clinical events is presented in Table 39.

Table 39: Summary of mixed effects model used to derive patient utility (fixed effects only)

Variable	Coefficient	SE	p-value
Intercept	0.6193	0.0120	<0.0001
Time (days)*	0.0000	0.0000	<0.0001
KCCQ-TSS quartile 2	0.1046	0.0032	<0.0001
KCCQ-TSS quartile 3	0.1728	0.0033	<0.0001
KCCQ-TSS quartile 4	0.2328	0.0035	<0.0001
T2DM	-0.0175	0.0034	<0.0001
Age	-0.0003	0.0002	0.0347
Sex: Male	0.0322	0.0041	<0.0001
Europe	-0.0300	0.0045	<0.0001
North America	-0.0267	0.0058	<0.0001
South America	-0.0231	0.0055	<0.0001
hHF/uHFv event	-0.0357	0.0101	0.0011
hHF: 1 - <2 months	-0.0303	0.0122	0.0131
hHF: 2 - <4 months	-0.0288	0.0093	0.0020
hHF: 4 - <12 months	-0.0247	0.0072	0.0006
Stroke event	-0.2064	0.0333	<0.0001
MI event	-0.1082	0.0353	0.0021
Volume depletion	-0.0513	0.0123	<0.0001
Renal event	-0.0762	0.0141	<0.0001
Hypoglycaemic event	-0.2631	0.0890	0.0031
Fracture	-0.1488	0.0325	<0.0001

Source: DAPA-HF trial
Abbreviations: hHF, hospitalisation for heart failure; KCCQ-TSS, Kansas City Cardiomyopathy Questionnaire Total Symptom Score; T2DM, type 2 diabetes mellitus; uHFv, urgent heart failure visit; SE, standard error.

B.3.4.2 Mapping

EQ-5D-5L responses from the DAPA-HF trial were mapped to EQ-5D-3L applying the mapping function developed by van Hout et al. (90), in line with NICE technology assessment guidelines (91) and assuming that reported domain scores within individual questionnaires were uncorrelated.

B.3.4.3 Health-related quality-of-life studies

An SLR was conducted to identify studies reporting on preference-based HSUVs associated with HF. Full details of the methodology and results of included studies are presented in Appendix H.

A total of 36 publications reporting HSUVs were identified (11, 64, 93-126). Of these, 31 were full publications (11, 64, 93-108, 110, 113-121, 123, 124, 126), and five were conference abstracts (109, 111, 112, 122, 125). The HSUV data were derived from a range of countries including the UK (n=11) (11, 64, 94, 95, 97, 103, 105, 106, 112, 115, 118), USA (n=3) (101, 119, 120), Sweden (n=2) (116, 121), Greece (n=2) (107, 117), China (n=1) (125), the Netherlands (n=1) (108), Germany (n=1) (126), and South Korea (n=1) (104), or were multi-national (n=10) (93, 98-100, 102, 110, 113, 114, 124, 127). The country was unclear in four publications (109, 111, 122, 123).

Of the 36 studies, 18 reported HSUVs in patients with HFrEF (64, 93-96, 98-101, 105, 109, 111, 114, 119, 120, 122-124), nine reported HSUVs in patients with HF (ejection fraction [EF] not stated) (11, 97, 108, 115, 116, 118, 121, 125, 126), three studies reported data from patients who had a reduction in EF after an acute MI (102, 110, 113), three studies elicited HSUVs using time trade-off (TTO) method from the general population (104, 106, 112), two studies examined patients who had been hospitalised due to emergency HF (103) or where undergoing cardiac surgery (107) and one study reported HSUVs in patients with both HF and coronary heart disease (CHD) (117).

Twenty six studies reported intervention-specific utilities (64, 93-99, 101-103, 105, 107, 109-111, 113-116, 119, 121-124, 126). The most common interventions included those which incorporated use of drug therapies such as sacubitril valsartan (101, 111, 122), ivabradine (64, 109, 126), eplerenone (102, 124), enalapril (101, 122), captopril (110), valsartan (110), and intravenous ferric carboxymaltose (99) followed by intervention strategies including LVADs, implantable cardioverter defibrillator (ICDs) or cardiac resynchronisation therapy (CRT) (n=9) (96-98, 113-115, 119, 121, 123). Alternative strategies considered for treatment involved, person-centred care (116), cardiac rehabilitation (95), aerobic exercise (93, 105), lifestyle advice (103), and surgery (107). Ten studies did not examine interventions (11, 100, 104, 106, 108, 112, 117, 118, 120, 125).

The most common instrument used to estimate HSUVs was EQ-5D. The majority of studies did not explicitly state the version used (n=27) (11, 64, 93-103, 105, 109-111, 114-117, 120-124, 126), although for eight studies this was assumed to be EQ-5D-3L based on the description of the questionnaire in the publication (93, 96, 98, 99, 107, 110, 120, 121). Only two studies specified use of EQ-5D-5L alone (118, 125). The remaining seven studies used various instruments to measure HSUVs. Three studies used TTO alone (106, 112, 119), two reported use of time trade off (TTO) alongside either EQ-5D-5L (104), or EQ-5D-3L (108), one study administered EQ-5D and short form 6-dimensions (SF-6D) (107) and another reported using Health Utilities Index Mark 3 (HUI3) (113).

The majority of studies did not report the societal tariff applied to value health states (n=20) (11, 94, 95, 97, 99, 101, 103, 105, 109, 111, 114-117, 120, 122-126). Of those that did, one reported use of the US tariff (93), seven reported use of the UK tariff (64, 96, 98, 107, 108, 118, 121), one reported a Canadian tariff (113), and one used a Korean tariff (104). Three studies used multiple tariffs to value health states (100, 102, 110) and another three studies used TTO method to elicit HSUVs so no tariff was required (106, 112, 119).

The NICE reference case specifies that utilities should be derived by patients using the preferred EQ-5D and health states should be valued using UK societal preferences elicited using a choice-based method of valuation (standard gamble or TTO) (128). For a majority of studies, it was unclear whether these requirements were met as they did not state which societal preferences were applied (n=20) (11, 63, 94, 97, 99, 101, 103, 105, 109, 111, 114-117, 120, 122-126). There were also six studies that did not meet the NICE reference case requirements due to either applying non-UK tariffs (93, 104, 113) or by using an alternative instrument to measure HSUVs (106, 112, 119). In total, there were only ten studies that fully met the NICE requirements (64, 96, 98, 100, 102, 107, 108, 110, 118, 121).

A summary of the 36 included HSUV studies is provided in Appendix H. The base case analysis in the current STA document used utility values derived from the DAPA-HF study. This was considered the most robust and applicable source of utility data for this population.

B.3.4.4 Adverse reactions

The DAPA-HF trial collected severe AEs, AEs associated with drug discontinuation, AEs of special interest (see Section B.2.10), and diagnoses of Fournier's gangrene. The AEs of special interest were: volume depletion, renal events, major hypoglycaemic events, bone fractures, DKA, and amputation. In the cost-effectiveness model, a proportion of the modelled cohort incurred AE-related utility decrements, conditional on receipt of treatment and modelled incidence of each AE in a given cycle (see Section B.3.3.1.5).

The impact of AEs on HRQoL is described below. The disutility values applied to AEs in the cost-effectiveness model are summarised in Table 40.

B.3.4.4.1 Volume depletion

The impact of volume depletion was captured in the cost-effectiveness model based on the disutility associated with volume depletion in the mixed effects models of utility values from DAPA-HF (0.051, Table 39). No disutility value for volume depletion could be identified from the literature. Volume depletion is the sustained reduction of extracellular volume. The impact on quality of life is likely to be limited with mild volume depletion, as clinical symptoms only become evident with large fluid losses, leading to postural dizziness, postural hypotension, fatigue, confusion, muscle cramps and chest pain.

B.3.4.4.2 Renal events

Renal events in the trial were defined as a range of events, including acute kidney injury (AKI), dialysis, oliguria, and renal failure. The impact of renal events was captured in the cost-effectiveness model based on the disutility associated with renal events (0.076) in the mixed effects models of utility values from DAPA-HF (Table 39).

An alternative disutility for renal events can be estimated from the 'renal failure, not otherwise specified' category from Sullivan et al. 2011, a publication providing a catalogue of disutility values for the UK derived from EQ-5D questionnaires (129). The EQ-5D questionnaire responses were from the US-based medical Expenditure Panel Survey (N=79,522), and the community-based UK EQ-5D index scores were applied to drive utility values relevant to the UK. The marginal disutilities for a range of chronic condition were generated using an ordinary least square, Tobit and censored least absolute deviation regression method, controlling for covariates.

The disutility value for renal events derived from DAPA-HF is likely to be more representative of the types of renal events experienced by HF patients, when treated with placebo or dapagliflozin. Therefore, the disutility value derived from DAPA-HF was selected for use in the cost-effectiveness model.

B.3.4.4.3 Major hypoglycaemic events

The disutility coefficient generated for hypoglycaemic events in the mixed-effects model based on data from DAPA-HF was -0.26 (Table 39) which is unrealistically large. As such, the disutility derived for hypoglycaemic events from DAPA-HF was not used and alternative disutility values were instead sought. A systematic literature review of utility values for economic modelling in T2DM by Beaudet et al. 2014 (130) identified Currie et al. 2006 (131) to provide disutility estimates for hypoglycaemia events.

The impact of major hypoglycaemic events in the model was captured in the cost-effectiveness model as the disutility associated with symptomatic hypoglycaemia from Currie et al. 2006 (131). This study used a multivariate model to predict the impact of severity and frequency of hypoglycaemic events on utility values as measured by EQ-5D. This analysis was from a UK population of 1,305 patients with diabetes. A symptomatic hypoglycaemic episode was found to be associated with a 0.014 utility decrement.

Exploratory analyses in Currie et al. 2006 revealed the Hypoglycaemia Fear Survey (HFS) score to be a major predictor of EQ-5D, and the number of prior hypoglycaemic events was found to be a predictor of the HFS score. As a scenario analysis (see Section B.3.8.3), the disutility associated with a change in the HFS score corresponding to a severe hypoglycaemic event (0.047) was applied in the model to also capture the impact of the fear associated with hypoglycaemia.

B.3.4.4.4 Bone fractures

The impact of fractures was captured in the cost-effectiveness model based on the disutility associated with fractures (0.149) in the mixed effects models of utility values from DAPA-HF (Table 39).

An alternative disutility for bone fractures can be estimated from Sullivan et al. 2016 (129), a publication providing a catalogue of disutility values for the UK. This was a study of EQ-5D scores for diabetes-related chronic conditions, based on a nationally representative SF-12 survey response (n=20,705) from the US which were mapped to EQ-5D-3L, and subsequently valued using UK-specific EQ-5D tariffs. The multivariate regression model included all diabetes-related comorbidities as independent variables and two comorbidity indexes, and was controlled for region, age, sex, race, ethnicity, education, insurance coverage, family income and body mass index (BMI) category. Fracture was found to be associated with a 0.068 marginal disutility.

The disutility value for fractures derived from DAPA-HF is likely to be more representative of the types of fractures experienced by HF patients, when treated with placebo or dapagliflozin. Additionally, given the larger disutility values observed in DAPA-HF compared to Sullivan et al, the disutility for fractures from DAPA-HF is likely to be more conservative with respect to dapagliflozin. Therefore, the disutility value derived from DAPA-HF was selected for use in the cost-effectiveness model.

B.3.4.4.5 DKA

No disutility value could be identified for DKA in T2DM patients and therefore this AE was assumed to be associated with 0 disutilities. This assumption is in line with the modelling for the NICE T1D guideline (NG17) (132).

As a scenario analysis (see Section B.3.8.3), a disutility of 0.0091 was applied for DKA, based on Peasgood et al. 2016 (random-effects model) (133). This disutility value was not applied in the base case, because the study did not find DKA to be a statistically significant predictor of EQ-5D in either the fixed- or random-effects models and the study reported a positive coefficient in the fixed-effects model (i.e. DKA was found to be associated with a numerical improvement in EQ-5D).

B.3.4.4.6 Amputations

A systematic literature review of utility value for economic modelling in T2DM by Beaudet et al. 2014 (130), identified the United Kingdom Prospective Diabetes Study Group (UKPDS) 62

publication to provide disutility estimates for complications. Data from 3,192 UKPDS respondents to the EQ-5D questionnaire was analysed using Tobit and censored least absolute deviations regression analyses to estimate the utility impact of major complications. Amputation was found to be associated with a 0.28 utility decrement.

B.3.4.4.7 Fournier's gangrene

Only one case of Fournier's gangrene was observed in DAPA-HF, in the placebo arm, and as such, this adverse event was not included in the cost-effectiveness model.

B.3.4.4.8 Urinary tract infection and genital infection

Consistent with previous NICE appraisals of dapagliflozin in T2DM and T1DM (134-137), urinary tract infection (UTI) and genital infections were assumed to incur the same utility decrement of 0.003 per event. This value was derived from a published economic evaluation of interventions for UTIs in women, by Barry et al. (138). The implemented value represents the mid-estimate from the study, converted from quality-adjusted life months to QALYs. Upper and lower values were assessed in scenario analyses as in the previous NICE appraisals of dapagliflozin in T2DM (134-137).

B.3.4.5 Health-related quality-of-life (HRQOL) data used in the cost-effectiveness analysis

B.3.4.5.1 HRQOL experienced in each health state

Each of the KCCQ-TSS quartile health states were associated with a utility weighting, and the proportion of patients residing within each heath state in each cycle informed the accrual of QALYs over time. The impact of hHF and uHFv events was captured as one-off decrements to the proportion of patients who experience the event, and the decrement was multiplicatively applied to the relevant KCCQ-TSS quartile health state value. Similarly, the impact of AEs was captured as one-off utility decrements to the proportion of patients who experienced the AE, in a multiplicative manner. Patients with T2DM at baseline had a T2DM-related utility decrement multiplicatively applied to their health states in each of the cycles in accordance with NICE guidelines (139).

B.3.4.5.2 Health effects excluded from the analysis

The cost-effectiveness analysis included the impact of hHF, uHFv, and AEs. No disutility value could be identified for DKA, and therefore no disutility value was included for DKA in the base case. Scenario analyses were conducted with assumed disutility values for DKA, to test the sensitivity of the model to this AE disutility assumptions.

B.3.4.5.3 Cost-effectiveness model inputs

Health state utility values and hHF and uHFv disutility values in the model were derived from the mixed effects model based on data from the DAPA-HF trial (Table 39). Disutility values for AEs were taken from the DAPA-HF mixed-effect model or identified from the literature through targeted searches. The health state utility values and the event disutilities applied in the cost-effectiveness model are summarised in Table 40.

Table 40: Summary of utility values for cost-effectiveness analysis

	Mean	SE	Source and justification	Reference in submission
Health states				
KCCQ-TSS: 1 - <58	0.600	0.016	DAPA-HF	Table 39
KCCQ-TSS: 58 - <77	0.705	0.016	DAPA-HF	Table 39
KCCQ-TSS: 77 - <92	0.773	0.016	DAPA-HF	Table 39
KCCQ-TSS: 92 - 100	0.833	0.016	DAPA-HF	Table 39
T2DM (decrement)	0.017	0.003	DAPA-HF	Table 39
hHF (decrement)	0.321	0.020	DAPA-HF	Table 39
uHFv (decrement)	0.036	0.011	DAPA-HF	Table 39
Adverse events				
Volume depletion	0.051	0.012	DAPA-HF	Table 39
Renal events	0.076	0.014	DAPA-HF	Table 39
Hypoglycaemic events	0.014	0.001	Currie et al. (131) (symptomatic hypoglycaemic event), identified systematically by Beaudet et al. (130). No other utility values identified.	B.3.4.4.3
Fractures	0.149	0.033	DAPA-HF	Table 39
DKA	0.000	0.000	Assumed; no evidence identified	B.3.4.4.5
Amputation	0.280	0.053	UKPDS 62 (140), identified systematically by Beaudet et al. (130). No other utility values identified.	B.3.4.4.6
UTI	0.003	0.001	Barry et al. (138), as per previous NICE appraisals of dapagliflozin in T2DM and T1DM	B.3.4.4.8
Genital infection	0.003	0.001	Barry et al. (138), as per previous NICE appraisals of dapagliflozin in T2DM and T1DM	B.3.4.4.8

Source: DAPA-HF trial
Abbreviations: DKA, diabetic ketoacidosis; hHF, hospitalisation for heart failure; KCCQ-TSS, Kansas City Cardiomyopathy Questionnaire Total Symptom Score; T2DM, type 2 diabetes mellitus; uHFv, urgent heart failure visit; UTI, urinary tract infection; SE, standard error.

B.3.4.5.4 Inputs from clinical experts

Some clinical experts stated that NYHA class classification is used in clinical practice to help stratify patients to treatment, e.g. NYHA I class patients are not offered MRA and sacubitril valsartan; other clinical experts do not make use of NYHA class classification other than during initial diagnosis. The NYHA class classification system was viewed as an easy tool to stratify patients, although it was considered subjective, poorly reproducible, and as an assessment made by a clinician, as opposed to by the patient, not appropriate for estimating patients QoL, prognosis, and health care resource use.

Clinical experts acknowledged that as a patient-reported outcome, and one which incorporates a more holistic assessment of wellbeing, the KCCQ is a more sophisticated measure of patients'

QoL and health status in clinical trials, although the questionnaire is longer compared to NYHA class classification and not routinely used in clinical practice. This supports the use of health states by KCCQ-TSS quartile in the Markov model for dapagliflozin.

B.3.5 Cost and healthcare resource use identification, measurement and valuation

An SLR was conducted to identify studies reporting on UK-based costs and healthcare resource use associated with HF. Details of the SLR of studies reporting cost and resource use data are presented in Appendix I.

A total of 14 publications (89, 141-153) reporting on 13 unique studies (two abstracts reported on a single clinical-linkage database study (145, 148)) were identified that reported costs and/or resource use in the management of HF in the UK. Of the 14 included publications 11 were full texts (89, 141-144, 147, 149-153) and three were reported as conference abstracts (145, 146, 148).

Five publications (reporting data from four unique studies) reported direct costs only for the management of HF (89, 144, 145, 148, 149), four publications reported resource use only (142, 143, 150, 153), with the remaining five reporting both resource use and costs (141, 146, 147, 151, 152). The majority of studies reporting cost data used the bottom up cost-collection approach (n=9) (89, 141, 144, 145, 147-149, 151, 152), with one abstract publication not reporting this information (146).

Twelve publications reported on either the cost (144, 145, 148) or resource use (141-143, 146, 147, 150, 153) or both (151, 152) associated with HF-related hospitalisations. Drug costs were reported in four publications, with the cost of ACEis being reported in two publications (149, 152), beta-blockers in one (141) and sacubitril valsartan in another (89). The costs of managing adverse events were reported as supplementary data in a single study only (89).

One study identified in the SLR (McMurray, 2018 (89)) was used to inform the resource use for HF management in the *de novo* model for dapagliflozin.

A summary of the identified studies is provided in Appendix I.

All costs applied in the model were inflated to a 2018/19 cost-year, based on the Hospital and Community Health Services (HCHS) pay and price inflation index (up to and including 2016/17) and the NHS Cost Inflation Index (HCSCII, from 2015/2016 onwards), as reported in the relevant Personal Social Services Research Unit (PSSRU) publications (Unit Costs of Health and Social Care). Please see Appendix M for details of the inflation indices used.

B.3.5.1 Intervention and comparators' costs and resource use

In base case analysis #1, dapagliflozin is compared versus sacubitril valsartan. The annual treatment costs of dapagliflozin and sacubitril valsartan are shown in Table 41.

In base case analyses #2 and #3, dapagliflozin is used as an add-on to standard care, defined as ACEi/ARB, beta-blocker, ±MRA or sacubitril valsartan, beta-blocker, ±MRA, respectively. The annual treatment cost for standard care (background therapy), applied to both treatment arms in the model for base case analyses #2 and #3, is summarised in Table 42. The total cost of treatment in the dapagliflozin arm was the sum of the cost of dapagliflozin and the cost of standard

care therapy. The total annual cost of treatment in the placebo arm is the same as the total annual cost of background therapy outlined in Table 42. The weighted average annual cost of standard care was based on the additive cost of the component drug classes and the market share of drugs within each drug class, as detailed in Appendix N.

In scenario analyses, the cost of standard care therapy and thereby also the total treatment cost in the dapagliflozin arm, were varied to test the impact of background therapy on the cost-effectiveness of dapagliflozin.

The cost of treatment administration and titration of therapies were assumed to be captured as part of the background health state costs. However, clinical experts indicated that ACEi/ARB and beta-blockers required 3–5 appointments with the HF specialist or HF nurse to up-titrate to optimal doses, and that 3–6 months is needed to reach optimal doses of triple therapy (ACEi/ARB, beta-blocker and MRA) (36). Initiation and up-titration of sacubitril valsartan is also expected to require four HF nurse or HF specialist appointments (36). In base case analyses #2 and #3, the assumption in the model was unlikely to have a significant impact on the ICER, as dapagliflozin is an add-on therapy to standard care. However, in base case analysis #1 evaluating dapagliflozin versus sacubitril valsartan, this assumption is conservative with respect to dapagliflozin, as the titration costs associated with the sacubitril valsartan arm (but not associated with the dapagliflozin arm) were uncaptured.

Table 41: Unit costs associated with the technology and comparator (base case analysis #1 only) in the economic model

Items	Annual cost	Source
Annual cost of dapagliflozin	£476.98	MIMS
Annual cost of sacubitril valsartan	£1,193.55	MIMS

Table 42: Unit costs associated with standard care (background therapy, applied to both arms of the economic model)

Items	Therapies	Proportion of patients on therapies	Source	Annual cost of therapy	Source	Total annual cost
Annual cost of SC (base case analysis #2)	ACEi	56%	DAPA-HF	£6.89	Appendix N	£42.10
	ARB	28%		£36.27		
	MRA	71%		£39.56		
Annual cost of SC (base case analysis #3)	ACEi	56%	DAPA-HF	£6.89	Appendix N	£173.39
	ARB	28%		£36.27		
	MRA	71%		£39.56		
	Sacubitril valsartan	11%		£1,193.55		

Abbreviations: ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; MRA, mineralocorticoid receptor antagonist; SC, standard care.

B.3.5.2 Health-state unit costs and resource use

The annual health state costs associated with HF were sourced from McMurray et al. (89), to capture GP visits, A&E referrals, cardiologist outpatient visits, and other outpatient visits (Table

43). Unit costs used in the McMurray et al. 2018 publication were updated using the latest PSSRU unit costs report and the 2017/18 NHS National Reference Costs, and all other costs were uplifted to a cost year of 2018/19. Additionally, the cost of beta-blocker and diuretics prescription was calculated based on recommended doses and included as part of the annual health state costs.

In the cost-effectiveness model, background health state costs were constant across the different KCCQ-TSS quartile health states, and increased costs of HF with worsening disease severity were captured as an increasing incidence of hHF.

Cost for the management of T2DM was sourced from Alva et al. (154), a study estimating the inpatient (£459) and outpatient (£532) costs incurred by T2DM in the UKPDS. The total direct cost of T2DM in the UK was estimated as the sum of the average inpatient costs and the average outpatient costs and uplifted to a cost year of 2018/19.

Table 43: List of health states and associated costs in the economic model

Health states / events	Annual cost		Source
	Mean	SE	
Background HF management, including cost of beta-blockers and diuretics	£932.75	£93.28	McMurray et al. (89) Assume all patients to take recommended doses of bisoprolol (beta-blocker) and furosemide (diuretic), unit costs from eMIT 2019
T2DM	£1,090.56	£42.83	Alva et al. (154); uplifted to 2018/19
hHF	£2,831.72	£283.17	NHS Reference Costs 2017/18; weighted by finished consultant episode (EB03A-E, heart failure or shock, non-elective long stay)
uHFv	£401.62	£40.16	NHS Reference Costs 2017/18; weighted by finished consultant episode (EB03A-E, heart failure or shock, day case)
CV death	£1,673.80	£567.92	Alva et al. (154), cost of fatal myocardial infarction (conservatively selected; MI was the lowest cost fatal CV event reported); uplifted to 2018/19

Abbreviations: CV, cardiovascular; hHF, hospitalisation for heart failure; SE, standard error; T2DM, type 2 diabetes mellitus; uHFv, urgent heart failure visit.

B.3.5.3 Adverse reaction unit costs and resource use

Table 44 summarises the per-event costs applied to AEs captured in the cost-effectiveness model. Treatment discontinuation associated with AEs was assumed to incur no additional costs.

The costs of treating volume depletion, UTI, and genital infection were represented by the cost of a GP visit, as it was assumed the majority of these AEs could be treated by oral rehydration therapy, antibiotics, and topical antifungals, respectively.

Renal events in the trial were defined as a range of events, including AKI, dialysis, oliguria, and renal failure. The cost of renal events was represented by the weighted average NHS national reference cost, total Healthcare Resource Group (HRG), for acute kidney injury with interventions (LA07).

The cost of hypoglycaemic events was informed by Hammer et al. 2009 (155), which surveyed the health care resource used by T1DM and T2DM patients who had experienced a severe hypoglycaemic event. In UK patients with T2DM, the estimated average cost per serious hypoglycaemic event was €537. This value was converted to pounds using a conversion rate of £1.00 = €1.473 provided in the paper and uplifted to a cost year of 2018/19.

The cost of fractures was estimated by calculating the weighted average NHS national reference cost, total HRG, for fractures in various parts of the body (HE11, HE21, HE41, HE31, HE51, and HE71).

The cost of a DKA events was estimated from Dhatariya et al. 2017 (156), a costing study based on a national survey of UK hospitals on aspects of their care during acute hospital admissions of DKA. The total cost per DKA estimated by Dhatariya et al. 2017 included costs for diagnostic and laboratory assessments, nurse and physician contacts, drug usage during the acute phase of DKA admission, and per diem ward costs following resolution of DKA. The total cost per DKA was uplifted to a cost year of 2018/19.

The cost of amputation was informed by Alva et al. 2015 (154), which accounted for inpatient care costs and outpatient care costs associated with amputation in the UKPDS T2DM study. The study found amputation to be associated with £9,546 and £2,699 of inpatient and outpatient care costs, respectively. The inpatient and outpatient care costs were summed and uplifted to 2018/19 cost year to inform the cost of amputation in the current cost-effectiveness model.

Table 44: List of adverse reactions and summary of costs in the economic model

Adverse reactions	Per event cost		Source
	Mean	SE	
Volume depletion	£39.00	£3.90	PSSRU 2019, assume one GP visit
Renal events	£1,865.01	£186.50	NHS National Reference Costs 2017/18; total HRG, weighted average of LA07 unit costs
Hypoglycaemic events	£453.70	£45.37	Hammer et al. 2009 (155); severe hypoglycaemic events, €537, conversion to Euros at rate of 1.473 (Hammer et al. 2009), uplifted from 2007 cost year to 2018/19
Fractures	£2,428.76	£242.88	NHS National Reference Costs 2017/18; total HRG, weighted average of HE11, HE21, HE41, HE31, HE51 and HE71
Diabetic ketoacidosis	£2,208.80	£208.30	Dhatariya et al 2017 (156); £2,064 in 2014, uplifted to 2018/19 cost year
Amputation	£13,475.12	£2,120.25	Alva et al. 2015 (154); inpatient care cost and outpatient care cost, uplifted to 2018/19 cost year
Genital infection	£39.00	£3.90	PSSRU 2019 (157), assume one GP visit
Urinary tract infection	£39.00	£3.90	PSSRU 2019 (157), assume one GP visit

Abbreviations: GP, general practitioner; HRG, Healthcare Resource Group; NHS, National Health Service; PSSRU, Personal Social Services Research Unit; SE, standard error.

B.3.5.4 Miscellaneous unit costs and resource use

All relevant costs have been captured in the above sections.

B.3.6 Summary of base case analysis inputs and assumptions

B.3.6.1 Summary of base case analysis inputs

Table 45: Summary of variables applied in the economic model

Variable	Value	SE	Distribution	Reference
Baseline characteristics (base case analysis #1)				
Age (years)	63.80	0.12	Normal	Table 31
Female	0.22	0.01	Beta	
BMI (kg/m2)	28.15	0.12	Beta	
KCCQ-TSS Q1: 0-<58	0.23	0.01	Beta	
KCCQ-TSS Q2: 58-<77	0.25	0.01	Beta	
KCCQ-TSS Q3: 77-<92	0.28	0.01	Beta	
KCCQ-TSS Q4: 92-100	0.24	0.01	Beta	
NT-proBNP (pg/mL)	2342.53	43.52	Beta	
Ischaemic HF	0.60	0.01	Beta	
Duration of HF >2 years	0.62	0.01	Beta	
Prior hHF	0.63	0.01	Beta	
LVEF	0.30	0.12	Beta	
Creatinine (µmol/L)	99.89	0.29	Beta	
T2DM	0.35	0.01	Beta	
Baseline characteristics (base case analysis #2)				
Age (years)	66.32	0.16	Normal	Table 31
Female	0.240	0.01	Beta	
BMI (kg/m2)	28.020	0.09	Beta	
KCCQ-TSS Q1: 0-<58	0.230	0.01	Beta	
KCCQ-TSS Q2: 58-<77	0.250	0.01	Beta	
KCCQ-TSS Q3: 77-<92	0.280	0.01	Beta	
KCCQ-TSS Q4: 92-100	0.240	0.01	Beta	
NT-proBNP (pg/mL)	2345.940	43.94	Beta	
Ischaemic HF	0.570	0.01	Beta	
Duration of HF >2 years	0.610	0.01	Beta	

Variable	Value	SE	Distribution	Reference
Prior hHF	0.480	0.01	Beta	
LVEF	0.313	0.00	Beta	
Creatinine (µmol/L)	104.070	0.46	Beta	
T2DM	0.45	0.01	Beta	
Baseline characteristics (base case analysis #3)				
Age (years)	66.66	0.61	Normal	Table 31
Female	0.19	0.02	Beta	
BMI (kg/m2)	29.85	0.35	Beta	
KCCQ-TSS Q1: 0-<58	0.27	0.02	Beta	
KCCQ-TSS Q2: 58-<77	0.24	0.02	Beta	
KCCQ-TSS Q3: 77-<92	0.25	0.02	Beta	
KCCQ-TSS Q4: 92-100	0.24	0.02	Beta	
NT-proBNP (pg/mL)	2298.05	212.23	Beta	
Ischaemic HF	0.50	0.03	Beta	
Duration of HF >2 years	0.73	0.02	Beta	
Prior hHF	0.40	0.03	Beta	
LVEF	0.28	0.00	Beta	
Creatinine (µmol/L)	109.33	1.64	Beta	
T2DM	0.44	0.03	Beta	
Monthly KCCQ-TSS transition matrix – months 0–4, dapagliflozin + SC				
KCCQ[1,1]	0.86240	0.00015	Beta	Table 32
KCCQ[1,2]	0.08042	0.00012	Beta	
KCCQ[1,3]	0.03679	0.00008	Beta	
KCCQ[1,4]	0.02043	0.00006	Beta	
KCCQ[2,1]	0.03126	0.00007	Beta	
KCCQ[2,2]	0.85790	0.00015	Beta	
KCCQ[2,3]	0.07122	0.00011	Beta	
KCCQ[2,4]	0.03959	0.00008	Beta	
KCCQ[3,1]	0.00903	0.00004	Beta	
KCCQ[3,2]	0.03829	0.00008	Beta	
KCCQ[3,3]	0.86130	0.00015	Beta	
KCCQ[3,4]	0.09133	0.00012	Beta	
KCCQ[4,1]	0.00713	0.00004	Beta	

Variable	Value	SE	Distribution	Reference
KCCQ[4,2]	0.01519	0.00005	Beta	
KCCQ[4,3]	0.04547	0.00009	Beta	
KCCQ[4,4]	0.93220	0.00011	Beta	
Monthly KCCQ-TSS transition matrix – months 5+, dapagliflozin + SC				
KCCQ[1,1]	0.94360	0.00007	Beta	Table 32
KCCQ[1,2]	0.03682	0.00006	Beta	
KCCQ[1,3]	0.01409	0.00004	Beta	
KCCQ[1,4]	0.00551	0.00002	Beta	
KCCQ[2,1]	0.02629	0.00004	Beta	
KCCQ[2,2]	0.92200	0.00007	Beta	
KCCQ[2,3]	0.03781	0.00005	Beta	
KCCQ[2,4]	0.01392	0.00003	Beta	
KCCQ[3,1]	0.00820	0.00002	Beta	
KCCQ[3,2]	0.02750	0.00004	Beta	
KCCQ[3,3]	0.92090	0.00006	Beta	
KCCQ[3,4]	0.04339	0.00005	Beta	
KCCQ[4,1]	0.00259	0.00001	Beta	
KCCQ[4,2]	0.01024	0.00002	Beta	
KCCQ[4,3]	0.03300	0.00004	Beta	
KCCQ[4,4]	0.95420	0.00004	Beta	
Monthly KCCQ-TSS transition matrix – months 0–4, placebo + SC				
KCCQ[1,1]	0.88180	0.00015	Beta	Table 32
KCCQ[1,2]	0.07071	0.00012	Beta	
KCCQ[1,3]	0.03164	0.00008	Beta	
KCCQ[1,4]	0.01582	0.00006	Beta	
KCCQ[2,1]	0.03870	0.00008	Beta	
KCCQ[2,2]	0.85300	0.00015	Beta	
KCCQ[2,3]	0.06635	0.00010	Beta	
KCCQ[2,4]	0.04194	0.00008	Beta	
KCCQ[3,1]	0.01665	0.00006	Beta	
KCCQ[3,2]	0.04910	0.00009	Beta	
KCCQ[3,3]	0.85680	0.00015	Beta	
KCCQ[3,4]	0.07747	0.00012	Beta	
KCCQ[4,1]	0.00513	0.00003	Beta	
KCCQ[4,2]	0.01676	0.00006	Beta	
KCCQ[4,3]	0.05305	0.00010	Beta	
KCCQ[4,4]	0.92510	0.00012	Beta	
Monthly KCCQ-TSS transition matrix – months 5+, placebo + SC				

Variable	Value	SE	Distribution	Reference
KCCQ[1,1]	0.94140	0.00007	Beta	Table 32
KCCQ[1,2]	0.03876	0.00006	Beta	
KCCQ[1,3]	0.01212	0.00003	Beta	
KCCQ[1,4]	0.00776	0.00003	Beta	
KCCQ[2,1]	0.03220	0.00005	Beta	
KCCQ[2,2]	0.91550	0.00007	Beta	
KCCQ[2,3]	0.03708	0.00005	Beta	
KCCQ[2,4]	0.01519	0.00003	Beta	
KCCQ[3,1]	0.00747	0.00002	Beta	
KCCQ[3,2]	0.03459	0.00004	Beta	
KCCQ[3,3]	0.91960	0.00006	Beta	
KCCQ[3,4]	0.03833	0.00005	Beta	
KCCQ[4,1]	0.00426	0.00002	Beta	
KCCQ[4,2]	0.01359	0.00003	Beta	
KCCQ[4,3]	0.03852	0.00004	Beta	
KCCQ[4,4]	0.94360	0.00005	Beta	
Adjusted CV mortality survival equation (Weibull)				
Shape	1.222	0.052	Normal	Table 33
Scale	209901.536	89817.275	Normal	
Dapagliflozin	0.144	0.077	Normal	
Female	0.381	0.103	Normal	
LVEF (centred)	0.017	0.005	Normal	
NT-proBNP (log)	-0.571	0.047	Normal	
Type 2 diabetes	-0.208	0.077	Normal	
Ischaemic HF	-0.235	0.081	Normal	
KCCQ: 58–77	0.460	0.100	Normal	
KCCQ: 77–92	0.809	0.110	Normal	
KCCQ: >92	0.880	0.115	Normal	
HF >2 years	-0.289	0.086	Normal	
Adjusted all-cause mortality survival equation (Weibull)				
Shape	1.245	0.048	Normal	Table 33
Scale	139304.051	51809.337	Normal	
Dapagliflozin	0.133	0.068	Normal	
Female	0.383	0.091	Normal	
LVEF (centred)	-	-	Normal	
NT-proBNP (log)	-0.545	0.041	Normal	
Type 2 diabetes	-0.175	0.068	Normal	
Ischaemic HF	-0.217	0.072	Normal	

Variable	Value	SE	Distribution	Reference
KCCQ: 58–77	0.436	0.089	Normal	
KCCQ: 77–92	0.790	0.097	Normal	
KCCQ: >92	0.902	0.104	Normal	
HF >2 years	-0.303	0.076	Normal	
Adjusted generalised estimating equations predicting hHF events				
Intercept	-9.321	0.366	Normal	Table 36
Dapagliflozin	-0.309	0.074	Normal	
KCCQ: 58–77	-0.488	0.096	Normal	
KCCQ: 77–92	-0.682	0.098	Normal	
KCCQ: >92	-1.101	0.113	Normal	
LVEF (centred)	-0.029	0.005	Normal	
NT-proBNP (log)	0.590	0.043	Normal	
Prior hHF	0.435	0.075	Normal	
Type 2 diabetes	0.387	0.076	Normal	
BMI (kg/m^2) (centred)	0.020	0.006	Normal	
Creatinine (µmol/L) (centred)	0.005	0.001	Normal	
HF >2 years	0.438	0.084	Normal	
Time since baseline (days)	0.0004	0.0002	Normal	
Unadjusted generalised estimating equations predicting uHFv events				
Intercept	-7.280	0.225	Normal	Table 37
Dapagliflozin	-1.075	0.388	Normal	
Annual probability of adverse events – dapagliflozin + SC				
Volume depletion	0.050	0.009	Beta	Table 38
Renal events	0.041	0.008	Beta	
Hypoglycaemic events	0.001	0.001	Beta	
Fractures	0.014	0.005	Beta	
Diabetic ketoacidosis	0.001	0.001	Beta	
Amputation	0.003	0.002	Beta	
Genital infections	0.009	0.001	Beta	
UTI	0.016	0.002	Beta	
Annual probability of adverse events – placebo + SC				
Volume depletion	0.045	0.008	Beta	Table 38
Renal events	0.047	0.009	Beta	
Hypoglycaemic events	0.001	0.001	Beta	

Variable	Value	SE	Distribution	Reference
Fractures	0.014	0.005	Beta	
Diabetic ketoacidosis	0.000	0.000	Beta	
Amputation	0.003	0.002	Beta	
Genital infections	0.001	0.000	Beta	
UTI	0.015	0.002	Beta	
Treatment discontinuation				
Dapagliflozin	0.07	0.01	Beta	B.3.3.1.6
Utility values – health states and events				
KCCQ-TSS: 1 - <58	0.600	0.016	Beta	Table 40
KCCQ-TSS: 58 - <77	0.705	0.016	Beta	
KCCQ-TSS: 77 - <92	0.773	0.016	Beta	
KCCQ-TSS: 92 - 100	0.833	0.016	Beta	
T2DM (decrement)	0.017	0.003	Beta	
hHF (decrement)	0.321	0.020	Beta	
uHFv (decrement)	0.036	0.011	Beta	
Disutility values – adverse events				
Volume depletion	0.051	0.012	Beta	Table 40
Renal events	0.076	0.014	Beta	
Hypoglycaemic events	0.014	0.001	Beta	
Fractures	0.149	0.033	Beta	
DKA	0.000	0.000	Beta	
Amputation	0.280	0.053	Beta	
UTI	0.003	0.001	Beta	
Genital infection	0.003	0.001	Beta	
Annual treatment costs				
Annual cost of dapagliflozin	£476.98	N/A	N/A	Table 41
Annual cost of sacubitril valsartan (base case analysis #1 only)	£1,193.55	N/A	N/A	
Annual cost of SC (applied to both arms in the model, base case analysis #2)	£42.10	N/A	N/A	Table 42

Variable	Value	SE	Distribution	Reference
Annual cost of SC (applied to both arms in the model, base case analysis #3)	£173.39	N/A	N/A	
Health state and event costs				
Background HF management, including cost of beta-blockers and diuretics	£932.75	£93.28	Gamma	Table 43
T2DM	£1,090.56	£42.83	Gamma	
hHF	£2,831.72	£283.17	Gamma	
uHFv	£401.62	£40.16	Gamma	
CV death	£1,673.80	£567.92	Gamma	
Adverse event costs				
Volume depletion	£39.00	£3.90	Gamma	Table 44
Renal events	£1,865.01	£186.50	Gamma	
Hypoglycaemic events	£453.70	£45.37	Gamma	
Fractures	£2,428.76	£242.88	Gamma	
Diabetic ketoacidosis	£2,208.80	£208.30	Gamma	
Amputation	£13,475.12	£2,120.25	Gamma	
Genital infection	£39.00	£3.90	Gamma	
Urinary tract infection	£39.00	£3.90	Gamma	

B.3.6.2 Assumptions

The treatment effect of dapagliflozin in the model was based on survival equations and risk equations fitted to the DAPA-HF trial data and extrapolated over time. The survival equations for all-cause mortality and CV mortality, and the risk equation for hHF, were adjusted for covariables, including time-updated KCCQ-TSS quartiles.

In the base case, the model assumed that the distribution of patients across the KCCQ-TSS quartile health states is the same for patients with and without T2DM. This assumption was unlikely to have a major impact on the cost-effectiveness results, given the similarity in KCCQ-TSS quartile distribution in patients with and without T2DM. In scenario analyses of subgroups of patients with and without T2DM, the subgroup specific distributions of KCCQ-TSS quartile were used.

The model assumed that patients could not move between the T2DM and non-T2DM health states. This assumption was based on the small number of new onset T2DM observed within the DAPA-HF trial (64 and 93 in the dapagliflozin and placebo arms, respectively). This assumption was conservative with respect to dapagliflozin as it omitted the benefits of dapagliflozin on blood glucose control in the prevalent T2DM subgroup, despite the extensive evidence available on the

treatment effect of dapagliflozin in T2DM on glycaemic control, blood pressure, and weight (158-163).

Changes in NT-proBNP over time (measure of disease severity) were not modelled. This was not expected to impact the cost-effectiveness results, as changes in disease severity over time were captured by the KCCQ-TSS quartile health states in the model. Time-updated KCCQ-TSS quartile occupancy was included in the survival equations and risk equations to capture the impact of disease severity on event risk.

The model assumed health state utility values to be constant with age. The coefficient for age in the mixed effects model used to derive the health state utility values was extremely small (-0.0004), and therefore no age-related utility changes were incorporated in the cost-effectiveness model. The impact of age on health state utility values is expected to be minimal as the mean life years in the model for patients in the dapagliflozin arm was ~6 years only.

AE-associated mortality was not modelled. The impact of not modelling AE-associated mortality is likely to favour the placebo arm, as the incidence of AEs with an outcome of death (9.6% with dapagliflozin versus 10.6% with placebo) was higher in the placebo arm. The incidence rates of other AEs of special interest were generally balanced between the two trial arms of DAPA-HF. While diabetic ketoacidosis occurred only in the dapagliflozin group, it occurred in only 0.1% of patients. The incidence rates of genital infections and UTIs, modelled based on data from DECLARE TIMI-58, were higher in the dapagliflozin arm compared with the placebo arm; however, these AEs are routinely treated by topical antifungals and antibiotics and are unlikely to result in deaths.

The cost of background standard care therapy was calculated based on recommended doses and the proportions of patients on each drug class (ACEi, ARB, MRA) in DAPA-HF. The estimated background standard care therapy cost was likely to be an overestimate, as the proportions of patients on ACEi, ARB, and MRA are lower in UK clinical practice compared with the DAPA-HF trial. This assumption is unlikely to bias the results as the same background standard care therapy costs are applied to both arms of the model. A scenario analysis was conducted based on proportions of patients on each drug class from Clinical Practice Research Datalink (CPRD) data.

The model assumed costs of treatment titration were captured as part of the background annual health state costs. In clinical practice, ACEi, ARB, beta-blockers, MRA, and sacubitril valsartan require multiple HF specialist or HF nurse appointments for up-titration to optimal doses (36). In base case analyses #2 and #3, this assumption was unlikely to have a significant impact on the ICER, as dapagliflozin was modelled as an add-on therapy to standard care or as an add-on therapy to sacubitril valsartan. However, in base case analysis #1 evaluating dapagliflozin versus sacubitril valsartan, this assumption was conservative with respect to dapagliflozin, as the titration costs associated with the sacubitril valsartan arm (but not associated with the dapagliflozin arm) were uncaptured.

B.3.7 Base case results

B.3.7.1 Base case analysis #1 incremental cost-effectiveness analysis results

Table 46 shows the discounted results of the base case analysis #1 analysis comparing dapagliflozin versus sacubitril valsartan. Dapagliflozin was dominant over sacubitril valsartan and was associated with cost-savings of £3,131 over a lifetime time horizon. There was no difference in

life years or QALYs, as this analysis assumed dapagliflozin and sacubitril valsartan to have the same efficacy, based on the results of the MAIC (Section B.2.9.2).

Table 46: Base case analysis #1 deterministic results – dapagliflozin versus sacubitril valsartan

	Dapagliflozin + SC (intervention)	Sacubitril valsartan + SC (comparator)	Incremental	ICER (£/QALY)
Life years	6.214	6.214	0.000	Dominant
QALYs	4.627	4.627	0.000	
Costs (£)	£14,514	£17,645	-£3,131	

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

B.3.7.2 Base case analysis #2 incremental cost-effectiveness analysis results

Table 47 shows the discounted results of base case analysis #2 comparing dapagliflozin as an add-on to standard care (ACEi/ARB, beta-blocker, ±MRA) with placebo plus standard care (ACEi/ARB, beta-blocker, ±MRA) over a lifetime horizon. Placebo plus standard care was associated with 5.609 life years, 4.125 QALYs, and £12,226 per person. Treatment with dapagliflozin as an add-on to standard care was associated with increased life years (+0.575 per person) and QALYs (+0.472 per person), at an additional cost of £2,750 per person. Dapagliflozin as an add-on to standard care was highly cost-effective versus placebo plus standard care and associated with an ICER of £5,830 per QALY gained.

The additional costs associated with the dapagliflozin arm were due to additional costs associated with dapagliflozin treatment (main driver of incremental costs), and additional cost of background therapy due to increased life years. There was also a small additional cost associated with AEs. These additional costs were partially offset by cost-savings from reduced incidence of hHF, uHFv, and CV death.

The incremental QALY gains were driven by increased life years and longer duration spent in the alive health states (+0.469 QALYs), especially KCCQ-TSS Q4. The reduced incidence of hHF also contributed to QALY gains (+0.003 QALYs).

Table 47: Base case analysis #2 deterministic results – dapagliflozin add-on to ACEi/ARB, beta-blocker, ±MRA

	Dapagliflozin + SC (intervention)	Placebo + SC (comparator)	Incremental	ICER (£/QALY)
Life years	6.184	5.609	0.575	£5,830
QALYs	4.597	4.125	0.472	
Costs (£)	£14,976	£12,226	£2,750	

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life year, SC, standard care.

Clinical outcomes from the model are provided in Appendix J.

Disaggregated results of the base case cost-effectiveness analysis are provided in Appendix J.

B.3.7.3 Base case analysis #3 incremental cost-effectiveness analysis results

Table 48 shows the discounted results of base case analysis #3 comparing dapagliflozin as an add-on to standard care (sacubitril valsartan, beta-blocker, ±MRA) with placebo plus standard care (sacubitril valsartan, beta-blocker, ±MRA) alone over a lifetime horizon. Placebo plus standard care was associated with 5.428 life years, 3.983 QALYs, and £12,913 per person. Treatment with dapagliflozin as an add-on to standard care was associated with increased life years (+0.563 per person) and QALYs (+0.461 per person), at an additional cost of £2,707 per person. Dapagliflozin as an add-on to standard care was highly cost-effective versus placebo plus standard care and associated with an ICER of £5,866 per QALY gained.

The additional costs associated with the dapagliflozin arm were due to additional costs associated with dapagliflozin treatment (main driver of incremental costs), and additional cost of background therapy due to increased life years. There was also a small additional cost associated with AEs. These additional costs were partially offset by cost-savings from reduced incidence of hHF, uHFv, and CV death.

The incremental QALY gains were driven by increased life years and longer duration spent in the alive health states (+0.459 QALYs), especially KCCQ-TSS Q4. The reduced incidence of hHF also contributed to QALY gains (+0.003 QALYs).

Table 48: Base case analysis #3 deterministic results – dapagliflozin add-on to sacubitril valsartan, beta-blocker, ±MRA

	Dapagliflozin + SC (intervention)	Placebo + SC (comparator)	Incremental	ICER (£/QALY)
Life years	5.990	5.428	0.563	£5,866
QALYs	4.444	3.983	0.461	
Costs (£)	£15,620	£12,913	£2,707	

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life year, SC, standard care.

Clinical outcomes from the model are provided in Appendix J.

Disaggregated results of the base case cost-effectiveness analysis are provided in Appendix J.

B.3.8 Sensitivity analyses

B.3.8.1 Probabilistic sensitivity analysis

Probabilistic sensitivity analysis (PSA) was performed to explore the effect of uncertainty associated with all model inputs. Two hundred PSA iterations were run in order to obtain stable estimates of the mean model results (see ICER convergence curves below), and the mean total costs and mean total QALYs were calculated to estimate the probabilistic ICER.

In the PSA, all values were drawn from a distribution at the beginning of each simulated cohort in order to vary parameters that would otherwise remain fixed in the deterministic case. Model input values were sampled from distributions around the mean value input parameters (used in the deterministic analysis), based on the standard error associated with the input parameter. In general, beta distributions were used for utilities, proportions and probability estimates, gamma

distributions were used for costs, and normal distributions were used for the other parameters. Details on the parameters, SEs, and assumptions are provided throughout Section B.3 and summarised in Section B.3.4.5.3.

Base case analysis #1 was a cost-minimisation analysis and therefore a PSA was not conducted. Instead the robustness of the model was assessed through deterministic sensitivity analysis (DSA, Section B.3.8.2.1).

The results from the 200 iterations are summarised in cost-effectiveness scatterplots for base case analyses #2 and #3. The cost-effectiveness acceptability curves summarise the likelihood of cost-effectiveness at different willingness-to-pay thresholds.

B.3.8.1.1 Base case analysis #2

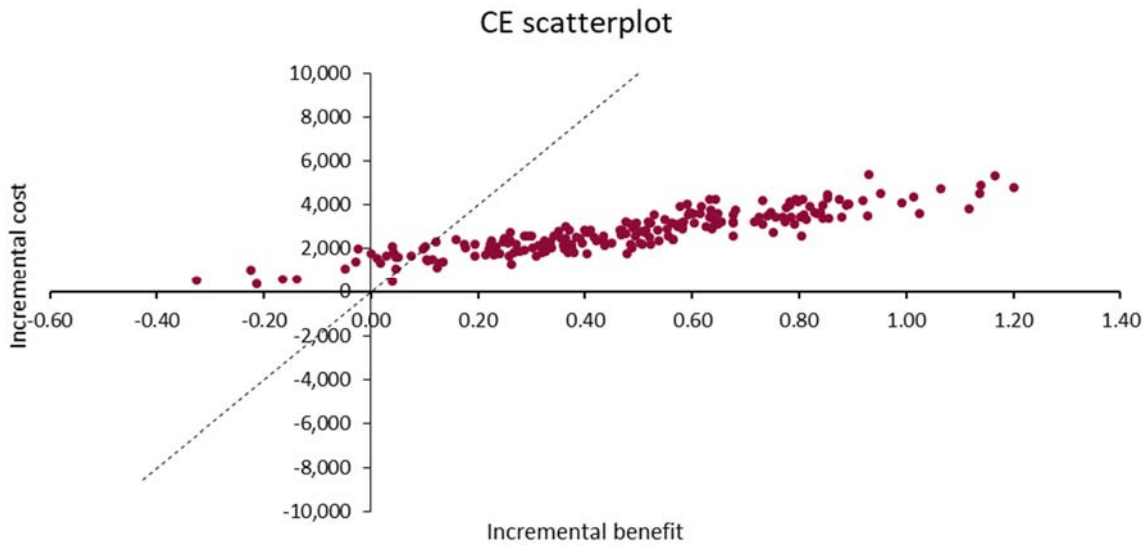
The results of the PSA (Table 49) were comparable with the results from the deterministic base case analysis (Table 47). The incremental QALYs and costs of dapagliflozin versus placebo were 0.484 QALYs and £2,760 in the PSA, compared with 0.472 QALYs and £2,750 in the deterministic base case. The ICER from the probabilistic sensitivity analyses was £5,701 and the likelihood of cost-effectiveness was 94.5% assuming a cost-effectiveness threshold of £20,000 per QALY gained and 96.5% assuming a cost-effectiveness threshold of £30,000 per QALY (Figure 30).

Table 49: Base case analysis #2 probabilistic results - dapagliflozin as add-on therapy to ACEi/ARB, beta-blocker, ±MRA

	Dapagliflozin + SC (total)	Placebo + SC (total)	Incremental	ICER (£/QALY)
Life years	6.061	5.468	0.593	£5,701
QALYs	4.506	4.022	0.484	
Costs (£)	£14,671	£11,911	£2,760	

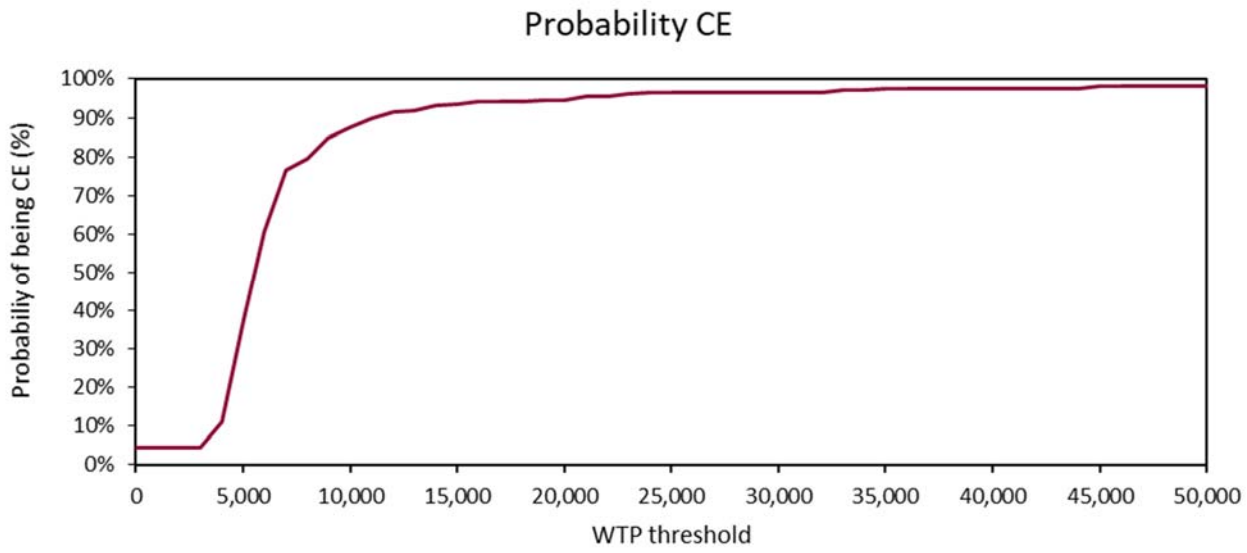
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality-adjusted life year, SC, standard care.

Figure 28: Cost-effectiveness scatterplot – base case analysis #2



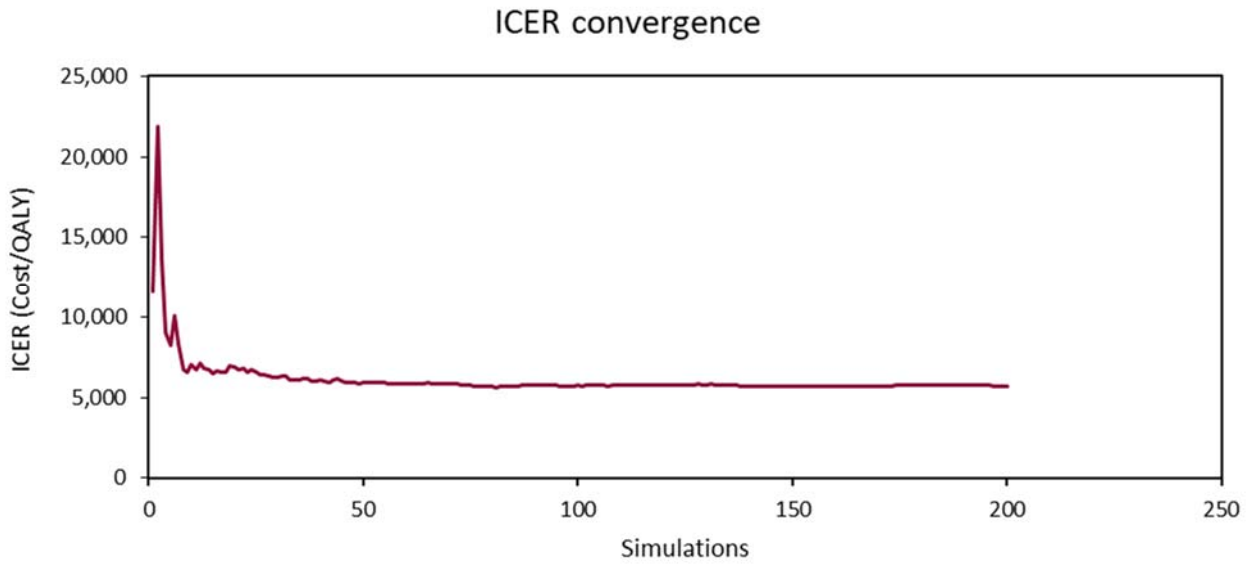
Abbreviations: CE, cost-effectiveness.

Figure 29: Cost-effectiveness acceptability curve – base case analysis #2



Abbreviations: CE, cost-effective; WTP, willingness to pay.

Figure 30: ICER convergence curve – base case analysis #2



Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

B.3.8.1.2 Base case analysis #3

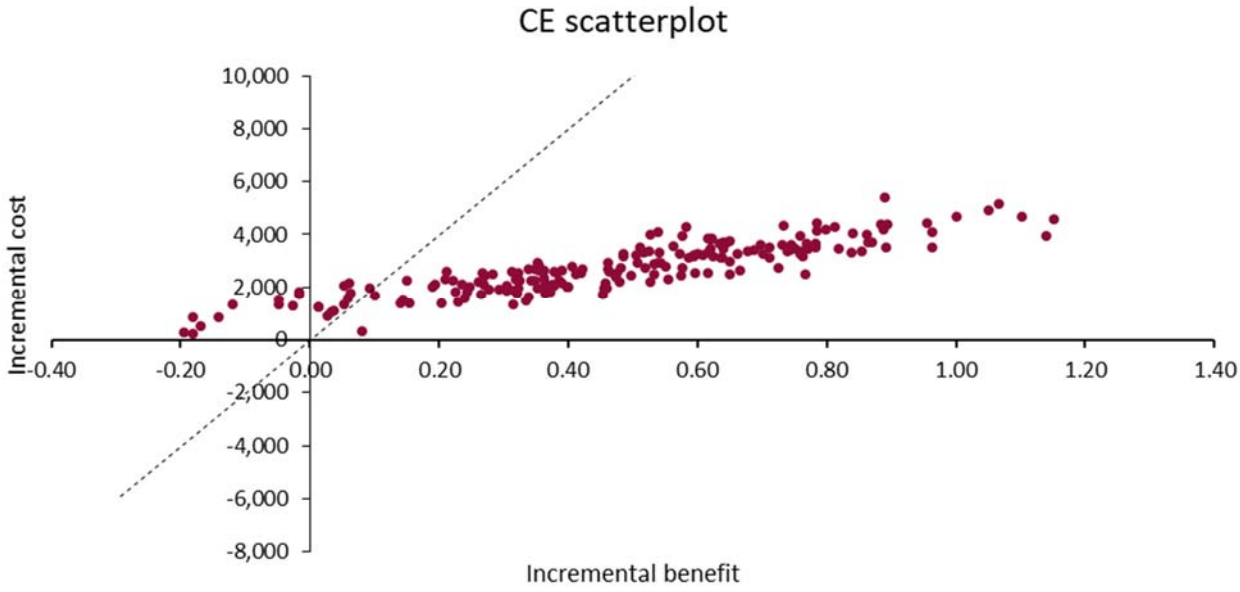
The results of the PSA (Table 50) were comparable with the results from the deterministic base case analysis (Table 48). The incremental QALYs and costs of dapagliflozin versus placebo were 0.472 QALYs and £2,718 in the PSA, compared with 0.461 QALYs and £2,707 in the deterministic base case. The ICER from the probabilistic sensitivity analyses was £5,757 and the likelihood of cost-effectiveness was 94.5% assuming a cost-effectiveness threshold of £20,000 per QALY gained and 96.5% assuming a cost-effectiveness threshold of £30,000 per QALY (Figure 32).

Table 50: Base case analysis #3 probabilistic results – dapagliflozin as add-on therapy to sacubitril valsartan, beta-blocker, ±MRA

	Dapagliflozin + SC (total)	Placebo + SC (total)	Incremental	ICER (£/QALY)
Life years	5.852	5.274	0.578	£5,757
QALYs	4.343	3.871	0.472	
Costs (£)	£15,235	£12,518	£2,718	

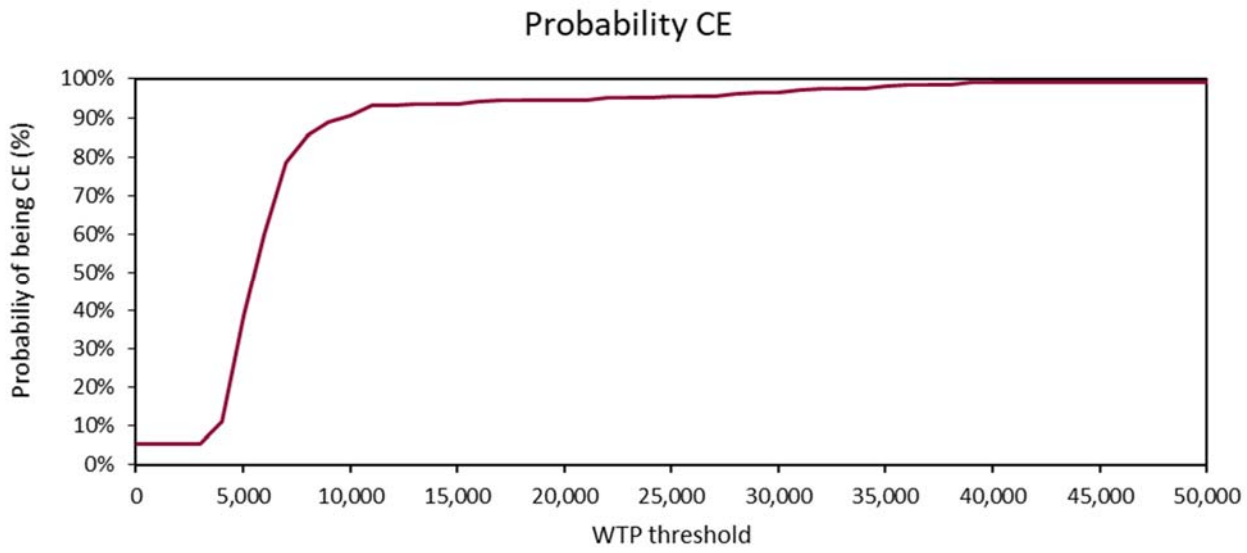
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality-adjusted life year, SC, standard care.

Figure 31: Cost-effectiveness scatterplot – base case analysis #3



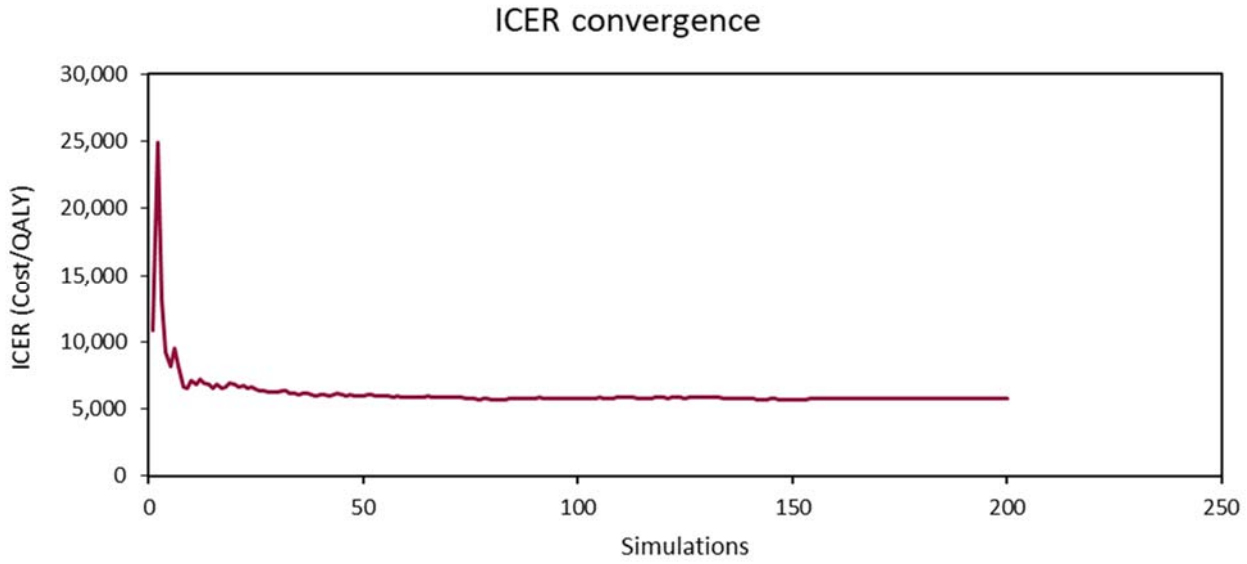
Abbreviations: CE, cost-effectiveness.

Figure 32: Cost-effectiveness acceptability curve – base case analysis #3



Abbreviations: CE, cost-effective; WTP, willingness to pay.

Figure 33: ICER convergence curve – base case analysis #3



Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

B.3.8.2 Deterministic sensitivity analysis

DSA was performed to explore the effect of uncertainty associated with varying individual model inputs or groups of individual model inputs. The DSA model inputs were varied by 20% from baseline or to 0% or 6% for the discounting factor.

Tornado diagrams are presented below for each of the base cases summarising the results of the DSA.

In the deterministic sensitivity analyses for base case analysis #1, a reduction in cost discounting to 0% (from 3.5% in base case), had the largest effect on reducing the incremental costs

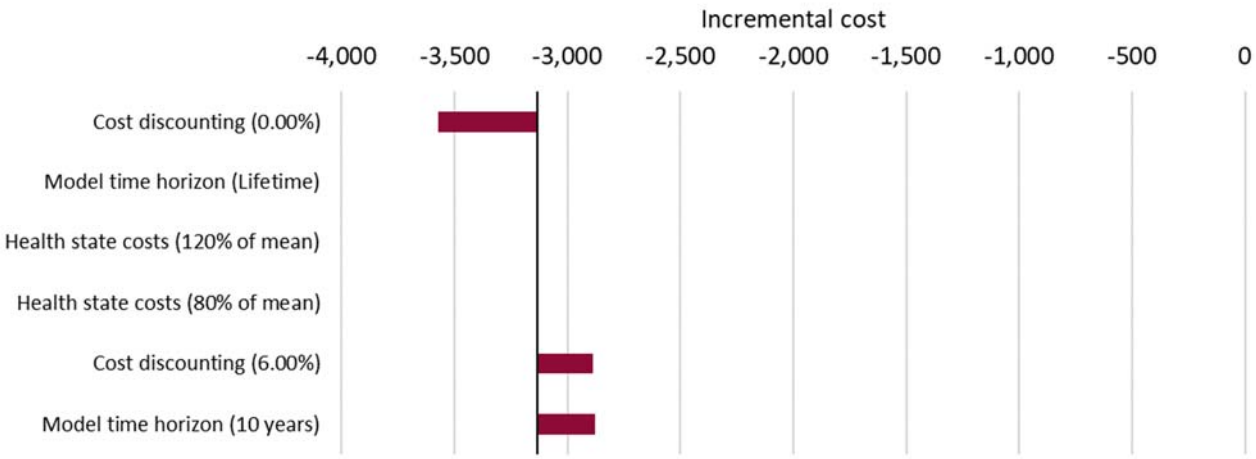
(increasing the cost-savings associated with dapagliflozin) to -£3,574, whereas a reduction in time horizon to 10 years (from life-time in the base case) had the largest effect on increasing the incremental costs (reducing the cost-savings associated with dapagliflozin) to -£2,878. Dapagliflozin remained dominant and cost-saving versus sacubitril valsartan in all deterministic sensitivity analyses for base case analysis #1.

In the scenario analyses for base case analysis #2 and base case analysis #3, a change of the discounting factor for benefits to 0% had the largest effect on reducing the ICER, to an ICER of £4,379/QALY (base case analysis #2) and £4,447/QALY (base case analysis #3), whereas a decrease of health state utility values by 20% had the largest effect on increasing the ICER, to an ICER of £7,267/QALY (base case analysis #2) and £7,311/QALY (base case analysis #3).

In summary, dapagliflozin remained dominant over sacubitril valsartan in all scenarios for base case analysis #1 and dapagliflozin remained highly cost-effective with ICERs well below £7,500/QALY in all scenarios for base case analysis #2 and base case analysis #3.

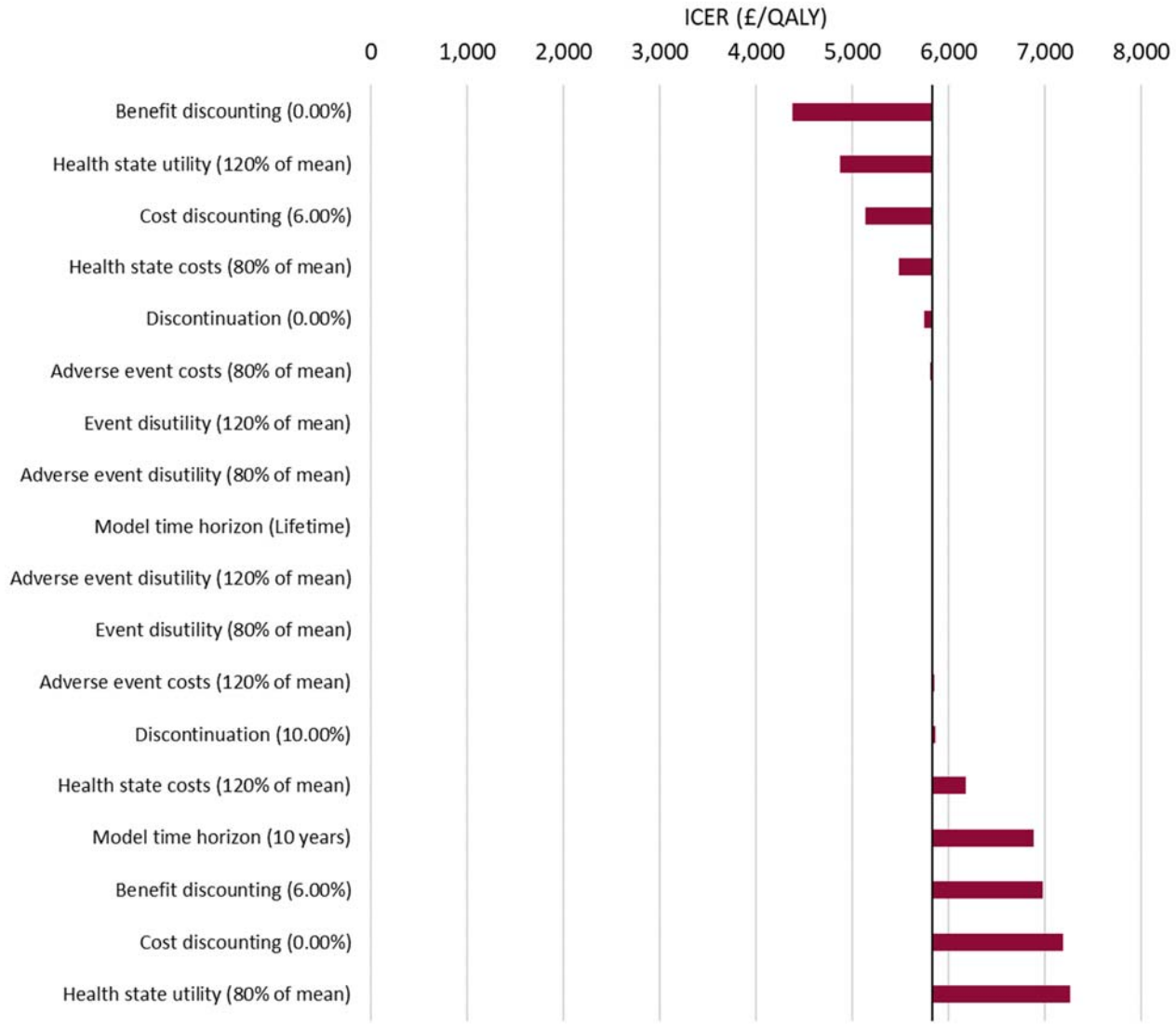
B.3.8.2.1 Base case analysis #1

Figure 34: Tornado plot of deterministic sensitivity analysis results – base case analysis #1



B.3.8.2.2 Base case analysis #2

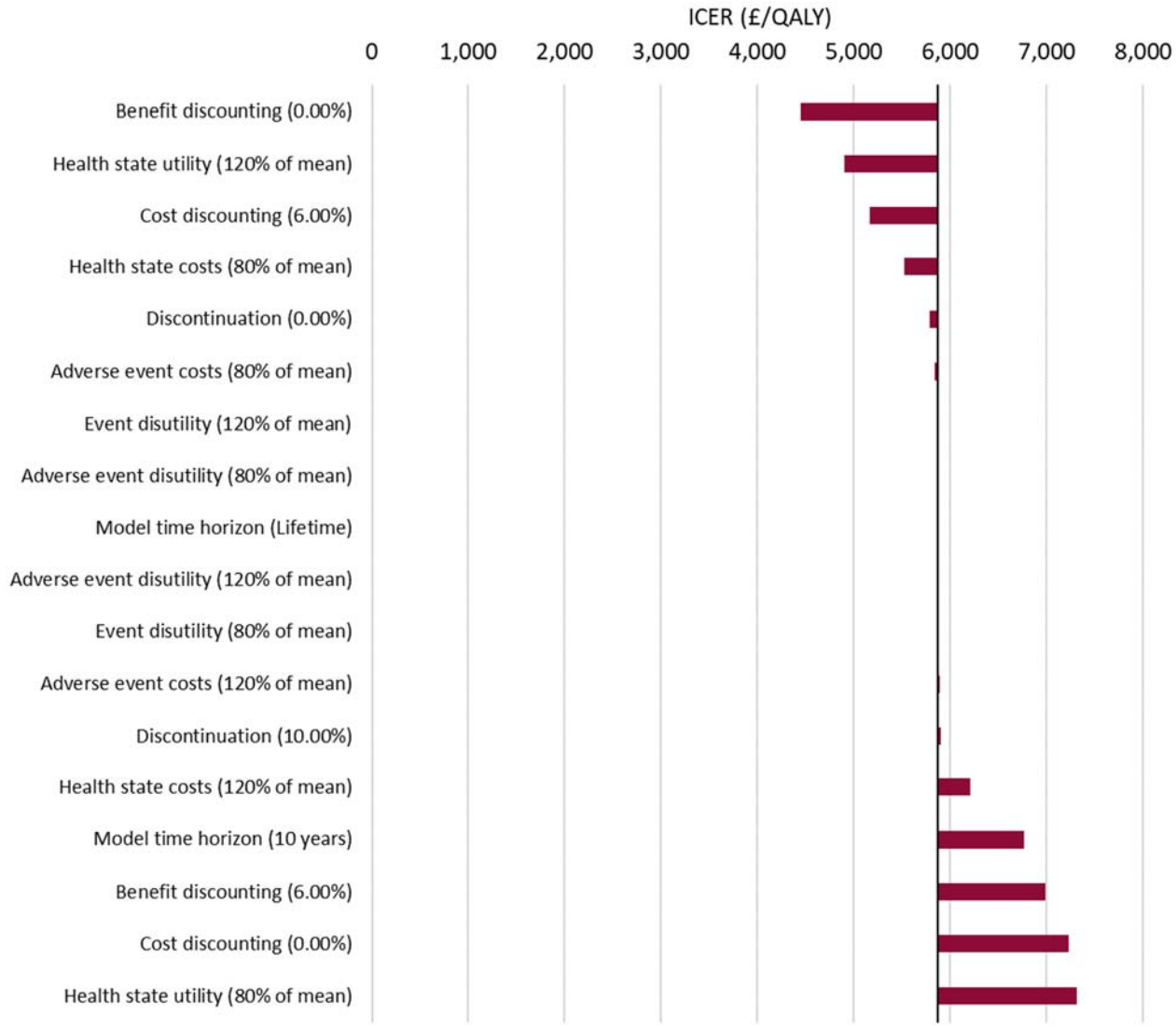
Figure 35: Tornado plot of deterministic sensitivity analysis results – base case analysis #2



Abbreviations: ICER, incremental cost-effectiveness ratio.

B.3.8.2.3 Base case analysis #3

Figure 36: Tornado plot of deterministic sensitivity analysis results – base case analysis #3



Abbreviations: ICER, incremental cost-effectiveness ratio.

B.3.8.3 Scenario analyses

Scenario analyses were conducted with alternative model inputs and assumptions (Table 51) to test the robustness of the model.

Table 51: Summary of scenario analyses conducted for base case analysis #2

Scenario	Base case	#	Alternative assumption or value
Mortality survival equations (all-cause mortality and CV mortality)	Weibull equation derived from ITT population	1.1	Gompertz equations derived from ITT population Other model inputs as per base case analysis #2
		1.2	Gompertz equations derived from ITT population Other model inputs as per base case analysis #3
		2.1	Log-logistic equations derived from ITT population Other model inputs as per base case analysis #2
		2.2	Log-logistic equations derived from ITT population Other model inputs as per base case analysis #3
		3.1	Lognormal equations derived from ITT population Other model inputs as per base case analysis #2
		3.2	Lognormal equations derived from ITT population Other model inputs as per base case analysis #3
Non-CV mortality	Highest rate of non-CV mortality from DAPA-HF and UK life tables	4.1	Non-CV mortality based on DAPA-HF only (based on all-cause mortality and CV mortality in DAPA-HF) Other model inputs as per base case analysis #2
		4.2	Non-CV mortality based on DAPA-HF only (based on all-cause mortality and CV mortality in DAPA-HF) Other model inputs as per base case analysis #3

Scenario	Base case	#	Alternative assumption or value
Treatment effect and background therapy	Adjusted equations derived from DAPA-HF ITT population Baseline characteristics: ACEi/ARB, beta-blocker, ±MRA (base case analysis #2), sacubitril valsartan, beta-blocker, ±MRA (base case analysis #3) Background therapy costs: based on ACEi/ARB/MRA proportional use from DAPA-HF	5.1	Unadjusted equations derived from DAPA-HF ACEi/ARB, beta-blocker, ±MRA subgroup Baseline characteristics: DAPA-HF ACEi/ARB, beta-blocker, ±MRA subgroup Background therapy costs: based on ACEi/ARB/MRA proportional use from DAPA-HF (as base case analysis #2)
		5.2	Unadjusted equations derived from DAPA-HF sacubitril valsartan, beta-blocker, ±MRA subgroup Baseline characteristics: DAPA-HF sacubitril valsartan, beta-blocker, ±MRA subgroup Background therapy costs: based on ACEi/ARB/MRA/sacubitril valsartan proportional use from DAPA-HF (as base case analysis #3)
		6	Baseline characteristics: DAPA-HF ITT population Background therapy costs: based on ACEi/ARB/MRA/sacubitril valsartan proportional use from DAPA-HF (as base case analysis #3)
		7	Unadjusted equations derived from ITT population Baseline characteristics: DAPA-HF ITT population Background therapy costs: based on ACEi/ARB/MRA/sacubitril valsartan proportional use from DAPA-HF (as base case analysis #3)
Background therapy costs	Adjusted equations derived from DAPA-HF ITT population Base case analysis #2: based on ACEi/ARB/MRA proportional use from DAPA-HF Base case analysis #3: based on ACEi/ARB/MRA/sacubitril valsartan proportional use from DAPA-HF	8.1	Based on ACEi/ARB/MRA proportional use from CPRD Other model inputs as per base case analysis #2
		8.2	Based on ACEi/ARB/MRA/sacubitril valsartan proportional use from CPRD Other model inputs as per base case analysis #3
KCCQ-TSS at baseline	Adjusted equations derived from DAPA-HF ITT population Baseline characteristics: ACEi/ARB, beta-blocker, ±MRA (base case analysis #2), sacubitril valsartan, beta-	9.1	Baseline characteristics: KCCQ-TSS > median subgroup (higher KCCQ-TSS score corresponds to better health status) Mean KCCQ-TSS quartile distribution at baseline: 0/0/52/48 Other model inputs as per base case analysis #2
		9.2	Baseline characteristics: KCCQ-TSS > median subgroup (higher KCCQ-TSS score corresponds to better health status)

Scenario	Base case	#	Alternative assumption or value
	blocker, ±MRA (base case analysis #3) Mean KCCQ-TSS quartile distribution at baseline: 23/25/28/24 (base case analysis #2) / 27/24/25/24 (base case analysis #3)		Mean KCCQ-TSS quartile distribution at baseline: 0/0/52/48 Other model inputs as per base case analysis #3
		10.1	Baseline characteristics: KCCQ-TSS ≤ median subgroup (lower KCCQ-TSS score corresponds to worse health status) Mean KCCQ-TSS quartile distribution at baseline: 46/50/4/0 Other model inputs as per base case analysis #2
		10.2	Baseline characteristics: KCCQ-TSS ≤ median subgroup (lower KCCQ-TSS score corresponds to worse health status) Mean KCCQ-TSS quartile distribution at baseline: 46/50/4/0 Other model inputs as per base case analysis #3
T2DM at baseline	Adjusted equations derived from DAPA-HF ITT population Baseline characteristics: ACEi/ARB, beta-blocker, ±MRA (base case analysis #2), sacubitril valsartan, beta-blocker, ±MRA (base case analysis #3) Proportion of patients with T2DM at baseline: 45% (base case analysis #2) / 44% (base case analysis #3)	11.1	Baseline characteristics: T2DM subgroup, 100% T2DM Other model inputs as per base case analysis #2
		11.2	Baseline characteristics: T2DM subgroup, 100% T2DM Other model inputs as per base case analysis #3
		12.1	Baseline characteristics: No T2DM subgroup, 0% T2DM Other model inputs as per base case analysis #2
		12.2	Baseline characteristics: No T2DM subgroup, 0% T2DM Other model inputs as per base case analysis #3
Age at baseline	Adjusted equations derived from DAPA-HF ITT population Baseline characteristics: ACEi/ARB, beta-blocker, ±MRA (base case analysis #2), sacubitril valsartan, beta-blocker, ±MRA (base case analysis #3) Mean age at baseline: 66.3 (base case analysis #2) / 66.7% (base case analysis #3)	13.1	Baseline characteristics: Age >65 subgroup Other model inputs as per base case analysis #2
		13.2	Baseline characteristics: Age >65 subgroup Other model inputs as per base case analysis #3
		14.1	Baseline characteristics: Age ≤65 subgroup Other model inputs as per base case analysis #2
		14.2	Baseline characteristics: Age ≤65 subgroup Other model inputs as per base case analysis #3
Geographical region	Adjusted equations derived from DAPA-HF ITT population Baseline characteristics: ACEi/ARB, beta-blocker, ±MRA (base case	15.1	Baseline characteristics: Europe subgroup Other model inputs as per base case analysis #2
		15.2	Baseline characteristics: Europe subgroup

Scenario	Base case	#	Alternative assumption or value
	analysis #2), sacubitril valsartan, beta-blocker, ±MRA (base case analysis #3)		Other model inputs as per base case analysis #3
Hypoglycaemia disutility	0.014 (Currie et al. 2006)	16.1	Disutility including the fear of hypoglycaemia: 0.047 (Currie et al. 2006) Other model inputs as per base case analysis #2
		16.2	Disutility including the fear of hypoglycaemia: 0.047 (Currie et al. 2006) Other model inputs as per base case analysis #3
DKA disutility	No disutilities applied	17.1	Statistically non-significant disutility for DKA: 0.0091 (Peasgood et al. 2016, random effects model) Other model inputs as per base case analysis #2
		17.2	Statistically non-significant disutility for DKA: 0.0091 (Peasgood et al. 2016, random effects model) Other model inputs as per base case analysis #3

Abbreviations: ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; MRA, mineralocorticoid receptor antagonist; CV, cardiovascular; DKA, diabetic ketoacidosis; HR, hazard ratio; ITT, intent to treat; MRA, mineralocorticoid receptor antagonist; T2DM, type 2 diabetes mellitus.

B.3.8.3.1 Scenario analysis inputs

Table 52: Patient baseline characteristics for scenario analyses (1/2)

Characteristic	DAPA-HF ITT (scenarios #6 and #7)		KCCQ-TSS > median subgroup (scenario #9)		KCCQ-TSS ≤ median subgroup (scenario #10)		No T2DM (scenario #11)	
	Mean	SE	Mean	SE	Mean	SE	Mean	SE
Age (years)	66.34	0.16	66.61	0.23	66.02	0.23	66.20	0.23
Female	0.23	0.01	0.18	0.01	0.27	0.01	0.24	0.01
BMI (kg/m2)	28.15	0.09	27.21	0.11	29.36	0.14	27.21	0.11
KCCQ-TSS Q1: 0-<58	0.23	0.01	0.00	0.00	0.46	0.01	0.20	0.01
KCCQ-TSS Q2: 58-<77	0.25	0.01	0.00	0.00	0.50	0.01	0.25	0.01
KCCQ-TSS Q3: 77-<92	0.28	0.01	0.52	0.01	0.04	0.00	0.30	0.01
KCCQ-TSS Q4: 92-100	0.24	0.01	0.48	0.01	0.00	0.00	0.25	0.01
NT-proBNP (pg/mL)	2342.53	43.52	1926.06	42.10	2739.98	78.59	2242.03	57.20
Ischaemic HF	0.56	0.01	0.54	0.01	0.59	0.01	0.51	0.01
Duration of HF >2 years	0.62	0.01	0.61	0.01	0.65	0.01	0.62	0.02
Prior hHF	0.47	0.01	0.48	0.01	0.47	0.01	0.46	0.01
LVEF	0.31	0.00	0.31	0.00	0.31	0.00	0.31	0.00
Creatinine (µmol/L)	104.44	0.44	103.89	0.62	105.56	0.66	100.71	0.55
T2DM	0.45	0.01	0.43	0.01	0.48	0.01	0.00	0.00

Abbreviations: BMI, body mass index, HF, heart failure; hHF, hospitalisation for heart failure; ITT, intention to treat; KCCQ-TSS, Kansas City Cardiomyopathy Questionnaire – total symptom score; LVEF, left ventricular ejection fraction; Q, quartile; SE, standard error; T2DM, type 2 diabetes mellitus.

Table 53: Patient baseline characteristics for scenario analyses (2/2)

Characteristic	T2DM (scenario #12)		Age >65 (scenario #13)		Age ≤65 (scenario #14)		Europe (scenarios #15)	
	Mean	SE	Mean	SE	Mean	SE	Mean	SE
Age (years)	66.52	0.21	73.86	0.11	56.30	0.17	[redacted]	[redacted]
Female	0.22	0.01	0.25	0.01	0.21	0.01	[redacted]	[redacted]
BMI (kg/m2)	29.30	0.13	27.57	0.10	28.93	0.15	[redacted]	[redacted]
KCCQ-TSS Q1: 0-<58	0.27	0.01	0.21	0.01	0.26	0.01	[redacted]	[redacted]
KCCQ-TSS Q2: 58-<77	0.25	0.01	0.25	0.01	0.24	0.01	[redacted]	[redacted]
KCCQ-TSS Q3: 77-<92	0.25	0.01	0.29	0.01	0.26	0.01	[redacted]	[redacted]
KCCQ-TSS Q4: 92-100	0.23	0.01	0.25	0.01	0.23	0.01	[redacted]	[redacted]
NT-proBNP (pg/mL)	2464.83	66.72	2552.48	64.26	2062.04	53.82	[redacted]	[redacted]
Ischaemic HF	0.62	0.01	0.62	0.01	0.49	0.01	[redacted]	[redacted]
Duration of HF >2 years	0.64	0.02	0.67	0.02	0.56	0.02	[redacted]	[redacted]
Prior hHF	0.49	0.01	0.47	0.01	0.49	0.01	[redacted]	[redacted]
LVEF	0.31	0.00	0.32	0.00	0.30	0.00	[redacted]	[redacted]
Creatinine (µmol/L)	108.99	0.70	108.20	0.57	99.42	0.68	[redacted]	[redacted]
T2DM	1.00	0.00	0.45	0.01	0.46	0.01	[redacted]	[redacted]

Abbreviations: BMI, body mass index, HF, heart failure; hHF, hospitalisation for heart failure; ITT, intention to treat; KCCQ-TSS, Kansas City Cardiomyopathy Questionnaire – total symptom score; LVEF, left ventricular ejection fraction; Q, quartile; SE, standard error; T2DM, type 2 diabetes mellitus.

Table 54: Unadjusted CV-specific mortality and all-cause mortality survival equations, and unadjusted generalised estimating equations predicting hHF

Parameter	DAPA-HF ACEi/ARB, beta-blocker, ±MRA subgroup† (scenario #5.1)		DAPA-HF sacubitril valsartan, beta-blocker, ±MRA subgroup‡ (scenario #5.2)		DAPA-HF ITT population (scenario #7)	
	Mean	SE	Mean	SE	Mean	SE
CV-specific mortality (Weibull)						
Shape	1.132	0.050	1.609	0.294	1.152	0.049
Scale	3525.54	344.28	2258.16	695.64	3451.53	324.016
Dapagliflozin	0.164	0.082	0.241	0.258	0.170	0.078
All-cause mortality (Weibull)						
Shape	1.162	0.047	1.499	0.238	1.179	0.046
Scale	2880.71	235.13	2071.12	542.69	2827.70	221.425
Dapagliflozin	0.153	0.073	0.230	0.235	0.159	0.070
hHF						
Intercept	-4.521	0.067	-4.174	0.210	-4.494	0.063
Dapagliflozin	-0.306	0.100	-0.575	0.364	-0.328	0.097

† Subgroup defined as patients who are not treated with sacubitril valsartan at baseline
‡ subgroup defined as patients who are treated with sacubitril valsartan at baseline
Abbreviations: ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; hHF, hospitalisation for heart failure; MRA, mineralocorticoid receptor antagonist; CV, cardiovascular; ITT, intent to treat; MRA, mineralocorticoid receptor antagonist.

Table 55: Unit costs associated with standard care (background therapy) for scenario analyses

Items	Therapies	Proportion of patients on therapies	Source	Annual cost of therapy	Source	Total annual cost
Annual cost of SC (scenario #8.1)	ACEi	50.6%	CPRD, see Table 5	£6.89	See Appendix N: Weighted average therapy costs	£20.25
	ARB	21.9%		£36.27		
	MRA	22.3%		£39.56		
Annual cost of SC (scenario #8.2)	ACEi	50.6%	CPRD, see Table 5	£6.89	See Appendix N: Weighted average therapy costs	£35.77
	ARB	21.9%		£36.27		
	MRA	22.3%		£39.56		
	Sacubitril valsartan	1.3%		£1,193.55		

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blocker; CPRD, Clinical Practice Research Datalink; MRA, mineralocorticoid-receptor antagonist.

B.3.8.3.2 Scenario analysis results

Table 56: Summary of scenario analyses conducted

Scenario	#	Alternative assumption or value	ΔCosts (£)	ΔQALYs	ICER
Base case analysis #2			£2,750	0.472	£5,830
Base case analysis #3			£2,707	0.461	£5,866
Mortality survival equations (all-cause mortality and CV mortality)	1.1	Gompertz equations derived from ITT population Other model inputs as per base case analysis #2	£1,840	0.253	£7,264
	1.2	Gompertz equations derived from ITT population Other model inputs as per base case analysis #3	£1,811	0.253	£7,162
	2.1	Log-logistic equations derived from ITT population Other model inputs as per base case analysis #2	£2,918	0.494	£5,907
	2.2	Log-logistic equations derived from ITT population Other model inputs as per base case analysis #3	£2,894	0.491	£5,894
	3.1	Lognormal equations derived from ITT population Other model inputs as per base case analysis #2	£3,268	0.567	£5,768
	3.2	Lognormal equations derived from ITT population Other model inputs as per base case analysis #3	£3,266	0.569	£5,743
Non-CV mortality	4.1	Non-CV mortality based on DAPA-HF only (based on all-cause mortality and CV mortality in DAPA-HF) Other model inputs as per base case analysis #2	£2,794	0.485	£5,761
	4.2	Non-CV mortality based on DAPA-HF only (based on all-cause mortality and CV mortality in DAPA-HF) Other model inputs as per base case analysis #3	£2,772	0.479	£5,790

Scenario	#	Alternative assumption or value	ΔCosts (£)	ΔQALYs	ICER
Treatment effect and background therapy	5.1	Unadjusted equations derived from DAPA-HF ACEi/ARB, beta-blocker, ±MRA subgroup Baseline characteristics: DAPA-HF ACEi/ARB, beta-blocker, ±MRA subgroup Background therapy costs: based on ACEi/ARB/MRA proportional use from DAPA-HF (as base case analysis #2)	£2,781	0.428	£6,492
	5.2	Unadjusted equations derived from DAPA-HF sacubitril valsartan, beta-blocker, ±MRA subgroup Baseline characteristics: DAPA-HF sacubitril valsartan, beta-blocker, ±MRA subgroup Background therapy costs: based on ACEi/ARB/MRA/sacubitril valsartan proportional use from DAPA-HF (as base case analysis #3)	£2,626	0.577	£4,553
	6	Baseline characteristics: DAPA-HF ITT population Background therapy costs: based on ACEi/ARB/MRA/sacubitril valsartan proportional use from DAPA-HF (as base case analysis #3)	£2,817	0.471	£5,985
	7	Unadjusted equations derived from ITT population Baseline characteristics: DAPA-HF ITT population Background therapy costs: based on ACEi/ARB/MRA/sacubitril valsartan proportional use from DAPA-HF (as base case analysis #3)	£2,845	0.442	£6,429
Background therapy costs	8.1	Based on ACEi/ARB/MRA proportional use from CPRD Other model inputs as per base case analysis #2	£2,738	0.472	£5,804
	8.2	Based on ACEi/ARB/MRA/sacubitril valsartan proportional use from CPRD Other model inputs as per base case analysis #3	£2,630	0.461	£5,699
KCCQ-TSS at baseline	9.1	Baseline characteristics: KCCQ-TSS > median subgroup Mean KCCQ-TSS quartile distribution at baseline: 0/0/52/48 Other model inputs as per base case analysis #2	£2,946	0.491	£6,005
	9.2	Baseline characteristics: KCCQ-TSS > median subgroup Mean KCCQ-TSS quartile distribution at baseline: 0/0/52/48 Other model inputs as per base case analysis #3	£3,023	0.491	£6,162
	10.1	Baseline characteristics: KCCQ-TSS ≤ median subgroup Mean KCCQ-TSS quartile distribution at baseline: 46/50/4/0 Other model inputs as per base case analysis #2	£2,518	0.445	£5,659

Scenario	#	Alternative assumption or value	ΔCosts (£)	ΔQALYs	ICER
	10.2	Baseline characteristics: KCCQ-TSS ≤ median subgroup Mean KCCQ-TSS quartile distribution at baseline: 46/50/4/0 Other model inputs as per base case analysis #3	£2,591	0.445	£5,822
T2DM at baseline	11.1	Baseline characteristics: T2DM subgroup, 100% T2DM Other model inputs as per base case analysis #2	£2,802	0.442	£6,332
	11.2	Baseline characteristics: T2DM subgroup, 100% T2DM Other model inputs as per base case analysis #3	£2,874	0.442	£6,495
	12.1	Baseline characteristics: No T2DM subgroup, 0% T2DM Other model inputs as per base case analysis #2	£2,668	0.491	£5,435
	12.2	Baseline characteristics: No T2DM subgroup, 0% T2DM Other model inputs as per base case analysis #3	£2,745	0.491	£5,593
Age at baseline	13.1	Baseline characteristics: Age >65 subgroup Other model inputs as per base case analysis #2	£2,468	0.415	£5,944
	13.2	Baseline characteristics: Age >65 subgroup Other model inputs as per base case analysis #3	£2,534	0.415	£6,103
	14.1	Baseline characteristics: Age ≤65 subgroup Other model inputs as per base case analysis #2	£2,926	0.500	£5,854
	14.2	Baseline characteristics: Age ≤65 subgroup Other model inputs as per base case analysis #3	£3,006	0.500	£6,015
Geographical region	15.1	Baseline characteristics: Europe subgroup Other model inputs as per base case analysis #2	£2,688	0.462	£5,819
	15.2	Baseline characteristics: Europe subgroup Other model inputs as per base case analysis #3	£2,762	0.462	£5,980
Hypoglycaemia disutility	16.1	Disutility including the fear of hypoglycaemia: 0.047 (Currie et al. 2006) Other model inputs as per base case analysis #2	£2,750	0.472	£5,830
	16.2	Disutility including the fear of hypoglycaemia: 0.047 (Currie et al. 2006)	£2,707	0.461	£5,867

Scenario	#	Alternative assumption or value	ΔCosts (£)	ΔQALYs	ICER
		Other model inputs as per base case analysis #3			
DKA disutility	17.1	Statistically non-significant disutility for DKA: 0.0091 (Peasgood et al. 2016, random effects model) Other model inputs as per base case analysis #2	£2,750	0.472	£5,830
	17.2	Statistically non-significant disutility for DKA: 0.0091 (Peasgood et al. 2016, random effects model) Other model inputs as per base case analysis #3	£2,707	0.461	£5,867

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blocker; CV, cardiovascular; DKA, diabetic ketoacidosis; hHF, hospitalisation for heart failure; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; ITT, intent-to-treat; MRA, mineralocorticoid-receptor antagonist; QALY, quality adjusted life year; T2DM, type 2 diabetes mellitus.

B.3.8.4 Summary of sensitivity analyses results

Results from the PSAs were similar to the results of the deterministic base case results, showing the model to be robust to uncertainty associated with input parameters, and showing dapagliflozin to be cost-effective as an add-on therapy to ACEi/ARB, beta-blocker, ±MRA and as an add-on therapy to sacubitril valsartan, beta-blocker, ±MRA. Additionally, the cost-effectiveness conclusion of the base case analyses remained unchanged in the DSAs and the scenario analyses, further demonstrating the model to be robust to variation to model inputs and assumptions.

Notably, the scenario analyses showed base case analysis #1 to be robust in demonstrating dapagliflozin to be dominant over sacubitril valsartan, indicating that dapagliflozin should be used ahead of sacubitril valsartan in UK clinical practice in order to optimise use of NHS resources. Cost-effectiveness estimates for base case analyses #2 and #3 were consistently below £7,500 per QALY gained in all scenario analyses conducted, including the scenario analysis by T2DM status, age at baseline (>/≤ 65) and baseline KCCQ-TSS (>/≤ median) as a measure of disease severity.

Finally, the scenario analyses (#6) of the DAPA-HF ITT population provides evidence that dapagliflozin is cost-effective when used as an add-on therapy in a cohort with different combinations of background therapies.

B.3.9 Subgroup analysis

Please see scenario analyses in Section B.3.8.3. No further exploration of subgroups was considered in the cost-effectiveness assessment.

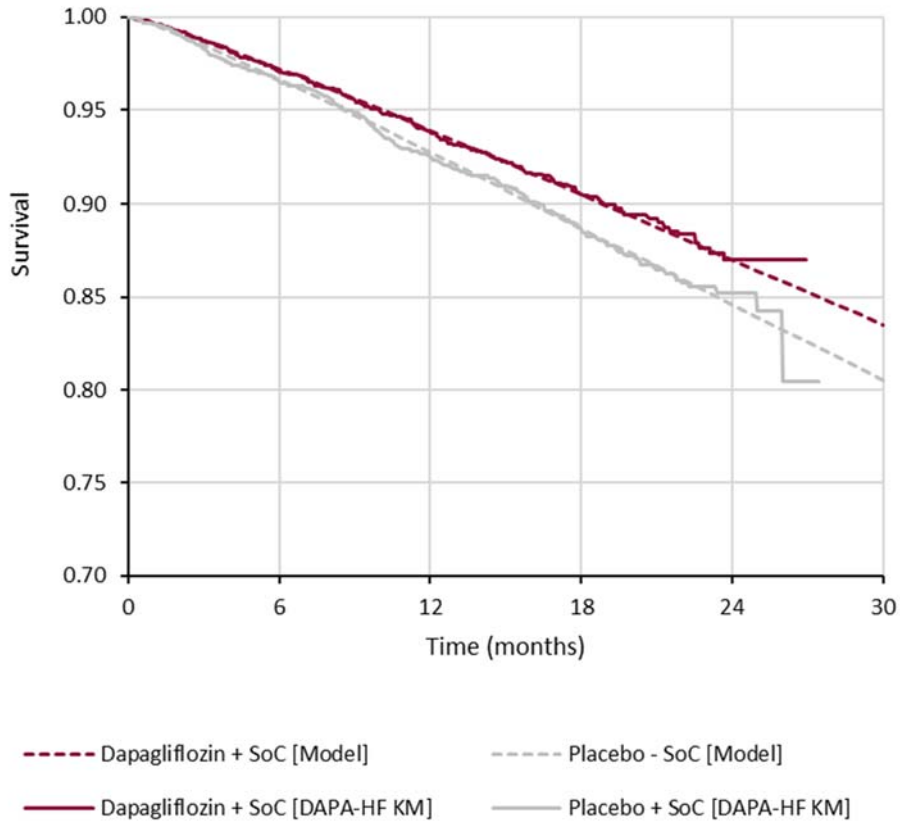
B.3.10 Validation

B.3.10.1 Validation of cost-effectiveness analysis

External validation of the model was carried out through clinical expert input throughout the development and validation process of the model.

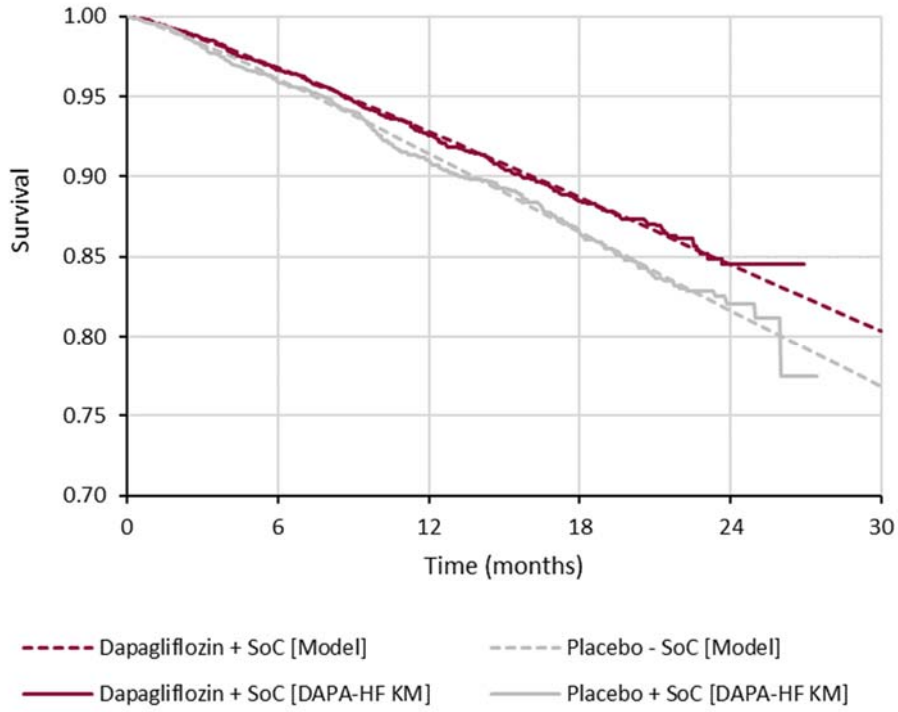
Internal validation was undertaken to the results of DAPA-HF to ensure the model's ability to reproduce observed outcomes. Predicted event incidence was compared with observed incidence in each subpopulation, with model performance assessed statistically and by inspection. The model produced results which closely aligned with trial outcomes, with treatment specific survival outcomes corresponding to trial outcomes with an R^2 of 0.994 for all-cause mortality, and a mean absolute percentage error of 2.8% in estimating the incidence of hHF across modelled subgroups. Furthermore, visual inspection did not show a tendency for the model to systematically under- or over-estimate event incidence from the trial. Validation plots of all-cause mortality, CV mortality, and hHF event incidence are shown in Figure 37–Figure 39. These figures show the outcomes in the DAPA-HF ITT population against the predicted outcomes – the DAPA-HF ITT population is displayed as the survival equations and risk equations were derived from IPD from the DAPA-HF ITT population.

Figure 37: Observed and predicted incidence of CV mortality – DAPA-HF ITT population



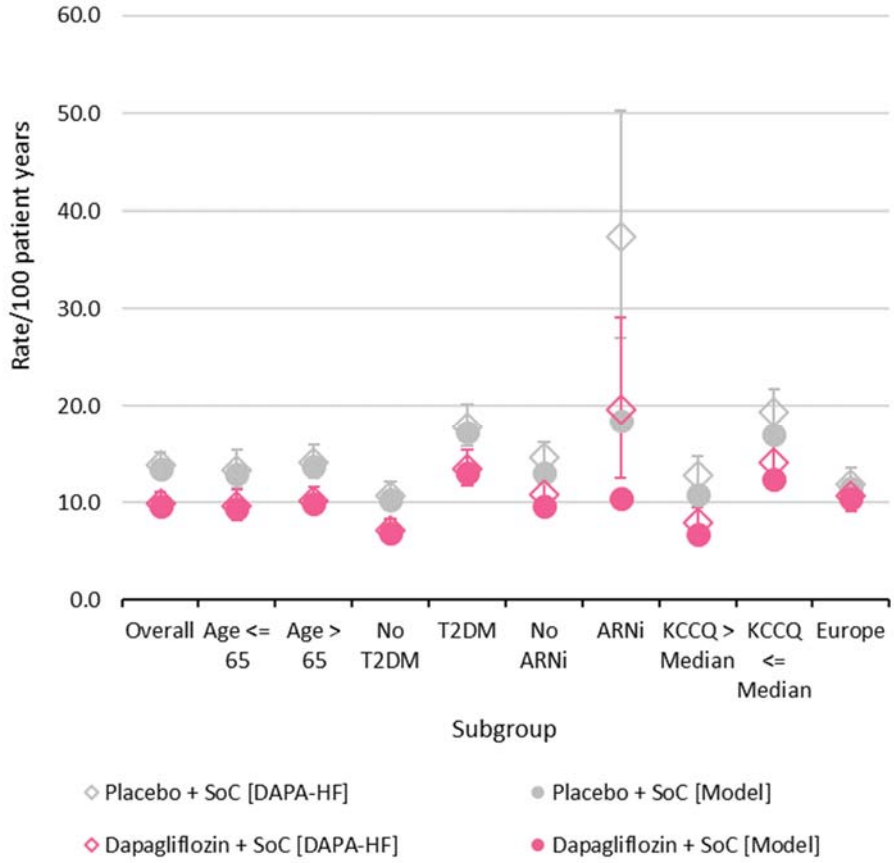
Abbreviations: CV, cardiovascular; KM, Kaplan-Meier; SC, standard care.

Figure 38: Observed and predicted incidence of all-cause mortality



Abbreviations: KM, Kaplan-Meier; SC, standard care.

Figure 39: Observed and predicted incidence of hHF events



Abbreviations: hHF, hospitalisation for heart failure; KM, Kaplan-Meier; SC, standard care.

B.3.11 Interpretation and conclusions of economic evidence

No previous economic evaluation of dapagliflozin for the treatment of HFrEF has been published. The cost-effectiveness model used for the economic evaluation of dapagliflozin builds on the modelling approaches previously accepted by the NICE Committee (43, 44), by including a larger number of health states to capture the impact of disease severity on event risk and HRQoL.

Model inputs were primarily derived from the DAPA-HF trial, including inputs for baseline characteristics, health state transition probabilities, health state utility values, event disutilities, survival equations, risk equations, AE incidence rates, and treatment discontinuation rates. Additional model inputs for AE disutilities, unit costs, and resource use were identified from the literature or from NHS National Reference Costs.

Base case analysis #1, based on the results from a MAIC and comparing dapagliflozin versus sacubitril valsartan, showed dapagliflozin to be dominant over sacubitril valsartan. As such, there is cost-effectiveness evidence to suggest that dapagliflozin should be used ahead of sacubitril valsartan in clinical practice to optimise use of NHS resources.

In base case analyses #2 and #3, dapagliflozin was found to be highly cost-effective as an add-on therapy to standard care for the treatment of HFrEF versus placebo, with standard care defined as ACEi/ARB, beta-blocker, ±MRA or sacubitril valsartan, beta-blocker, ±MRA, respectively. The ICERs associated with dapagliflozin add-on therapy was £5,830 per QALY gained and £5,866 per QALY gained, respectively.

Probabilistic and deterministic sensitivity analyses showed the cost-effectiveness model to be robust to variation in model parameters. The probabilistic base case results were closely aligned with the deterministic base case results, and all the scenarios in the DSA and in the scenario analyses were associated with a dominant result or ICERs below £7,500 per QALY gained.

In summary, the cost-effectiveness analysis showed dapagliflozin to represent a cost-effective use of NHS resources, as an alternative to sacubitril valsartan and as an add-on therapy to standard care for the treatment of HFrEF, regardless of the definition of standard care.

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Appendices

C. Appendix C: Summary of product characteristics (SmPC) and European public assessment report (EPAR)

D. Appendix D: Identification, selection and synthesis of clinical evidence

E. Appendix E: Subgroup analyses

F. Appendix F: Additional MAIC data

G. Appendix G: Published cost-effectiveness studies

H. Appendix H: Health-related quality-of-life studies

I. Appendix I: Cost and healthcare resource identification, measurement and valuation

J. Appendix J: Clinical outcomes and disaggregated results from the model

K. Appendix K: Checklist of confidential information

L. Appendix L: Additional clinical data – DECLARE-TIMI 58

M. Appendix M: Inflation factors

N. Appendix N: Weighted average therapy costs

O. Appendix O: UK life tables

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Dapagliflozin for treating heart failure with reduced ejection fraction [ID1656]

Clarification questions

June 2020

File name	Version	Contains confidential information	Date
ID1656 Dapagliflozin ERG Clarification Qs Response [redacted]	V1	No	3rd July 2020

Notes for company

Highlighting in the template

Square brackets and grey highlighting are used in this template to indicate text that should be replaced with your own text or deleted. These are set up as form fields, so to replace the prompt text in [grey highlighting] with your own text, click anywhere within the highlighted text and type. Your text will overwrite the highlighted section.

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Section A: Clarification on effectiveness data

Decision problem

A1. Priority question: Dapagliflozin + standard care (SC) is compared separately to sacubitril valsartan + SC and SC alone in two separate analyses, i.e. base case #1 and base case #2, respectively. However, SC for both analyses is angiotensin-converting-enzyme inhibitor (ACEi, or angiotensin receptor blocker (ARB), beta-blocker, ± mineralocorticoid receptor antagonist (MRA), which is positioned in the primary care setting in Figure 3 of the company submission.

a. **TA388 states that sacubitril valsartan should be started by a heart failure specialist with access to a multidisciplinary heart failure team. Does the current positioning of base case #1 in the treatment pathway reflect the population that would have sacubitril valsartan in UK clinical practice? If not, please provide an updated figure.**

Yes, the current positioning of base case analysis #1 reflects the population that would have sacubitril valsartan in UK clinical practice, that is, in accordance with the marketing authorisation of sacubitril valsartan, this population excluded patients with EF>35% and excludes patients with high potassium and/or hypotension. It is proposed that the population in base case analysis #1 would not need to wait for a specialist appointment to initiate treatment with dapagliflozin, as initiation could be undertaken in primary care, given the extensive clinical experience primary care clinicians have accumulated in initiating dapagliflozin for type 2 diabetes patients, over more than 7 years. Sacubitril valsartan would remain as a specialist initiation treatment for this patient population.

The current proposed positioning of dapagliflozin immediately post standard care (ACEi/ARB + BB ± MRA) is split between 2 distinct populations:

1. Patients that would currently progress to receiving sacubitril valsartan (base case analysis #1). These patients need to align with the marketing authorisation of sacubitril valsartan, i.e. patients

need to have EF ≤35% and must not have hyperkalaemia (serum potassium >5.4 mmol/L) and/or hypotension.

2. Patients that would not progress to receiving sacubitril valsartan and would remain on SC alone (base case analysis #2). These patients are ineligible for sacubitril valsartan, or do not progress to receiving sacubitril valsartan due to other reasons, for example due to the complexity associated with sacubitril valsartan initiation and titration.

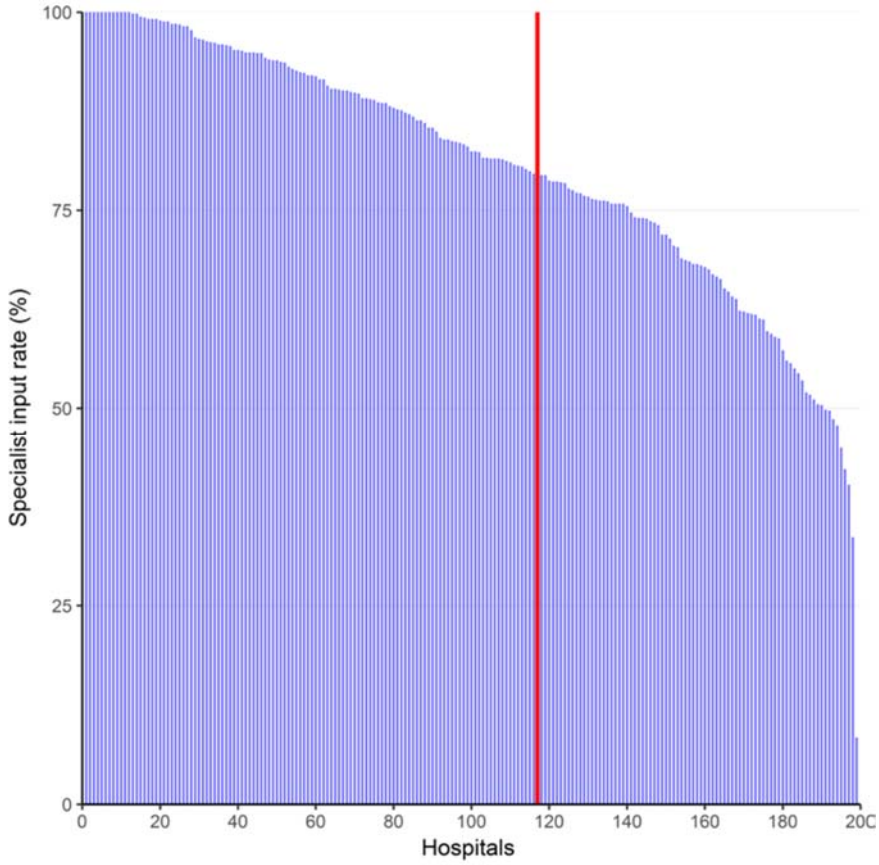
b. Please provide more information on the extent of sacubitril valsartan use in current NHS practice with supporting references.

Monthly dispensing of sacubitril valsartan equates to use in approximately 34,021 patients (IQVIA UK data; month Feb 2020 pre COVID-19). Applying this to 66% of the UK HF population (i.e. the HFrEF population according to the NICOR HF audit) equates to sacubitril valsartan use in approximately 8.3% of the UK HFrEF population (based on UK population of 66.65 million and diagnosed HF prevalence according to QOF 2018/19 of 0.93% (1)).

A2. Please provide more information on the geographical variation in the access to specialist care mentioned in Table 1 of the company submission.

According to the NICOR 2019 Heart Failure Audit, there is substantial inter-hospital variation of specialist input for heart failure admissions. Only 59% of hospitals achieved specialist review rates of over 80%, whilst specialist review rates were less than 80% of patients in 41% of hospitals. This variability is highlighted in Figure 1 below, taken from the report.

Figure 1: NICOR 2019 Heart Failure Audit; Inter-hospital variation in percentage of HF patients seen by a specialist (2017/18)



Note: Hospitals to the right of the red line are not achieving target of 80% of heart failure patients seen by a specialist. Data from 199 hospitals, 4 hospitals reporting <20 cases are excluded.
Source: National Heart Failure Audit 2019 Summary Report (2).

A3. The following questions relate to Section B.1.3.3 of the company submission:

a. Please provide values for the overall crude HF incidence rate for 2002 and 2014 in a) the full UK population and b) people aged ≥85 years.

The text in Section B.1.3.3 "While the overall crude incidence rate for HF per 100 000 population in the UK decreased by 7%" is erroneous; this should state "While the overall **standardised** incidence rate for HF per 100 000 population in the **EU** decreased by 7%". Conrad et al, 2018 does not report crude incidence per 100,000 of population for the UK (3); standardised incidence rate for the overall EU population was 358 per 100,000 in 2002 and 332 per 100,000. Standardised or crude incidence rates are not reported for people aged ≥85 years.

b. Please provide the number of individuals in the UK with new-onset HF in 2002 and 2014.

Conrad et al, 2018, reports that "new diagnoses of heart failure increased by 12% from 170,727 in 2002 to 190,798 in 2014" for the UK.

c. Please provide the number of people in the UK living with HF in 2002 and 2014.

Conrad et al, 2018 report that “absolute number of people living with heart failure in the UK increased by 23% over the study period, from 750,127 in 2002 (1.3% of the total population) to 920,616 in 2014 (1.4% of the total population)”. It should be noted that this estimate is higher than that estimated in the QOF (0.93%) (1), which may be due to differences in data collection methods.

A4. Section B.1.3.8.3 of the company submission mentions that “there is extensive experience of safety profile of dapagliflozin, particularly from primary care, from its use for over 7 years as an anti-diabetes medication”.

a. Please provide the percentage of people with diabetes who are prescribed dapagliflozin for diabetes in the primary care setting without assessment by specialist care team, with supporting references.

According to IQVIA data, in February 2020 (last month before COVID-19), there were 1,314 items of Forxiga dispensed in the hospital setting, vs. 138,864 in the community. Dispensing in primary care therefore represented 99% of total dispensing in February. Although this may not factor in those patients who are assessed by a specialist and subsequently referred to primary care for a prescription, there are no reliable data sources to answer this exact question, although it is worth noting that the type 2 diabetes guidelines NG28 only recommend specialist referral for specific complications of diabetes, unexplained discrepancies in laboratory measurements, and for initiation of GLP-1 agonists.

b. Please elaborate on whether specialist supervision would be required when treating people with dapagliflozin for HFrEF in the UK (as indicated in the British Society for Heart Failure (BSH) submission to NICE for this appraisal).

AstraZeneca does not believe that specialist care is required for initiation of dapagliflozin in people with HFrEF, as discussed in the company submission in Section B.1.3.8.3. AstraZeneca understands the position of the BSH and agrees that in some clinical situations certain therapies should only be initiated by specialists. For example, therapies that have complex initiation practicalities, significant side effects, narrow therapeutic window or underlying disease that requires intense monitoring in the early period post initiation. Necessarily, specialist initiation limits access to certain therapies, however this must be carefully balanced against the risk that eligible patients may in some situations have benefits of treatment unnecessarily restricted due to lack of access to specialists. AstraZeneca notes that in NG106, ACEi/ARB, beta-blocker and MRA do not require specialist invitation in HFrEF patients. We have therefore given careful consideration as to whether dapagliflozin should require specialist initiation for indicated patients with HFrEF. While we believe that in many circumstances dapagliflozin will be initiated by a HF specialist, expert opinion has led us to understand that HFrEF patients, when increasingly symptomatic, will present to their GP. For GPs that are experienced in managing such patients and have experience using dapagliflozin (or other SGLT2 inhibitors) in people with type 2 diabetes, initiation of dapagliflozin either independently of, or in parallel with referral to a HF specialist, would be appropriate. In such a situation, if dapagliflozin was limited to specialist initiation only, these patients would have clinical benefit unnecessarily delayed or entirely restricted.

It is also important to understand the context of how HF services are delivered in the UK. A recent publication in the British Journal of Cardiac Nursing (4) described the significant challenges of delivering specialist HF services in the UK. The review highlighted a survey conducted by the British Society of Heart Failure that many HF specialist nurse services had 'unmanageable caseloads', with several services reporting to have less than the recommended 1 HF specialist nurse per 100,000 population. The review went on to recommend that due to increasing prevalence of HF and the need for HF nurses to manage HF with preserved ejection fraction, 3 to 4 HF nurses per 100,000 people would be desirable. In this context, restriction of dapagliflozin to specialist initiation when not clinically warranted could unnecessarily stretch and overburden already challenged HF specialist services. AstraZeneca therefore believes it is critical for people living with HF that NICE does not limit the recommendation of dapagliflozin to be specialist initiation only.

For additional clarity, the rationale for non-specialist prescribing for dapagliflozin is:

- There is extensive experience of safety profile of dapagliflozin, particularly from primary care, from its use for over 7 years as an anti-diabetes medication; in addition, HFrEF is a common comorbid condition of type 2 diabetes, (5) and therefore primary care clinicians will likely already have experience in using dapagliflozin in patients with HFrEF who also have diabetes.
- Dapagliflozin has no titration requirements and can therefore be easily initiated in primary care.
- The clinical benefits of dapagliflozin are observed early on following initiation (in an exploratory analysis of cumulative data, the p-value was <0.05 for the primary endpoint from 28-days onwards) (6) and continue with prolonged treatment (5); restriction to specialist initiation will delay treatment, and patients may therefore miss out on early benefits associated dapagliflozin treatment.
- The treatment effect of dapagliflozin is consistent regardless of background therapy for HF (7).
- Dapagliflozin has a favourable safety profile, with no serious adverse events (SAEs) with a frequency of >1% occurring more frequently with dapagliflozin than with placebo in DAPA-HF (5).
- The cost of dapagliflozin is substantially lower than the cost of recently recommended specialist treatments for HFrEF.

Systematic literature review

A5. Priority question: Please provide information regarding all aspects of the systematic review process, e.g. data extraction and risk of bias assessment, and justification of the methods of evidence synthesis

A total of four systematic literature reviews (SLRs) were conducted to identify the clinical, cost effectiveness, cost and resource use and health state utility value data for this submission. In all

cases Embase, Medline and the Cochrane library were searched. In addition, EconLit was interrogated for the cost and resource use and cost effectiveness SLRs. Relevant conference proceedings and clinical trials registries were also searched. Identified studies were independently assessed by two reviewers in order to determine whether they met the pre-defined inclusion/exclusion criteria; any discrepancies were resolved by a third reviewer. All studies identified as eligible studies during abstract screening were then screened at a full-text stage. Data from relevant publications were extracted into tables within the submission. Risk of bias was assessed using the relevant validated tool appropriate to the study design. No evidence synthesis was conducted as part of the SLRs.

A6. Please provide full details for the searches of conference proceedings and health technology assessment (HTA) body websites referred to in Appendices D.1.4 and G.2.4, including the specific resources searched, the search strategies, search terms used, and results.

These data are reported in Appendix D Table 61 of the submission.

A7. Please provide full search strategies for the clinical trial registries searches (clinicaltrials.gov and World Health Organization's International Clinical Trials Registry Platform) in Appendices D.1.4 and G.2.4.

This information is detailed in Table 1 below.

Table 1: Search strategies for clinical trial registry searches

Trial registry	Methods of search	Date searched	Keywords, hits
US NIH registry & results database	Relevant ongoing trials were identified by keyword search of https://clinicaltrials.gov	27/11/2019	Heart failure with reduced ejection fraction, 129 hits
WHO ICTRP registry	Relevant ongoing trials were identified by keyword search of http://apps.who.int/trialsearch/	28/11/2019	Heart failure with reduced ejection fraction, 324 records for 166 trials

A8. Please confirm that no literature searches were conducted to identify adverse event data for section B.2.10 (Adverse reactions).

No specific searches were conducted to identify adverse events alone. Relevant publications were identified via the clinical search.

A9. Please specify the host used to access EconLit for the search reported in Appendix G.

The host used to access EconLit was Ovid.

A10. Please justify the exclusion of full non-English publications in the systematic literature review (Table 57 of the company submission) and provide references for all publications excluded by this criterion.

In this systematic review, publications where the full text was non-English were excluded. Whilst this could potentially lead to language bias, this is common practice in many reviews with some publications reporting that English language studies have better study design standards or higher report completeness rates versus non-English language studies. The Cochrane Handbook acknowledges the risk of bias in reviews containing exclusively English language studies and recommends a 'case-by-case' decisions concerning the inclusion of non-English studies. On review of the publications that had been excluded as non-English language studies, these publications could also have been excluded from the review for other reasons. Therefore, in this case, we can be sure that the issue of language bias did not arise.

DAPA-HF trial

A11. Priority question: Section B.2.2 of the company submission specifies that people with New York Heart Association (NYHA) functional class ≥II were eligible to enter the DAPA-HF study.

a. **People are stratified into NYHA class II/III or IV in Table 7 of the company submission, but class II and 'III or IV' in the clinical study report (Table 14.2.2.3). Please provide the methodology for this stratification in the pre-specified subgroup analyses and provide all relevant results.**

For purposes of clarification, there is only one stratification of NYHA classes. This is

a) Class II

b) Class III or IV

The prespecified subgroups listed in Table 7 of the company submission were likely misinterpreted by the ERG, and NYHA class II/III is not a subgroup. Clinical results for the NYHA subgroup analysis are provided in Table 11 of the company submission.

Patients were stratified according to their NYHA class at the enrolment visit. The investigator evaluated the patient's NYHA class according to the study plan, based on definitions in Table 2 below, and the result for the assessment was recorded in the eCRF.

Table 2: NYHA Functional Classification

NYHA stage	Criteria
I	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnoea (shortness of breath).
II	Slight limitation of physical activity. Comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnoea (shortness of breath).
III	Marked limitation of physical activity. Comfortable at rest. Less than ordinary activity causes fatigue, palpitation, or dyspnoea.
IV	Unable to carry on any physical activity without discomfort. Symptoms of heart failure at rest. If any physical activity is undertaken, discomfort increases.

Source: Appendix D for DAPA-HF Clinical Study Protocol.
Abbreviations: NYHA, New York Heart Association.

A12. Priority question: According to the Summary of Product Characteristics (Table 2 of the company submission) dapagliflozin is indicated in adults for the treatment of insufficiently controlled type 1 and type 2 diabetes mellitus (T1DM and T2DM).

a. **Please justify why people with insufficiently controlled T1DM were considered eligible for dapagliflozin.**

Dapagliflozin was originally licensed in 2012 for the T2DM indication. In 2019, following the DEPICT trial programme, the license was extended to T1DM as a separate indication.

b. **Please clarify why people with type 1 diabetes mellitus (T1DM) were excluded from the DAPA-HF trial and, consequently, from the systematic literature review (as per Table 57, Appendix D of company submission).**

At the time of designing the DAPA-HF trial in 2016, the safety profile for dapagliflozin in T1DM had not yet become available from the DEPICT trial programme. A key consideration for not including patients with T1DM was to avoid the extra monitoring and the high frequency of visits required for T1DM to adequately explore the safety profile in HFrEF patients with comorbid T1DM patients. The extra monitoring and higher frequency of visits would have greatly increased the burden on investigators and patients without T1DM, compared to a trial that excludes patients with comorbid T1DM. It was also decided that it would not be commensurate to introduce additional complexity of the trial through special monitoring instructions for T1DM patients, given the small proportion of patients expected to have comorbid T1DM.

c. **Please provide detailed treatment pathways (showing the positioning of dapagliflozin) for people with both HFrEF and insufficiently controlled T1DM or T2DM. Please comment on potential differences and implications compared to Figure 3 of the company submission.**

The DAPA-HF trial excluded patients with T1DM and data are not available for patients with HFrEF with comorbid T1DM; it would therefore be inappropriate for AstraZeneca to suggest how dapagliflozin

should be used in these patients and a separate treatment pathway has not been provided. Prescribing of dapagliflozin in such patients should be at the clinician's discretion.

Figure 3 in the company submission applies to patients both with and without comorbid T2DM, as explained in Section B.1.3.8.4 of the submission dossier. It is possible that based on T2DM guidelines, a HFrEF patient with comorbid T2DM may already be taking dapagliflozin as part of the management of their T2DM and associated complications. For T2DM patients who are not already receiving an SGLT2i for the management of their T2DM and associated complications, the pathway outlined in Figure 3 of the company submission would apply.

A13. In the company submission, HFrEF is defined as HF with a left ventricular ejection fraction (LVEF) <40%. However, TA388 recommends sacubitril valsartan only in people with a LVEF <35%.

a. What proportion of people in both arms of the DAPA-HF trial had a LVEF ≥35% and <40%?

In the DAPA-HF trial, [redacted] patients in the dapagliflozin arm and the placebo arm, respectively, had a baseline LVEF ≥35% and <40%.

b. How were people with a LVEF ≥35% handled for base-case #1 and #3, as they were ineligible for treatment with sacubitril valsartan in the UK population?

The patient population evaluated in base case analysis #1 were matching-adjusted in the MAIC to the patient population in the PARADIGM-HF trial for sacubitril valsartan. As such, the patient population evaluated in base case analysis #1 could only have LVEF <35%, as per the criteria for the PARADIGM-HF trial.

The patient population evaluated in base case analysis #3 was limited to the subgroup of patients in DAPA-HF who received sacubitril valsartan at baseline. Intuitively, this subgroup of patients have a LVEF <35%, given they are eligible for treatment with sacubitril valsartan. The LVEF restriction in this subgroup of patients is reflected in the lower mean LVEF in the baseline characteristics of base case analysis #3 (28.5%) compared to base case analysis #2 (31.3%).

c. Please clarify how LVEF was measured/ ascertained in the DAPA-HF trial.

The methods used to assess LVEF in DAPA-HF were: echocardiogram, radionuclide ventriculogram, contrast angiography or cardiac magnetic resonance imaging. The specific measure used to assess LVEF for each patient was not recorded.

A14. Please specify types of "cardiovascular procedures" and list all "other cardiovascular causes" included in the definition of CV death as an endpoint (Table 8 of company submission)

No additional details of these events were reported in the adjudicated results used for the CSR. The incidence of "cardiovascular procedures" and "other cardiovascular causes", included as part of CV death endpoint, is summarised in Table 3. There were a very small number of events (1 death due to

cardiovascular procedures in the dapagliflozin arm, 2 deaths due to other cardiovascular causes in the dapagliflozin arm, and 4 deaths due to other cardiovascular causes in the placebo arm). As such, these events had a very limited contribution to the CV-death endpoint.

Table 3: CV deaths in DAPA-HF

CV death	Dapagliflozin (N=2,373)	Placebo (N=2,371)
Any CV death	[redacted]	[redacted]
Death due to acute myocardial infarction	[redacted]	[redacted]
Sudden cardiac death	[redacted]	[redacted]
Death due to heart failure	[redacted]	[redacted]
Death due to stroke	[redacted]	[redacted]
Death due to cardiovascular procedures	[redacted]	[redacted]
Death due to cardiovascular haemorrhage	[redacted]	[redacted]
Death due to other cardiovascular causes	[redacted]	[redacted]

Source: DAPA-HF CSR, Table 14.2.6.3.
Abbreviations: CV, cardiovascular.

A15. According to section B.2.3.1 of the company submission, people with current acute decompensated HF (also known as acute HF) were excluded from the DAPA-HF trial. Please confirm that evidence presented is not relevant to people with acute HF.

As DAPA-HF did not include patients with acute decompensated HF the evidence presented is not relevant to this population.

A16. The following queries relate to page 17 of Appendix D of the company submission:

a. Some positive inotropic drugs are missing. Please provide a full list.

The full list of treatments included in the SLR is provided in Table 57 of the submission; no other treatments were considered. In line with the NICE scope, digoxin was not considered in the SLR.

b. Please clarify “other outcomes”.

“Other outcomes” refer to outcomes not listed in the inclusion criteria column, i.e. trials which did not report an outcome listed in the inclusion criteria column were excluded.

c. Please justify the exclusion of “RCTs providing only prognostic data”.

Such studies were excluded if they reported data that use particular patient characteristics/ factors to predict the disease course in patients, rather than reporting the response of a population to a relevant intervention.

Clinical effectiveness results

A17. Priority question: According to Figure 11 of the company submission, [redacted] As noted in the submission, while the effect size in the European subgroup was slightly less than in the overall population, there was no indication of interaction (p=0.38), the subgroup analyses were not powered to detect statistically significant differences between treatment groups, and geographic location was not identified as a treatment effect modifier. The ITT data from DAPA-HF are therefore most relevant in the current assessment.

Additional efficacy outcomes for (1) CV events and (2) hHF and urgent HF visits by region are presented in Table 4. Some of the 95% CIs presented in Table 4 overlap with 1, which is expected as the DAPA-HF trial was not powered for subgroup analyses. The results from the subgroup analyses across primary and secondary endpoints consistently show that there is no interaction between region and treatment effect, as indicated by the consistently high p-value for interaction (0.17–0.38).

Safety results by region are provided in Table 5. There is no indication to suggest that the adverse event profile in patients from Europe differ from the ITT population. Furthermore, the lack of interaction in the HR for all-cause mortality with region (see Table 4, p-value for interaction: 0.37) is consistent with the observation that the adverse event profile for the Europe subgroup does not differ from the ITT population.

Table 4: Efficacy outcomes in DAPA-HF by region subgroup

Outcome	Geographic subgroup region	Dapagliflozin		Placebo		HR (95% CI)	Interaction p-value
		N	Proportion with event	N	Proportion with event		
CV death, hHF or urgent HF visit (primary endpoint)	Asia	543	14.2%	553	20.6%	0.65 (0.49, 0.87)	0.3818
	Europe	1,094	17.6%	1,060	20.6%	0.84 (0.69, 1.01)	
	N. America	335	16.1%	342	21.3%	0.73 (0.51, 1.03)	
	S. America	401	15.5%	416	23.3%	0.64 (0.47, 0.88)	
CV death (component of primary endpoint)	Asia	543	[redacted]	553	[redacted]	[redacted]	[redacted]
	Europe	1,094	[redacted]	1,060	[redacted]	[redacted]	
	N. America	335	[redacted]	342	[redacted]	[redacted]	
	S. America	401	[redacted]	416	[redacted]	[redacted]	
hHF or urgent HF visit (component of primary endpoint)	Asia	543	[redacted]	553	[redacted]	[redacted]	[redacted]
	Europe	1,094	[redacted]	1,060	[redacted]	[redacted]	
	N. America	335	[redacted]	342	[redacted]	[redacted]	
	S. America	401	[redacted]	416	[redacted]	[redacted]	
CV death or hHF (secondary endpoint)	Asia	543	[redacted]	553	[redacted]	[redacted]	[redacted]
	Europe	1,094	[redacted]	1,060	[redacted]	[redacted]	
	N. America	335	[redacted]	342	[redacted]	[redacted]	
	S. America	401	[redacted]	416	[redacted]	[redacted]	
All-cause death (secondary endpoint)	Asia	543	[redacted]	553	[redacted]	[redacted]	[redacted]
	Europe	1,094	[redacted]	1,060	[redacted]	[redacted]	
	N. America	335	[redacted]	342	[redacted]	[redacted]	
	S. America	401	[redacted]	416	[redacted]	[redacted]	

Source: DAPA-HF CSR Tables 14.2.2.3 (primary endpoint), 14.2.2.5 (CV death), 14.2.2.6 (hHF or urgent HF visit), 14.2.2.4 (CV death or hHF), 14.2.6.2 (all-cause death)
Abbreviations: CI, confidence interval; hHF, hospitalisation for heart failure; HR, hazard ratio.

Table 5: AEs specified as of interest in DAPA-HF, European subgroup

AE, n (%)	Dapagliflozin (N=1,094)	Placebo (N=1,059)
On treatment†		
AE with an outcome of death	[redacted]	[redacted]
SAE	[redacted]	[redacted]
AE leading to discontinuation	[redacted]	[redacted]
AE leading to dose interruption	[redacted]	[redacted]
AE leading to dose reduction	[redacted]	[redacted]
AE possibly related to investigational product	[redacted]	[redacted]
Definite or probable diabetic ketoacidosis	[redacted]	[redacted]
Major hypoglycaemic event	[redacted]	[redacted]
Symptoms of volume depletion	[redacted]	[redacted]
Fracture AE	[redacted]	[redacted]
Renal AE	[redacted]	[redacted]
Amputation	[redacted]	[redacted]
On and off treatment‡		
AE with an outcome of death	[redacted]	[redacted]
SAE	[redacted]	[redacted]
AE leading to discontinuation	[redacted]	[redacted]
AE leading to dose interruption	[redacted]	[redacted]
AE leading to dose reduction	[redacted]	[redacted]
AE possibly related to investigational product	[redacted]	[redacted]
Definite or probable diabetic ketoacidosis	[redacted]	[redacted]
Major hypoglycaemic event	[redacted]	[redacted]
Symptoms of volume depletion	[redacted]	[redacted]
Fracture AE	[redacted]	[redacted]
Renal AE	[redacted]	[redacted]
Amputation	[redacted]	[redacted]

†On treatment includes AEs with an onset date on or after date of first dose and up to and including 30 days following last dose of study drug.
‡On and off treatment includes AEs with an onset date on or after date of first dose of study drug.
Abbreviations: AE, adverse event; SAE, serious adverse event.

A18. Priority question: The follow questions pertain to the use of Kansas City Cardiomyopathy Questionnaire-Total Symptom Score (KCCQ-TSS) (Section B.2.6.3.3 of the company submission):

a. **Please explain why the 8-month timepoint was used to measure the change in KCCQ-TSS, given that data were collected at 4, 8, 12 and 24 months and the results of EQ-5D-5L are presented at 24 months.**

For the KCCQ-TSS endpoint, one single time point had to be chosen for the analysis of KCCQ-TSS as a secondary endpoint as part of the hierarchical testing under type I error control. Based on discussions with the FDA during the design of the DAPA-HF trial, it was considered most appropriate to use either 8-months or 12-months as the timepoint for the KCCQ-TSS secondary endpoint to allow sufficient time for a treatment effect to accrue and to demonstrate a long-term benefit, whilst avoiding excessive missing data due to death. The 8-months endpoint was chosen for DAPA-HF as this timepoint was also used for previous studies in HFrEF (8), and as this earlier timepoint is associated with less missing data.

The EQ-5D-5L was an exploratory endpoint and was descriptively analysed at 4, 8, 12 and 24 months. No primary timepoint was set for the analysis of the EQ-5D-5L data, as the analysis of these data were exploratory.

b. Please provide the percentage of people that had increased and reduced KCCQ-TSS scores at 8 months for the treatment and placebo groups. The data in Table 14 of the company submission is not consistent with the DAPA-HF clinical study report (Tables 23 to 25).

A corrected version of Table 14 of the company submission is provided in Table 6, based on the percentages reported in the CSR instead of the Kosiborod et al. 2019 publication used to inform the original table in the company submission. The proportions of patients with increased or reduced scores differ between the CSR and Kosiborod et al., as the CSR only included patients who were observed to achieve the given KCCQ-TSS threshold, whilst Kosiborod et al. also included patients with missing data for reasons other than death, whose imputed value reach the given KCCQ-TSS threshold.

The ORs and p-values reported in Kosiborod et al. 2019 are consistent with those in the CSR, as the same imputed data set were used for the statistical inference analyses for the CSR and in the Kosiborod et al. publication.

Table 6. Updated Table 14 from company submission: Secondary efficacy outcome in DAPA-HF: KCCQ-TSS

Outcome	Dapagliflozin (N=2,373)	Placebo (N=2,371)
Change in KCCQ-TSS at 8 months, mean±SD	6.1±18.6	3.3±19.2
Win ratio vs placebo (95% CI)†	1.18 (1.11, 1.26; p<0.001)	-
Increases in KCCQ-TSS at 8 months		
≥5-point increase %	57.4%	50.0%
OR‡ (95% CI) vs placebo	1.15 (1.08, 1.23; p<0.0001)	-
≥10-point increase %	53.9%	46.9%
OR‡ (95% CI) vs placebo	1.15 (1.08, 1.22; p<0.0001)	
≥15-point increase %	53.7%	47.7%
OR‡ (95% CI) vs placebo	1.14 (1.07, 1.22; p<0.0001)	
Reductions in KCCQ-TSS at 8 months		
≥5-point reduction, n (%)	25.1%	33.1%
OR§ (95% CI) vs placebo	0.84 (0.78, 0.90; p<0.001)	-

Source: DAPA-HF CSR Table 23–25.
Abbreviations: CI, confidence interval; KCCQ, Kansas City Cardiomyopathy Questionnaire; OR, odds ratio; SD, standard deviation; TSS, Total Symptom Score.
†Win ratio >1 indicates superiority of dapagliflozin over placebo. ‡ OR >1 for ≥5-point increase in KCCQ-TSS indicates superiority of dapagliflozin over placebo. § OR <1 for ≥5-point reduction in KCCQ-TSS indicates superiority of dapagliflozin over placebo.

c. The DAPA-HF protocol

[redacted]**. Please clarify and justify the need for this amendment, as win ratios and corresponding 95% confidence intervals at 8 months were very similar between treatment groups for the Total Symptom Score (TSS), Clinical and Overall Summary (Table 22 clinical study report).**

[redacted]

The fact that our point estimates (win ratios) and 95% confidence intervals for TSS, CSS and OSS are all very similar, does not take away from the fact that the interpretations of TSS, CSS and OSS differ.

The TSS, CSS and OSS are not disjoint entities and indeed the TSS is a component in both CSS and OSS (which is just a weighted average of CSS and other scores). An effect on one of TSS, CSS and OSS is not interchangeable with an effect on the other (especially not for TSS and OSS).

d. Please confirm what the 'win ratio' measures, how it is calculated and provide a relevant reference.

The win ratio uses the order between outcomes to compare each subject in for example an active treatment group to each subject in a placebo group and assigns "win", "loss" or "tie" to each comparison. In DAPA-HF patients were compared with regard to the rank of change from baseline at 8 months of the KCCQ-TSS, including patients who died prior to 8 months as the worst rank. Among deaths, ranking was based on the last value while alive. The win ratio is calculated as the total number of wins in the dapagliflozin group (instances where a patient in the dapagliflozin group was ranked higher) divided by total number of losses (ties are split evenly between "wins" and "losses"). Thus, the win ratio is the odds of winning of the active treatment against the placebo (9-11).

A19. According to section B.2 of the company submission, "dapagliflozin was superior to placebo for all secondary endpoints, except for worsening renal function".

Please clarify why the higher incidence of renal cancer identified in DECLARE-TIMI58 (NCT01730534) was not reported in the company submission (0.12% for dapagliflozin versus 0.08% for placebo).

As discussed in Section B.2.2 of the submission, DECLARE-TIMI 58 was conducted exclusively in patients with type 2 diabetes (12). While patients with HFrEF were not excluded from the trial population, only 3.9% of patients in DECLARE-TIMI 58 had HFrEF at baseline (12); DECLARE-TIMI 58 is consequently not relevant to the indication of interest in this submission. The data on renal cancer referred to in this question are also not included in the primary publication for DECLARE-TIMI 58, indicating that the investigators did not consider this an AE of note (12). The full results for cancers observed in DECLARE-TIMI58 reported on https://clinicaltrials.gov/ct2/show/results/NCT01730534 demonstrates that fewer cancers occurred at a higher rate (using an arbitrary ≥0.02% cut-off) in the dapagliflozin arm than in the placebo arm (Table 7). The summary of AEs in Table 7 demonstrates that the result for renal cancer is effectively 'signal noise' common to all clinical trials.

Table 7: AEs with ≥0.02% difference between arms of the DECLARE TIMI58 trial

AEs occurring at lower incidence for dapagliflozin (vs placebo)	AEs occurring at higher incidence for dapagliflozin (vs placebo)
Bladder cancer (0.14% vs 0.29%)	Bone cancer metastatic (0.03% vs 0.00%)
Breast cancer (0.00% vs 0.02%)	Non-small cell lung cancer stage iv (0.02% vs 0.00%)
Breast cancer metastatic (0.02% vs 0.05%)	Ovarian cancer metastatic (0.02% vs 0.00%)
Colon cancer metastatic (0.00% vs 0.02%)	Prostate cancer (0.80% vs 0.64%)
Colorectal cancer (0.01% vs 0.04%)	Renal cancer (0.12% vs 0.08%)
Gastric cancer (0.06% vs 0.09%)	Small cell lung cancer (0.06% vs 0.04%)
Gastric cancer stage iii (0.00% vs 0.02%)	Thyroid cancer (0.03% vs 0.01%)
Hepatic cancer (0.03% vs 0.06%)	
Lung cancer metastatic (0.13% vs 0.16%)	
Metastatic gastric cancer (0.02% vs 0.04%)	
Non-small cell lung cancer (0.01% vs 0.04%)	
Small cell lung cancer metastatic (0.00% vs 0.05%)	
Uterine cancer (0.02% vs 0.04%)	

Source: https://clinicaltrials.gov/ct2/show/results/NCT01730534
Abbreviations: AE, adverse event; vs, versus.

A20. Tables 26 and 27 of the company submission present serious adverse events occurring in ≥1% and ≥0.5% of participants, respectively.

a. Please clarify whether these thresholds were pre-specified and provide supporting references.

The thresholds in Table 26 and Table 27 were chosen as arbitrary cut-offs for data presentation purposes due to the size of the trial population, and consequently the large number of unique SAEs. The full list of serious adverse events can be found in Tables 13.3.4.3 (on treatment) and 13.3.4.4 (on and off treatment) of the CSR, as well as in the supplementary appendix of the DAPA-HF primary publication (13).

b. Please provide a full list of serious adverse events, i.e. without any threshold.

DAPA-HF was a large trial enrolling 4,736 patients, consequently there are approximately 500 unique SAEs. Please refer to Tables 13.3.4.3 (on treatment) and 13.3.4.4 (on and off treatment) of the CSR for the full list of serious adverse events.

Indirect treatment comparison (ITC)

A21. Priority question: The company provide no justification for choosing a matching adjusted indirect comparison (MAIC) to compare dapagliflozin and sacubitril over the more established

Bucher method. Page 61of NICE technical support document (TSD) 18 recommends that a MAIC for an anchored ITC (using RCTs with a common comparator) should be fulfil two criteria:

1. **"Evidence must be presented that there are grounds for considering one or more variables as effect modifiers on the appropriate transformed scale. This can be empirical evidence, or an argument based on biological plausibility."**

2. **"Quantitative evidence must be presented that population adjustment would have a material impact on relative effect estimates due to the removal of substantial bias."**

Table 69 in Appendix F of the company submission reports the "expected bias reduction" by adjustment on the log hazard ratio scale. However, this has not been performed for all characteristics.

a. **Please explain why some cells in Table 69 were left blank and specify exactly which characteristics were used to calculate the "overall" adjustment.**

In order to determine a parsimonious set of variables that correlated with treatment effect in DAPA-HF, (generalised) linear models were selected by a process of forward stepwise selection. The set of candidate variables for the linear predictor of these models included the complete set of covariates (covariates listed in Table 69 of company submission), treatment arm (dapagliflozin or placebo) and all first-order interactions between covariates, including treatment arm. Models were assessed for predictive accuracy by 10-fold cross-validation upon the full DAPA-HF IPD. The treatment interaction terms from this model were then used to select the covariates that would be used to form the matching weights for indirect comparison. These models were also used in an exercise to determine the expected bias reduction by matching the covariates (Table 69 of company submission). As such, Table 69 only includes estimates of expected bias reduction for those characteristics that were found to be treatment effect modifying covariates of each individual endpoint, for example, race, NYHA class, history of T2DM and history of hHF were treatment effect modifiers for the primary composite endpoint.

b. **Please provide justification for the MAIC using the criteria in TSD18 and populate all cells of Table 69.**

A MAIC was conducted to assess whether conclusions from an unadjusted (or naïve) comparison between DAPA-HF and PARADIGM-HF were robust to differences in patient characteristics observed between the two trials, notably patients' NYHA class at baseline (patients in DAPA-HF were more likely to have NYHA class III-IV) and prior hHF at baseline (patients in DAPA-HF were less likely to have been previously hospitalised), pre-specified subgroup analysis of the DAPA-HF trial also indicated that there was a potential for these factors to be numerically influential on the treatment effect of dapagliflozin. As such, a MAIC was conducted which demonstrated that the nominally (but not statistically significant) improvement seen in an unadjusted anchored comparison between the

two trials for dapagliflozin versus sacubitril valsartan was robust to adjustment for differences in patient characteristics. As both the unadjusted and adjusted comparisons did not show any significant differences between treatments for all-cause mortality, CV mortality and hHF, the efficacy of dapagliflozin and sacubitril valsartan was conservatively assumed to be equivalent for base case analysis #1.

c. Please conduct sensitivity analyses for the MAIC that use different sets of characteristics in the overall adjustment, including at least one scenario where all characteristics listed in Table 69 are incorporated for all outcomes, regardless of their effect on the variance.

Sensitivity analyses were conducted to explore the impact of adjustment for all patient characteristics included in Table 69 of the company submission (see Figure 2–Figure 4). The results of the analyses using all characteristics listed in Table 69 as the matching set ('all' in Figure 2–Figure 4) are consistent with results from the 'primary' (or overall) matching set, the 'outcome specific matching' set and the unadjusted comparisons (Figure 2–Figure 4).

Figure 2. Results of dapagliflozin + ACEi versus sacubitril valsartan, using different matching sets (MAIC subgroup 1)

Abbreviations: ACEi, angiotensin-converting-enzyme inhibitor; CV, cardiovascular; HHF, hospitalisation for heart failure.

Figure 3. Results of dapagliflozin + ARB versus sacubitril valsartan, using different matching sets (MAIC subgroup 2)

Abbreviations: ARB, angiotensin receptor blocker; CV, cardiovascular; HHF, hospitalisation for heart failure.

Figure 4. Results of dapagliflozin + ACEi and/or ARB versus sacubitril valsartan, using different matching sets (MAIC subgroup 3)

Abbreviations: ACEi, angiotensin-converting-enzyme inhibitor; ARB, angiotensin receptor blocker; CV, cardiovascular; HHF, hospitalisation for heart failure.

d. Please conduct an ITC using the Bucher method for all six outcomes estimated using the MAIC.

The unadjusted analysis based on a common anchor described in the submission dossier is analogous to the Bucher method. Estimates of the treatment effect of dapagliflozin versus sacubitril valsartan in anchored comparisons were consistent across unadjusted and adjusted comparisons (see Figure 2–Figure 4).

e. Please provide a full breakdown of the number and percentage of people who were taking each of the ACEIs or ARBs for each arm of the DAPA-HF and PARADIGM-HF trials.

Table 8 shows the proportion of patients in receipt of ACEi or ARB at baseline in each arm of DAPA-HF and PARADIGM-HF. Figures for PARADIGM-HF are based on pre-trial use of ACEi or ARB as patients were subsequently randomised to receive either ACEi (enalapril) or sacubitril valsartan. Matched analysis included only those patients in the DAPA-HF placebo arm that were in receipt of ACEi for consistency with the design of PARADIGM-HF, and those patients in the DAPA-HF dapagliflozin arm in receipt of ACEi (MAIC subgroup 1), ABR (MAIC subgroup 2), and ACEi and/or ARB (MAIC subgroup 3).

Table 8. ACEi and ARB use in DAPA-HF and PARADIGM-HF

	DAPA-HF		PARADIGM-HF	
	Dapagliflozin	Placebo	Sacubitril valsartan	Enalapril
N	2373	2371	4187	4212
ACE inhibitor - no. (%)	1332 (56.1)	1329 (56.1)	3266 (78.0)	3266 (77.5)
ARB - no. (%)	675 (28.4)	632 (26.7)	929 (22.2)	963 (22.9)

Abbreviations: ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker.

A22. Please provide full details of the statistical methods used for the “naive comparisons” presented in section B.2.9.2.2 of the company submission.

Unadjusted (or naïve) estimates of comparative treatment efficacy are based on the treatment effect observed in DAPA-HF (in the matched unadjusted subgroup of patients in receipt of ACEi) and the reported treatment effect from PARADIGM-HF for each endpoint. The hazard ratio of dapagliflozin + ACEi versus sacubitril valsartan is then estimated as the exponential of the difference of the log hazard ratios (i.e. the difference between Cox model coefficients). Confidence intervals are estimated based on the addition of the coefficient variance from each Cox model, of which the variance of the coefficient from PARADIGM-HF is obtained by difference of the log of the upper and lower confidence bound of the hazard ratio assuming Normality of this distribution.

A23. Section F.1.3 of Appendix F of the company submission states that the company "Exclude from the index study (DAPA-HF) any patients who are not present in the comparator study (PARADIGM-HF), and from the anchor (control) arm, exclude patients not intended to receive the anchoring therapy. Please explain how people present in the comparator study were identified in order to exclude them from DAPA-HF, given that only aggregate data were available for the comparator study.

This describes the application of any relevant inclusion or exclusion criteria to the patients enrolled in DAPA-HF, i.e. any patients who would not have been eligible for inclusion in PARADIGM-HF are excluded from DAPA-HF for the analysis. Importantly, patients in the DAPA-HF placebo arm (MAIC anchor) were only included if they received ACEi as part of their background therapy, for consistency with the enalapril arm (MAIC anchor) of the PARADIGM-HF trial.

A24. Section F.1.4 states that, “all calculations were performed on an x64-based PC running Windows 10 Pro (v1909), within the Microsoft R Open statistical environment version 3.5.1 as provided by the Microsoft R Application Network”.

Please provide the code and relevant datasets to enable the ERG to perform these calculations independently.

Relevant analysis datasets consist of individual patient data from DAPA-HF which cannot be shared. MAIC analysis code has subsequently been published and is now available on CRAN (https://CRAN.R-project.org/package=maic) for review.

The MAIC was based on IPD from the DAPA-HF trial and aggregated results from the PARADIGM trial. Internal permission for sharing IPD data with NICE and the ERG has recently been granted, and we will work with on the process required to securely share patient level data in confidence.

Section B: Clarification on cost-effectiveness data

Please note that all scenario analyses requested should be fully implementable in an updated economic model.

Model structure

B1. Please justify the use of the KCCQ-TSS quartiles to characterise/ define the health states rather than using:

a. the KCCQ quality of life domain, the KCCQ clinical summary score or the overall summary score

See response to questions B1b.

b. quintiles or other grouping approaches.

The cost-effectiveness model incorporates KCCQ score as a measure of HF disease severity, as such total symptom score is the measure most directly aligned to its usage in the model as KCCQ-TSS encompasses HF symptoms only, in contrast with the quality of life score, clinical summary score or overall summary scores which also encompass other aspects of HF disease, thereby potentially obscuring the measure of HF disease severity. Other approaches were explored for categorising KCCQ-TSS including tertiles and quarters (i.e. 0-25, 25-50, 50-75, 75-100). Quartiles were found to provide a better fit to the observed data than tertiles while still containing enough data to produce stable estimates of risk and utility associated with each category. Quarters were rejected as categories 0-25 and 25-50 did not contain enough data for robust analysis.

Incorporating clinical effectiveness data

B2. Priority question: For base case #1, equal effectiveness was assumed (i.e. a cost minimisation analysis performed) between dapagliflozin + standard care (SC) and sacubitril valsartan + SC. However, equal effectiveness has not been established.

a. Referring to your response in A1. Please redo the analysis for base-case #1 (if the populations for base case #1 and #2 are different) or conduct the full incremental analysis for base cases #1 and #2 combined (if the populations for each of the cases are the same) including the MAIC to estimate effectiveness for base-case #1 (instead of assuming equal effectiveness).

As explained in response to question A1, the populations evaluated in base case analysis #1 and base case analyses #2 are different.

The results of the MAIC of dapagliflozin versus sacubitril valsartan showed that there was no statistically significant difference in treatment effect, with numerical results in favour of dapagliflozin for all endpoint compared. As such, a conservative approach was taken for base case analysis #1 to assume equal effectiveness.

As requested by the ERG, a scenario analysis of base case analysis #1 was carried out by applying the non-statistically significant treatment effect of dapagliflozin versus sacubitril valsartan from the MAIC, to evaluate the cost-effectiveness of dapagliflozin versus sacubitril valsartan. In this analysis, dapagliflozin is dominant over sacubitril valsartan, i.e. dapagliflozin is associated with additional QALYs and cost-savings compared to sacubitril valsartan.

Because the populations evaluated in base case analysis #1 and #2 are different, a full incremental analysis is not relevant. A full incremental analysis can be provided if the ERG would still find such an analysis useful, following the clarifications and explanations provided in response to questions A1 and B2.

Table 9. Scenario analysis of base case analysis #1, using non-statistically significant treatment effect from the MAIC of dapagliflozin versus sacubitril valsartan, based on dapagliflozin + ACEi (MAIC subgroup 1)

	Dapagliflozin + SC (intervention)	Sacubitril valsartan + SC (comparator)	Incremental	ICER (£/QALY)
Life years	6.213	5.985	0.228	Dominant
QALYs	4.626	4.455	0.171	
Costs (£)	£14,234	£16,935	-£2,701	

These results were generated using the updated version of the model, which incorporates the exponential distribution for treatment discontinuation (see response to question B8).
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years, SC, standard care.

b. Please perform all analyses, requested in this letter, while including the MAIC to estimate effectiveness for base-case #1.

The results from the MAIC do not appear to be relevant to any other cost-effectiveness analyses request. As dapagliflozin is more cost-effective using the MAIC point estimates rather than the original assumption of equivalent efficacy, further scenario and sensitivity analysis using the MAIC point estimates would improve the cost-effectiveness of dapagliflozin. Therefore, the estimates based on the original assumption of equivalent efficacy are conservative with respect to dapagliflozin and can be considered as the upper bound for the cost-effectiveness estimate for this population.

c. Please provide scenario analyses for base-case #1 that only include people from DAPA-HF that were present in the comparator study (PARADIGM-HF), as described in clarification question A20.

This was included in the original submission, i.e. base case analysis #1 was carried out based on patients from the DAPA-HF trial who had been matching-adjusted to the PARADIGM-HF study (see Table 31 of company submission).

d. Please provide scenario analyses for base-case #1 that include standard indirect treatment comparisons methods (e.g. Bucher et al.), as requested in clarification question A20.

Results of a scenario analyses of the base case analysis #1, using ITC results based on the Bucher method as presented in response to question A21d is shown in Table 10. For completion, scenario analyses have also been carried out using the results from all the MAIC subgroups (see Section B.2.9.1.2 of the company submission) (Table 9, Table 11 and Table 12). The results from all these scenario analyses are consistent, i.e. all analyses show dapagliflozin to be associated with QALY gains and cost-savings compared to sacubitril valsartan (Figure 5).

Table 10. Scenario analysis of base case analysis #1, using non-statistically significant treatment effect from an indirect treatment of dapagliflozin versus sacubitril valsartan, based on methods described by Bucher et al.

	Dapagliflozin + SC (intervention)	Sacubitril valsartan + SC (comparator)	Incremental	ICER (£/QALY)
Life years	6.213	6.040	0.173	Dominant
QALYs	4.626	4.496	0.130	
Costs (£)	£14,496	£17,167	-£2,671	

These results were generated using the updated version of the model, which incorporates the exponential distribution for treatment discontinuation (see response to question B8).
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years, SC, standard care.

Table 11. Scenario analysis of base case analysis #1, using non-statistically significant treatment effect from the MAIC of dapagliflozin versus sacubitril valsartan, based on dapagliflozin + ARB (MAIC subgroup 2)

	Dapagliflozin + SC (intervention)	Sacubitril valsartan + SC (comparator)	Incremental	ICER (£/QALY)
Life years	6.213	5.563	0.650	Dominant
QALYs	4.626	4.142	0.484	
Costs (£)	£14,234	£15,886	-£1,652	

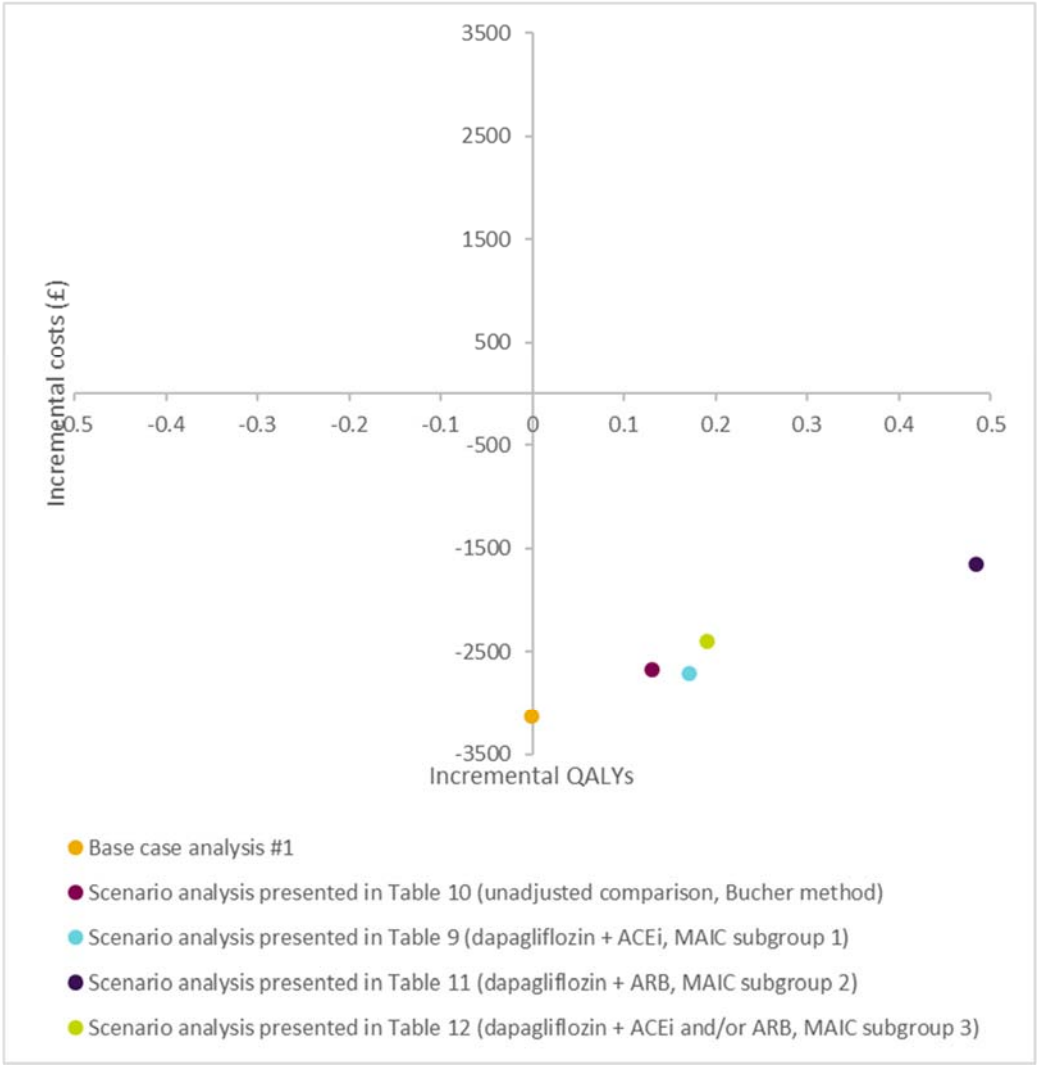
These results were generated using the updated version of the model, which incorporates the exponential distribution for treatment discontinuation (see response to question B8).
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years, SC, standard care.

Table 12. Scenario analysis of base case analysis #1, using non-statistically significant treatment effect from the MAIC of dapagliflozin versus sacubitril valsartan, based on dapagliflozin + ACEi and/or ARB (MAIC subgroup 3)

	Dapagliflozin + SC (intervention)	Sacubitril valsartan + SC (comparator)	Incremental	ICER (£/QALY)
Life years	6.213	5.958	0.255	Dominant
QALYs	4.626	4.436	0.190	
Costs (£)	£14,496	£16,896	-£2,400	

These results were generated using the updated version of the model, which incorporates the exponential distribution for treatment discontinuation (see response to question B8).
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years, SC, standard care.

Figure 5. Cost-effectiveness plane summarising the results of base case analysis #1 and scenario analyses



Abbreviations: ACEi, angiotensin-converting-enzyme inhibitor; ARB, angiotensin receptor blocker; MAIC, matching-adjusted indirect comparison; QALYs, quality-adjusted life years.

B3. Priority question: The selection of the Weibull distributions for all-cause and cardiovascular (CV)-specific mortality was only partly justified.

a. **Please provide a version of the economic model that incorporates the option to select different parametric survival distributions for all-cause and CV-specific mortality.**

All-cause and CV-specific mortality survival curves were constrained to use the same parametric survival distribution to prevent inconsistent extrapolation of within trial data. For example, selecting a Gompertz distribution for all-cause mortality and a Lognormal distribution for CV-specific mortality would result in the two survival curves intersecting with estimated CV-specific mortality in excess of all-cause mortality, as such modelling the two survival curves utilising different parametric distributions is inappropriate. A version of the economic model enabling this functionality has been provided where CV mortality is constrained to be less than or equal to all-cause mortality estimates. Cost-effectiveness estimates are robust to the choice of survival distribution with ICERs ranging between £5,768/QALY (Lognormal) and £7,264/QALY (Gompertz) for analysis #2 and £5,743/QALY (Lognormal) and £7,162/QALY (Gompertz) for analysis #3. Utilising different survival curves is not influential on cost-effectiveness estimates, for example utilising extremes of Gompertz for all-cause mortality and Lognormal for CV specific mortality (underestimating CV-specific mortality relative to all-cause mortality) results in an ICER of £6,883/QALY in analysis #2 and £6,762/QALY in analysis #3. Conversely, using a Lognormal distribution for all-cause mortality and a Gompertz distribution for CV-specific mortality (overestimating CV-specific mortality relative to all-cause mortality) yields an ICER of £6,831/QALY in analysis #2 and £6,781/QALY in analysis #3.

b. **Please justify why the parametric survival models were estimated using the intention-to-treat (ITT) population rather than the relevant population subset of patients (consistent with the estimation of transition probabilities between the KCCQ-TSS health states) based on the primary or specialist setting (as described in section B.1.3 of the CS), i.e. patients already treated with sacubitril valsartan (analysis #3) or not (analyses #1 and #2) and provide alternative scenarios (as well as a version of the economic model that incorporates this option) using the relevant subset of patients to estimate the parametric survival models.**

Parametric survival models were estimated based on the ITT population in order to maximise the available data to produce multivariable adjusted risk equations based on characteristics that were identified as prognostic of outcomes in the DAPA-HF trial. Sample sizes of patient subgroups are comparatively small, for example 508 patients were in receipt of sacubitril valsartan at baseline, which would not enable the robust estimation of multivariable risk equations. As such, the ITT approach includes the most available data, and enables cost-effectiveness analysis for any patient subgroup based on the inclusion of relevant baseline patient characteristics. Furthermore, DAPA-HF was not powered to detect differences in treatment effect between population subgroups and as such the ITT approach utilised incorporates the best available estimate of the efficacy of dapagliflozin as a treatment for HFrEF. Although the ITT approach is most appropriate, the model also includes

unadjusted survival curves with only a coefficient associated with dapagliflozin to enable sensitivity analysis; these estimates have been derived in the relevant patient subgroup only and as such include the treatment effect associated with that subgroup. Scenario analyses using these unadjusted survival equations were carried out as scenario analysis #5.1 and #5.2 in the company submission for base case analyses #2 and #3, respectively (see Section B.3.8.3 of company submission).

c. To examine the proportional hazard assumption for both all-cause and CV-specific mortality, please provide plots of the log cumulative hazard versus log time, separately for treatment with and without dapagliflozin.

Figure 6 shows log cumulative hazard versus log time (panel a), log hazard versus time (panel b), log survival odds versus log time (panel c) and standard normal quantiles versus log time (panel d) for all-cause mortality stratified by treatment arm. Solid lines show the observed data from DAPA-HF, with dashed lines showing corresponding model fits. Figure 7 presents the same analysis for CV-specific mortality.

Figure 6. All-cause mortality diagnostics

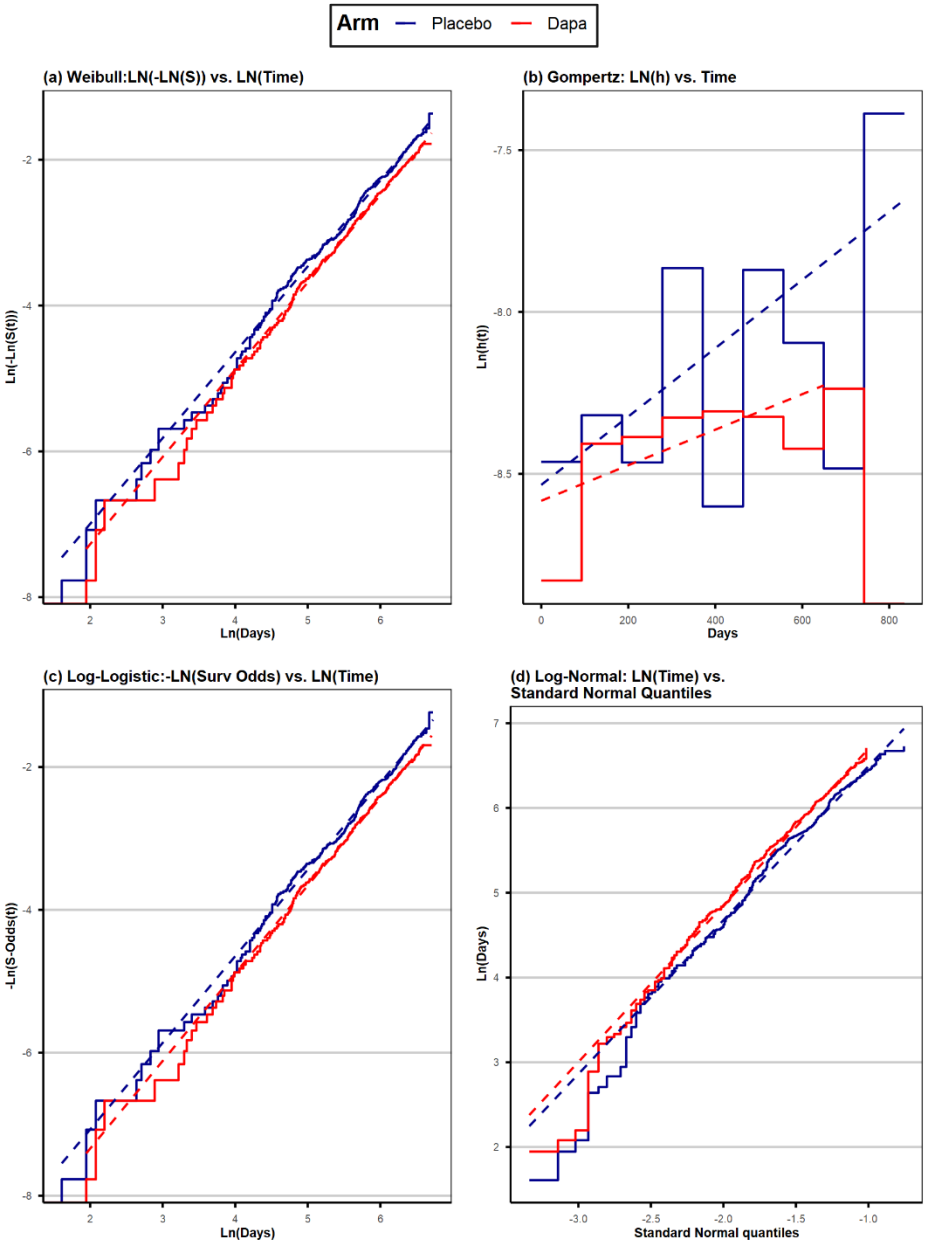
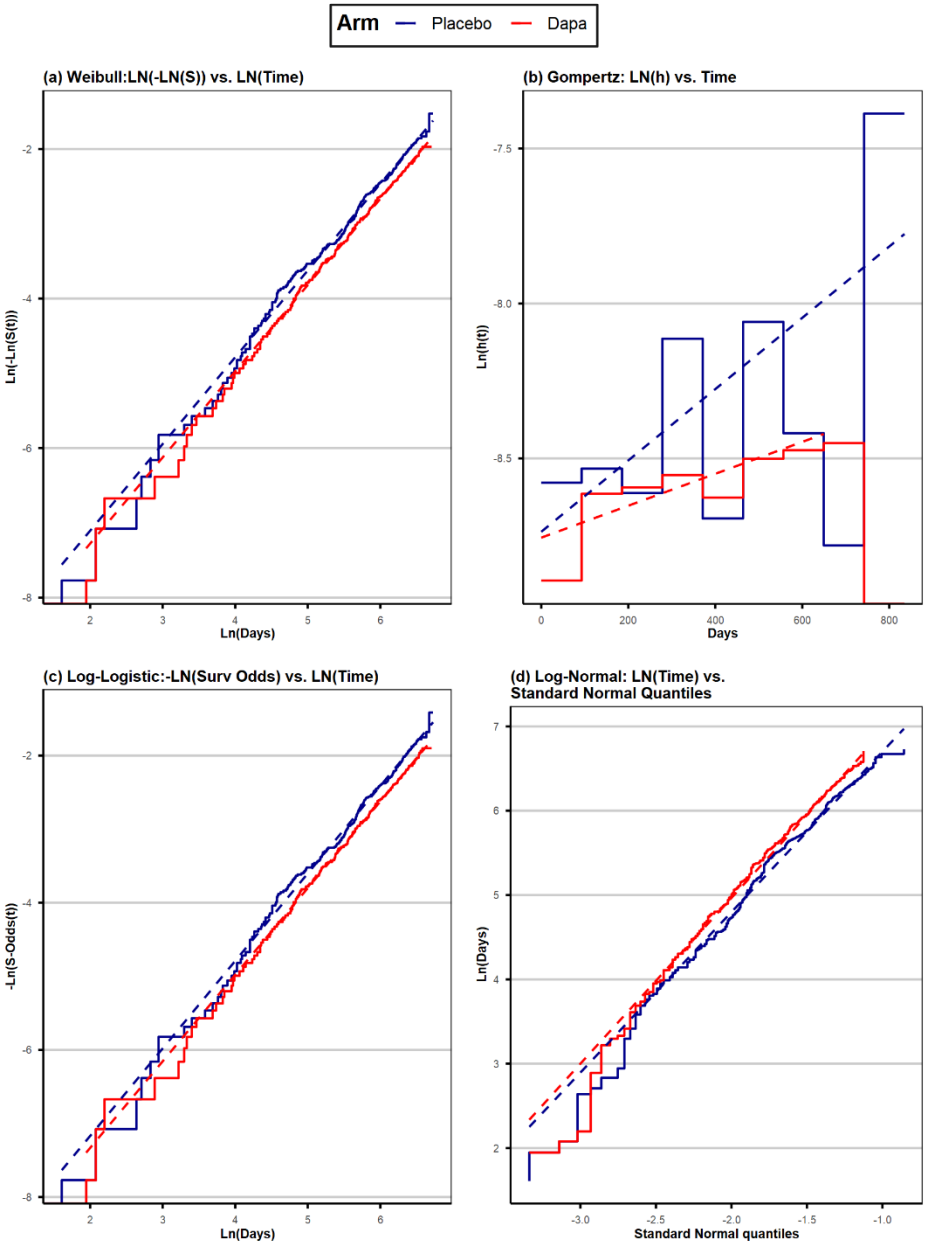


Figure 7. CV-specific mortality diagnostics



d. To examine the hazard function over time for both all-cause and CV-specific mortality, please provide plots of the smoothed hazard versus time, separately for treatment with and without dapagliflozin.

Please see response to question B2c and Figure 6 and Figure 7.

e. Please provide diagnostics of the different parametric survival models for both all-cause and CV-specific mortality, separately for treatment with and without dapagliflozin (For more information on the graphical test, see Table 1 in Ishak et al. PharmacoEconomics 2013, https://doi.org/10.1007/s40273-013-0064-3):

i. **Plot log cumulative hazard versus log time (Weibull)**

ii. **Plot log smoothed hazard versus time (Gompertz)**

iii. **Plot log survival odds versus log time (loglogistic)**

iv. **Plot standard normal quantiles versus log time (lognormal)**

Please see response to question B2c and Figure 6 and Figure 7.

f. **Please provide additional details of validation of the long-term extrapolation of the distributions. This should include the time-points, external data, and whether experts considered the extrapolations fit for purpose. Please also provide their justifications (i.e. why these specific time-points, external data, and experts). Please provide this separately for all-cause and CV-specific mortality.**

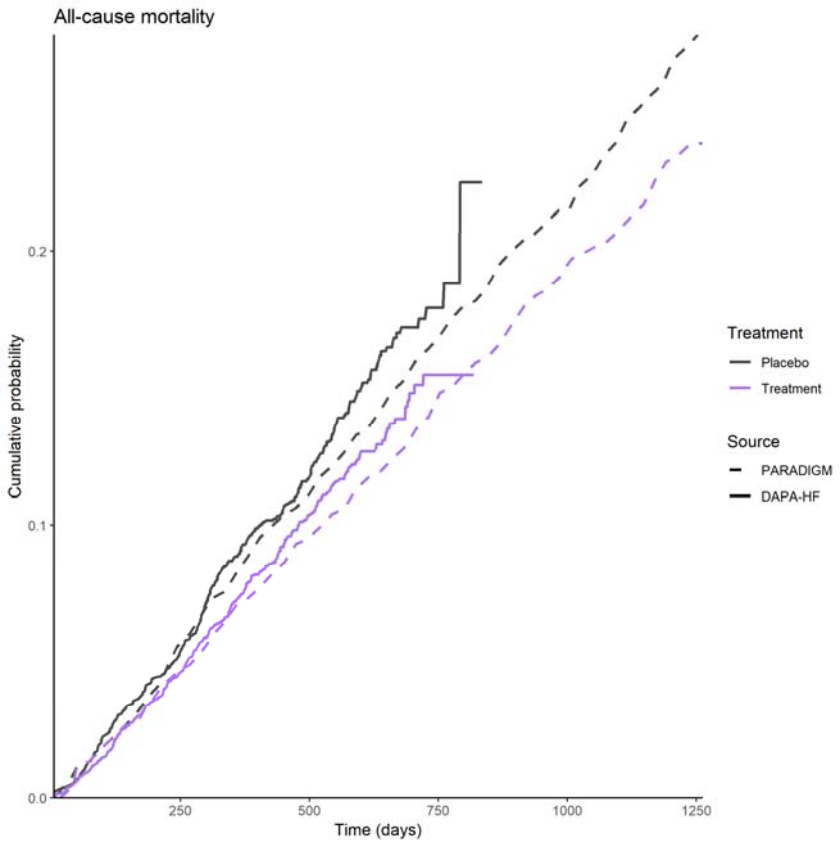
Survival models were validated against both within trial observations and external data. Long term extrapolations were assessed versus previously published estimates of patient survival based on PARADIGM-HF, chosen as another contemporary, large, multinational trial in patients with HFrEF and inclusion criteria aligned with DAPA-HF, such as those presented in McMurray et al. which estimated a mean life expectancy of 7.34-8.36 years for patients treated with ACEi in comparison with estimates from DAPA-HF survival models of 6.55 years for patients treated with ACEi or ARB (14). Estimates of life expectancy based on DAPA-HF data are expected to be marginally lower than those derived from PARADIGM-HF as the mortality rate was higher in DAPA-HF (Figure 8). Lognormal and loglogistic survival distribution predict mean patient survival in excess of estimates from PARADIGM-HF, suggesting that they are likely to overestimate patient survival. Conversely the Gompertz distribution predicts mean patient life expectancy of just 4.25 years for those treated with ACEi or ARB, far lower than previously published estimates. As such, a Weibull distribution is thought to best represent mean life expectancy in clinical practice, although with the potential to slightly underestimate patient survival.

Predictions made by the DAPA-HF models and the models derived based on PARADIGM-HF data included in TA388 were also compared to assess the consistency of long term extrapolations, with the Weibull distribution producing the most consistent estimates (Figure 9). Published cost-effectiveness analysis based on PARADIGM-HF has been based on all-cause mortality only, and as such validation of CV-specific mortality to PARADIGM-HF data was not possible.

Throughout the development of the all-cause mortality and CV-specific mortality risk equations for the cost-effectiveness model, [redacted] provided feedback with respect to clinical plausibility regarding the included risk factors and their impact on patient survival, and also to ensure that survival estimates

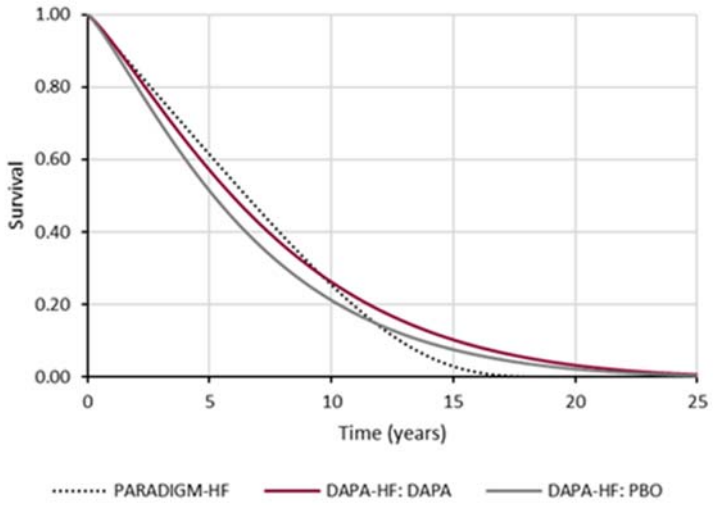
had face validity. Survival estimates presented and validated were overall mean patient survival and percentage survival at 1 year, 2 years and 5 years from baseline.

Figure 8. Naïve comparison between KM curves of all-cause mortality between DAPA-HF and PARADIGM-HF (based on digitised data)



Abbreviations: KM, Kaplan-Meier.

Figure 9. Model extrapolations (Weibull distribution) of overall survival for DAPA-HF stratified by treatment arm (solid lines) and based on the model of all-cause mortality presented in TA388 (dotted line)



Abbreviations: PBO, placebo.

g. Please provide supporting evidence for the statement that "clinical expert opinion suggested that predictions made using the Gompertz equations were likely to underestimate patient survival, and conversely, lognormal and log-logistic distributions were likely to overestimate patient survival", and elaborate on whether the Weibull distribution over- or underestimates survival.

See response to question B3f.

h. Inconsistent with NICE TSD14, the generalised gamma distribution is not considered for estimating the parametric survival models. Please provide, separately for all-cause and CV-specific mortality, scenario analyses that use the generalised gamma distribution to estimate survival.

The generalised gamma distribution was not included in the model as only 16.3% and 21.2% of patients experienced the primary composite endpoint in DAPA-HF, as such the KM data were comparatively incomplete. NICE TSD14 notes that the gamma distribution is particularly flexible, and as such it was not included in the analysis to prevent overfitting to the within trial data, and furthermore the included survival distributions explore a wide range of possible survival outcomes with mean life expectancy ranging between 4.25 years and 9.95 years for Gompertz and Lognormal respectively. Cost-effectiveness is robust to the choice of survival distribution, including the generalised gamma distribution; results of additional sensitivity analysis based on a generalised gamma distribution is presented in Table 13 for analysis #2 and Table 14 for analysis #3, respectively.

Table 13. Scenario analysis for analysis #2 based on a generalised gamma distribution for all-cause and CV-specific mortality.

	Dapagliflozin + SC (intervention)	Placebo + SC (comparator)	Incremental	ICER (£/QALY)
Life years	6.692	6.101	0.591	£5,856
QALYs	4.965	4.479	0.486	
Costs (£)	£16,088	£13,241	£2,847	

These results were generated using the updated version of the model, which incorporates the exponential distribution for treatment discontinuation (see response to question B8).
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years, SC, standard care.

Table 14. Scenario analysis for analysis #3 based on a generalised gamma distribution for all-cause and CV-specific mortality.

	Dapagliflozin + SC (intervention)	Placebo + SC (comparator)	Incremental	ICER (£/QALY)
Life years	6.437	5.854	0.583	£5,857
QALYs	4.768	4.289	0.479	
Costs (£)	£16,664	£13,859	£2,805	

These results were generated using the updated version of the model, which incorporates the exponential distribution for treatment discontinuation (see response to question B8).
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years, SC, standard care.

i. **Please list the predefined candidate covariables for the parametric survival models, for both all-cause and CV-specific mortality and provide detailed results of the covariable selection procedure (also specifying the cut-offs used). Please define the 'unadjusted survival equations' mentioned in section B.3.3.1.3 and clarify why their use in a scenario analysis reflects the sensitivity of the model to the numerical differences in the treatment effect in patient subgroups with different background therapies.**

Predefined candidate covariables for all-cause and CV-specific mortality were: treatment group, age, sex, race, region, KCCQ-TSS, LVEF, NT-proBNP, prior hHF, MRA use at baseline, T2DM at baseline, atrial fibrillation or flutter at baseline, aetiology of HF, BMI, creatinine, HF duration at baseline, baseline eGFR, patient baseline MAGGIC risk score and NYHA functional class. Models for all-cause mortality and CV-specific mortality were developed independently, and continuous candidate variables were explored for potential transformations which would fully capture the relationship between the covariable and the risk of death, and similarly, where possible different levels of groupings of categorical variables were also explored. The model development process involved initial development of univariate models for each candidate covariable to assess prognostic performance in isolation and assess the need for transformation or re-categorisation of covariables. All variables were then included in a multivariable model to identify independent predictors of death before development of parsimonious risk models. Backwards selection was used to eliminate variables in-turn from the fully adjusted model if their inclusion did not improve the model fit, which

was assessed through AIC and p-values, favouring models with the lower AIC or excluding covariates whose p-value exceeded 0.05.

In the base case analyses, the survival equations and risk equations using the cost-effectiveness model were adjusted for covariates (see Section B.3.3.1.3 and Section B.3.3.1.4 of the company submission) that are predictive of the outcome variable. Since the survival equations and risk equations are adjusted for influential patient characteristics, they can be used to estimate outcomes in any patient subgroup of the DAPA-HF trial.

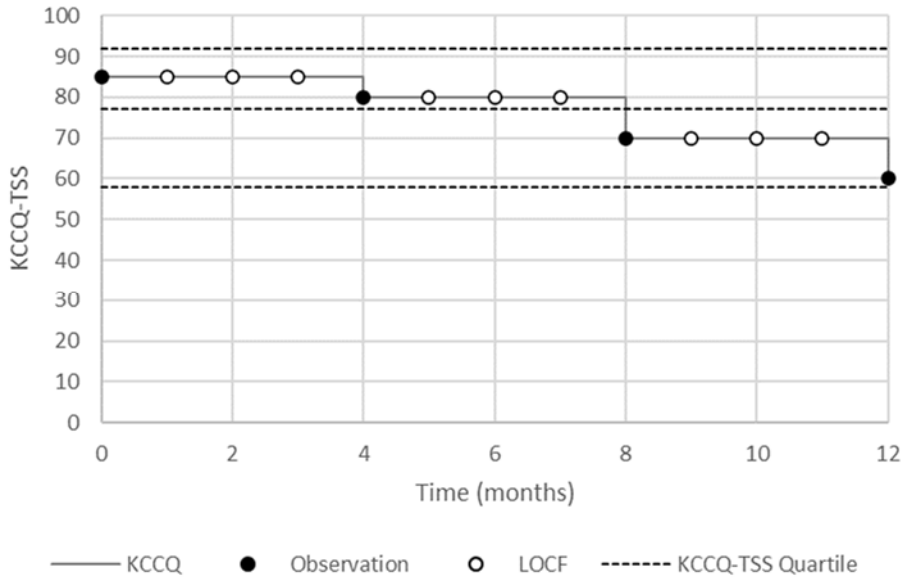
In contrast, the "unadjusted" survival curves and risk equations only include dapagliflozin as a covariate, and therefore these survival equations and risk equations are specific to the subgroup of patients used to derive the equations. For scenario analysis #5.1 and #5.2, the survival equations and risk equations for hHF were derived using data specifically from the subgroup of patients treated with ACEi/ARB, beta-blocker, ±MRA at baseline, and sacubitril valsartan, beta-blocker, ±MRA at baseline, respectively. This alternative approach was used in scenario analyses #5.1 and #5.2 to show that the cost-effectiveness estimates in base case analysis #2 and #3 are robust to variations in the methods used to model mortality and hHF. For scenario analysis #7, the unadjusted survival and risk questions were derived from the ITT population, to evaluate the treatment effect of dapagliflozin in a population with mixed background therapy, i.e. ACEi/ARB, beta-blocker, ±MRA, ±sacubitril valsartan.

B4. Priority question: The following questions relate to transition probabilities between health states defined by KCCQ-TSS quartiles:

a. **Please define 'monthly transition count data' used to derive KCCQ-TSS quartiles and summarise these data, indicating the amount imputed using last observation carried forward.**

Transitions were counted between KCCQ-TSS quartile health states in monthly intervals, please see Figure 10 and Table 15 for an illustrative example showing how KCCQ-TSS quartile transitions were counted based on observations for a hypothetical patient. As illustrated in Figure 10, imputations using last observation carried forward were primarily used for reconciling differences in the model cycle length (monthly) and the frequency of KCCQ-TSS measurements (four monthly), as such the majority of observations were imputed (80.5%, or approximately three-quarters as a result of the difference between model cycle length and trial measurements, and approximately 5% as a result of missingness). No transitions were imputed beyond the end of patient follow-up, either as a result of study closure or patient death.

Figure 10. Illustrative KCCQ-TSS trajectory



Abbreviations: KCCQ, Kansas City Cardiomyopathy Questionnaire; LOCF, last observation carried forward; TSS, Total Symptom Score.

Table 15. Transition count data based on illustrative KCCQ-TSS trajectory shown in Figure 10

		To			
		KCCQ-TSS Q4	KCCQ-TSS Q3	KCCQ-TSS Q2	KCCQ-TSS Q1
From	KCCQ-TSS Q4	0	0	0	0
	KCCQ-TSS Q3	0	7	1	0
	KCCQ-TSS Q2	0	0	4	0
	KCCQ-TSS Q1	0	0	0	0

Abbreviations: KCCQ-TSS: Kansas City Cardiomyopathy Questionnaire Total Symptom Score; Q: quartile

b. Please elaborate on the limitations of using [redacted] only (as per Table 14.2.4.2 of the clinical study report) to calculate the transition probabilities and specify implications on the economic model.

The approach to derive the monthly transition count data cannot capture any changes in patients KCCQ-TSS score between measurements each four months, however any durable changes in patients KCCQ-TSS score would be captured at most four months later at the next scheduled KCCQ-TSS measurement.

c. Given the focus on 8 month KCCQ-TSS in the clinical evidence, please justify the distinction between KCCQ-TSS transition probabilities before and after 4 months in the economic model, particularly given that the inflection point mentioned in the company

submission is observed at ~6-7 months from baseline (Figure 23) rather than 4 months (as stated in section B.3.3.1.2).

Distinct health state transition matrices were derived for observations up to month four, and month four onwards. The inflection point in mean KCCQ-TSS was observed between study visits occurring after four and eight months, as such four months was chosen as the limit between transition matrices.

d. Please provide alternative scenarios that assume the KCCQ-TSS score remains unchanged after 8 months for both treatments.

Scenario analysis applying KCCQ-TSS 0-4 month transition matrices up to eight months and assuming no change thereafter did not impact cost-effectiveness in analyses #2 (Table 16) or #3 (Table 17).

Table 16. Scenario analysis for analysis #2 assuming equivalent KCCQ-TSS transition probabilities from month eight onwards.

	Dapagliflozin + SC (intervention)	Placebo + SC (comparator)	Incremental	ICER (£/QALY)
Life years	6.604	6.035	0.569	£6,030
QALYs	5.028	4.559	0.469	
Costs (£)	£15,669	£12,840	£2,830	

These results were generated using the updated version of the model, which incorporates the exponential distribution for treatment discontinuation (see response to question B8).
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years, SC, standard care.

Table 17. Scenario analysis for analysis #3 assuming equivalent KCCQ-TSS transition probabilities from month eight onwards.

	Dapagliflozin + SC (intervention)	Placebo + SC (comparator)	Incremental	ICER (£/QALY)
Life years	6.604	6.035	0.569	£6,042
QALYs	5.028	4.559	0.469	
Costs (£)	£16,018	£13,183	£2,835	

These results were generated using the updated version of the model, which incorporates the exponential distribution for treatment discontinuation (see response to question B8).
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years, SC, standard care.

e. Please confirm if the last observation carried forward assumption was also used in case of competing events (e.g. mortality).

No transitions were imputed beyond the end of patient follow-up, either as a result of study closure or patient death.

f. Please clarify how competing events (e.g. mortality) were handled when estimating transition probabilities between health states defined by KCCQ-TSS quartiles.

Elaborate on the implications of this approach and provide alternative scenarios where appropriate.

No transitions were imputed beyond the end of patient follow-up, either as a result of study closure or patient death. The scenario analyses presented in response to question B4g give an indication of the effect of increasing the risk of transition to poorer KCCQ-TSS quartiles, within the 4-month window before the next KCCQ-TSS observation or before a patient dies. The results show that the cost-effectiveness of dapagliflozin is robust to alternative approaches for estimating the KCCQ-TSS transition probabilities.

g. **Please justify use of the last observation carried forward assumption and provide alternative scenarios that assume the probability of missing data increases if people have/ perceive worse symptoms/ lower (health-related) quality of life.**

Cost-effectiveness results were also robust to scenario analysis increasing the propensity for patients to progress to a lower KCCQ-TSS health state. Transition matrices were adjusted such that the probability of transitioning to the next lowest KCCQ-TSS quartile health state (i.e. quartile four to quartile three) were increased by 5% (approximately equivalent to the number of observations imputed using last observation carried forward) and conversely the probability of remaining the same KCCQ-TSS quartile health state was reduced by 5%. The results of this scenario for analyses #2 and #3 are shown in Table 18 and Table 19, respectively.

Table 18. Scenario analysis for analysis #2 assuming increased risk of reductions in KCCQ-TSS.

	Dapagliflozin + SC (intervention)	Placebo + SC (comparator)	Incremental	ICER (£/QALY)
Life years	5.394	4.922	0.472	£6,731
QALYs	3.796	3.442	0.354	
Costs (£)	£13,588	£11,205	£2,383	

These results were generated using the updated version of the model, which incorporates the exponential distribution for treatment discontinuation (see response to question B8).
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years, SC, standard care.

Table 19. Scenario analysis for analysis #3 assuming increased risk of reductions in KCCQ-TSS.

	Dapagliflozin + SC (intervention)	Placebo + SC (comparator)	Incremental	ICER (£/QALY)
Life years	5.247	4.783	0.465	£6,729
QALYs	3.687	3.338	0.349	
Costs (£)	£14,244	£11,897	£2,347	

These results were generated using the updated version of the model, which incorporates the exponential distribution for treatment discontinuation (see response to question B8).
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years, SC, standard care.

h. Given the uncertainties/ limitations associated with the estimation of the transition probabilities between health states defined by KCCQ-TSS quartiles, please provide alternative scenarios that assume KCCQ-TSS transition probabilities are treatment independent (i.e. equal for all treatments considered).

Dapagliflozin was associated with a significant improvement in KCCQ-TSS in comparison with patients treated with SC alone in DAPA-HF (see Section B.2.6.3.3 of company submission); as such, assuming equivalent KCCQ-TSS quartile health state transition probabilities does not adequately capture the benefit to patients observed in DAPA-HF. Furthermore, multivariable risk equations were derived in the context of the observed KCCQ-TSS benefit associated with dapagliflozin over time which was also linked to patient outcomes in the risk equations. As such, a proportion of the observed reductions in hHF and death is mediated through improved KCCQ-TSS for patients treated with dapagliflozin and as a result scenario analyses excluding this benefit will systematically underestimate the treatment benefit associated with dapagliflozin. Results for sensitivity analysis assuming equivalent KCCQ-TSS transition probabilities in each arm for analyses #2 and analysis #3 are shown in Table 20 and Table 21, respectively.

Table 20. Scenario analysis for analysis #2 assuming equivalent KCCQ-TSS in each treatment arm

	Dapagliflozin + SC (intervention)	Placebo + SC (comparator)	Incremental	ICER (£/QALY)
Life years	6.232	5.794	0.437	£7,781
QALYs	4.648	4.319	0.328	
Costs (£)	£15,025	£12,471	£2,554	

These results were generated using the updated version of the model, which incorporates the exponential distribution for treatment discontinuation (see response to question B8).
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years, SC, standard care.

Table 21. Scenario analysis for analysis #3 assuming equivalent KCCQ-TSS in each treatment arm

	Dapagliflozin + SC (intervention)	Placebo + SC (comparator)	Incremental	ICER (£/QALY)
Life years	6.034	5.599	0.435	£7,707
QALYs	4.490	4.164	0.327	
Costs (£)	£15,663	£13,147	£2,516	

These results were generated using the updated version of the model, which incorporates the exponential distribution for treatment discontinuation (see response to question B8).
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years, SC, standard care.

B5. Please clarify whether the following were estimated using the relevant subset of people in the primary care (analyses #1 and #2) or specialist setting (analysis #3) (section B.1.3 of the company submission). Please provide alternative scenarios that use the relevant subgroup, if this was not done, for the transition probabilities between KCCQ-TSS quartile health states.

Transition probabilities between KCCQ-TSS quartile health states were derived based on the ITT population of DAPA-HF in order to incorporate all available data describing disease progression. In base case #1, transition probabilities are assumed to be equivalent for patients treated with dapagliflozin and sacubitril valsartan so any potential differences would not impact the conclusions of the cost-minimisation analysis.

Regarding analyses #2 and #3, there is no evidence in DAPA-HF that KCCQ-TSS transition probabilities are conditional on a patient's background therapy regimen. Furthermore, sensitivity analysis including no treatment effect associated with dapagliflozin on KCCQ-TSS showed that dapagliflozin remains highly cost-effective, placing a conservative upper bound on the estimated ICERs and demonstrating that cost-effectiveness is robust to any uncertainty with respect to KCCQ-TSS quartile health state transitions (see response B4).

B6. The economic model considers hospitalisation for heart failure (hHF) and urgent heart failure visit (uHFv) using generalised estimating equations assuming that events are Poisson-distributed.

a. Please list predefined candidate covariables for the estimation of hHF and uHFv event incidence and provide detailed results of the covariable selection procedure (also specifying the cut-offs used).

The predefined candidate covariables for the negative binomial regression model predicting the incidence of hHF were: treatment group, age, sex, race, region, KCCQ-TSS, LVEF, NT-proBNP, prior hHF, MRA use at baseline, T2DM at baseline, atrial fibrillation or flutter at baseline, aetiology of HF, BMI, creatinine, HF duration at baseline, baseline eGFR, patient baseline MAGGIC risk score and NYHA functional class. Continuous candidate variables were explored for potential transformations which would fully capture the relationship between the covariable and the risk of hHF, and similarly, where possible different levels of groupings of categorical variables were also explored. The model development process involved initial development of univariate models for each candidate covariable to assess prognostic performance in isolation and assess the need for transformation or re-categorisation of covariables. All variables were then included in a multivariable model to identify independent predictors of death before development of parsimonious risk models. Backwards selection was used to eliminate variables in-turn from the fully adjusted model if their inclusion did not improve the model fit, which was assessed through AIC and p-values, favouring models with the lower AIC or excluding covariates whose p-value exceeded 0.05. uHFv events were not assessed through multivariable analysis due to the limited number of events (39 including recurrent uHFv events), as such only the treatment effect of dapagliflozin was included as a covariable.

b. Please provide details of the validation of the estimated hHF and uHFv event incidence, including the external data and which experts were consulted to support the estimates. If so, please provide their justification (i.e. why these external data, and experts).

The developed risk equation for hHF for the cost-effectiveness model was assessed for goodness of fit to within trial data and lifetime extrapolations of hHF and uHFv event incidence were validated by

[redacted] over a lifetime patient horizon. In addition to validating model estimates, [redacted] provided feedback with respect to clinical plausibility regarding the included risk factors and their impact on risk of hHF. Estimates are also consistent with those based on published analysis of PARADIGM-HF (another contemporary, large, multinational trial in patients with HFrEF and inclusion criteria aligned with DAPA-HF) such as King et al., who report cumulative incidence of hHF events per 100 patients treated with ACEi (enalapril) of 12.7, 24.5 and 34.6 from PARADIGM-HF after one, two and three years, respectively, and 13.2, 24.8 and 35.9 based on the cost-effectiveness model for sacubitril valsartan (15). Corresponding estimates from base case analysis #2 are 11.3, 22.8 and 34.0, and from base case analysis #3 are 13.3, 26.5 and 39.3, after one, two and three years, respectively.

B7. No treatment waning was assumed in the base case analyses. Please provide scenario analyses that illustrate the impact of potential treatment waning. This could be incorporated by increasing the long-term dapagliflozin discontinuation probabilities (assuming that people would discontinue in case of dapagliflozin treatment waning).

There is no evidence to suggest that treatment with dapagliflozin is associated with any treatment waning. The treatment effect of dapagliflozin is stable over the duration of the DAPA-HF trial as well as over the duration of previous trials in T2DM and T1DM patients, including the DECLARE TIMI58 trial with a median follow-up of 4.2 years.

[redacted] Furthermore, previous appraisals of treatments for HFrEF have assumed no treatment waning, including the NICE appraisal for sacubitril valsartan (TA388).

For base case analysis #1 evaluating dapagliflozin versus sacubitril valsartan, inclusion of treatment waning would not have any impact on the cost-effectiveness estimate, as any treatment waning applied for dapagliflozin should also be applied sacubitril valsartan, thereby reducing the treatment effects and costs equally in the dapagliflozin arm and the sacubitril valsartan arm.

In line with the suggested approach for scenario analysis by the ERG, the treatment duration of dapagliflozin was restricted to 3 years (the maximum follow-up in the DAPA-HF trial) in scenario analyses; this represents complete treatment waning and complete treatment discontinuation at Year 3. This scenario is not clinically relevant, given the chronic nature of HFrEF. The results of these scenario analyses show dapagliflozin remain highly cost-effective with ICERs ~£6,000/QALY (Table 22 and Table 23).

Table 22. Scenario analysis of base case analysis #2, assuming treatment waning/discontinuation at 3 years

	Dapagliflozin + SC (intervention)	Placebo + SC (comparator)	Incremental	ICER (£/QALY)
Life years	5.885	5.609	0.276	£6,171
QALYs	4.355	4.125	0.230	
Costs (£)	£13,625	£12,209	£1,416	

These results were generated using the updated version of the model, which incorporates the exponential distribution for treatment discontinuation (see response to question B8).
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life year, SC, standard care.

Table 23. Scenario analysis of base case analysis #3, assuming treatment waning/discontinuation at 3 years

	Dapagliflozin + SC (intervention)	Placebo + SC (comparator)	Incremental	ICER (£/QALY)
Life years	5.704	5.428	0.277	£6,182
QALYs	4.212	3.983	0.229	
Costs (£)	£14,312	£12,895	£1,417	

These results were generated using the updated version of the model, which incorporates the exponential distribution for treatment discontinuation (see response to question B8).
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life year, SC, standard care.

B8. Treatment discontinuation for dapagliflozin is incorporated into the model, assuming a constant probability over time.

a. Please clarify how the default annual probability of treatment discontinuation for dapagliflozin was estimated (0.07; standard error 0.01).

The annual probability of treatment discontinuation was based on the parameterisation of an exponential survival model fitted to individual patient data from DAPA-HF, with premature discontinuation of study drug included as the independent variable.

b. Please justify use of a constant probability over time (instead of a time dependent probability) and provide alternative scenarios that use time dependent discontinuation probabilities (e.g. using parametric survival models).

A constant probability over time was incorporated as a simplifying assumption as there was little evidence of time dependency in the data. Time dependent probability of discontinuation has been incorporated in the updated version of the model, based on parametric survival equations fit to individual patient data from DAPA-HF, with exponential, Weibull, Lognormal, Log-logistic, Gompertz and generalised gamma distributions available as options. Cost-effectiveness is robust to the choice of parametric survival distribution. The results of the sensitivity analysis are presented in Table 24.

Table 24. Scenario analysis for time dependent probabilities of discontinuation

Distribution for dapagliflozin discontinuation	ICER (£/QALY)	
	Analysis #2	Analysis #3
Exponential	£5,835	£5,872
Weibull	£5,795	£5,834
Gompertz	£5,766	£5,806
Lognormal	£5,792	£5,831
Log-logistic	£5,784	£5,824
Generalised gamma	£5,780	£5,820

Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years

c. People are unable to discontinue dapagliflozin treatment during the first cycle in the company model (i.e. all people alive in the second model cycle are on dapagliflozin treatment). Please provide alternative scenarios that allow this.

The model assumes that patients cannot discontinue in the first model cycle (one month), which means that patients incur costs associated with dapagliflozin for the full cycle. As modelled efficacy is based on ITT data, this approach can be considered conservative as any patients discontinuing dapagliflozin within the first month will incur costs without the associated benefit. The impact of this assumption on modelled output is negligible as at the end of the first month, approximately 0.6% of patients will have discontinued treatment, meaning that even if all of those patients discontinued at the beginning of the month, on average patients treated with dapagliflozin will incur an additional £0.23 in the first model cycle.

d. Please clarify how the “on treatment” data in (column N) of the “Control Trace” worksheet contributes to the model.

The on treatment model output in the control trace reflects the number of patients remaining on treatment in the control arm, in analysis #1 this will reflect the number of patients remaining on sacubitril valsartan, in analysis #2 and #3 this will reflect the number of patients still alive as discontinuation of SC is not considered.

B9. The KCCQ-TSS variable included in the parametric survival models was presumably estimated based on baseline KCCQ-TSS. This KCCQ-TSS score can, however, change over time, which is not explicitly incorporated in the parametric survival models. For instance, patients with a KCCQ-TSS baseline score of 50 (1st quartile) can move to a KCCQ-TSS score of 65 (2nd quartile). Hence, the estimation of the parametric survival models seems inconsistent with the economic model since the estimation of the parametric survival models assumed people remain in the same KCCQ-TSS category (based on baseline KCCQ-TSS) while in the economic model, people’s KCCQ-TSS score/ quartiles are allowed to change over time over time (as people can transit between KCCQ-TSS health states).

a. Please elaborate on the (potential) implications of the inconsistency described above.

Parametric survival models and negative binomial regression models for predicting mortality and hHF, respectively, were based on time-updated KCCQ-TSS quartiles and as such there is no inconsistency between the derivation of the equations and their application in the model.

b. Please provide scenario analyses that remove this inconsistency.

N/A

B10. Please clarify and justify how AEs were selected for inclusion in the economic model, i.e. what was considered “most common” or “serious”?

The safety profile of dapagliflozin is well established, and as such the adverse events included in the cost-effectiveness model were aligned to those of special interest as defined in the DAPA-HF study design (volume depletion, renal events, hypoglycaemic events, fractures, diabetic ketoacidosis and amputation; all levels of severity). In addition to adverse events of special interest, the incidence of genital infections and urinary tract infections were also incorporated based on safety data from DECLARE-TIMI 58. The inclusion of genital infections and urinary tract infections is conservative with respect to dapagliflozin as these events are more likely in the DECLARE-TIMI58 population due to their underlying diabetes, and overall less likely in the HFrEF population. Overall, dapagliflozin was associated with fewer serious adverse events in DAPA-HF than placebo.

B11. Please justify why the association between AEs and mortality was not incorporated in the model and provide alternative scenarios where appropriate.

The model includes estimates of all-cause mortality derived from the DAPA-HF trial, as such any mortality associated with the incidence of adverse events is already implicitly captured within the model results. As such, associating mortality with adverse events in addition would underestimate patient survival.

Quality of life

B12. The utility values associated with KCCQ TSS Q4: 92-100 and Q3 77<92 in the economic model (0.833 and 0.773 respectively) appear relatively high for people with HFrEF.

Please elaborate on the plausibility of this utility value (given that it is constant over time) in relation to the general population utility for people aged ≥65 years (supplemental data provided by Sullivan et al. Med Decis Making 2011, https://doi.org/10.1177/0272989x11401031, indicating a mean utility of 0.774 for people aged 60-69 years). Provide alternative scenario analyses where appropriate.

Utility estimates derived are consistent with previous estimates of quality of life in patients with HFrEF, such as those used by King et al. for the cost-effectiveness evaluation of sacubitril valsartan where NYHA class I was associated with a utility value of 0.815 and in TA388 where the intercept of the mixed effects utility model was 0.822 (15). Sensitivity analyses have been conducted utilising a utility

value of 0.774 (aligned to the general population estimate from Sullivan et al.) for patients in the KCCQ-TSS Q4 health state and applying relative differences between KCCQ-TSS Q1, Q2 and Q3 derived from DAPA-HF for the other health state utility estimates (Q4=0.774, Q3=0.714, Q2=0.646, Q1=0.541). Results from these sensitivity analyses are presented in Table 25 and Table 26 for analysis #2 and analysis #3, respectively, demonstrating that cost-effectiveness conclusions are not impacted by lower health state utilities.

Table 25. Scenario analysis for analysis #2 with utility values aligned to Sullivan et al.

	Dapagliflozin + SC (intervention)	Placebo + SC (comparator)	Incremental	ICER (£/QALY)
Life years	6.183	5.609	0.574	£6,284
QALYs	4.234	3.797	0.438	
Costs (£)	£14,958	£12,209	£2,749	

These results were generated using the updated version of the model, which incorporates the exponential distribution for treatment discontinuation (see response to question B8).
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years, SC, standard care.

Table 26. Scenario analysis for analysis #3 with utility values aligned to Sullivan et al.

	Dapagliflozin + SC (intervention)	Placebo + SC (comparator)	Incremental	ICER (£/QALY)
Life years	5.990	5.428	0.562	£6,324
QALYs	4.093	3.665	0.428	
Costs (£)	£15,601	£12,895	£2,706	

These results were generated using the updated version of the model, which incorporates the exponential distribution for treatment discontinuation (see response to question B8).
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years, SC, standard care.

Costs and resource use

B13. Priority question: Appendix N of the company submission provides an overview of weighted average therapy costs.

For all therapies considered in the economic model, please clarify how these were calculated and provide the required details for the calculations, including specific dosage used, number of administrations per time period (e.g. year) and unit price/drug acquisition costs per administration.

The weighted average annual cost of standard care was based on the additive cost of the component drug classes and the market share of drugs within each drug class. The market share assumptions were taken from the NICE resource impact template for sacubitril valsartan TA388 (16). The details for the weighted average calculations were shown in Table 27. Maximum daily dosages for each therapy was taken from the relevant SmPCs, the specific dosage used was selected to match the maximum daily dosage where possible. Pack costs were taken from the latest Drugs and pharmaceutical electronic market information tool (eMIT) (17), except for the pack costs of sacubitril valsartan and dapagliflozin which were taken from MIMS (18). Annual costs were assumed to be equivalent to the cost of therapy over 365 days.

Table 27. Annual weighted average cost of HF therapies

Drug class	Drugs	Maximum daily dosage (mg)	Dosage, pack size	Pack cost	Annual cost	Market share (of drug class)	Source	Weighted average annual cost
Dapagliflozin		10	10 mg, 28 pack	£36.59	£476.98	100%	MIMS for costs (18)	£476.98
ACEi	Enalapril	20	20 mg, 28 tablets	£0.95	£12.38	10%	eMIT for costs (17); assumption for market share in line with TA388 (16)	£6.89
	Ramipril	10	10 mg, 28 capsules	£0.34	£4.43	40%		
	Perindopril	4	4 mg, 30 tablets	£0.47	£5.72	25%		
	Lisinopril	35	20 mg, 28 tablets 10 mg, 28 tablets 5 mg, 28 tablets	£0.32 £0.23 £0.20	£9.78	25%		
ARB	Losartan	150	100mg, 28 tablets 50mg, 28 tablets	£1.87 £3.14	£65.31	40%		£36.27
	Candesartan	32	32mg, 28 tablets	£0.88	£11.47	40%		
	Valsartan	160	160mg, 28 capsules	£2.13	£27.77	20%		
MRA	Spironolactone	50	50mg, 28 tablets	£1.28	£16.69	50%	eMIT for costs (17); assumption for market share	£39.56
	Eplerenone	50	50mg, 28 tablets	£4.79	£62.44	50%		
Sacubitril valsartan		194	97/103mg, 56 tablets	£91.56	£1,193.55	100%	MIMS for costs (18)	£1,193.55

Abbreviations: ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; HF, heart failure; MRA, mineralocorticoid receptor antagonist.

B14. The company stated that “one study identified in the SLR (McMurray, 2018) was used to inform the resource use for HF management in the de novo model for dapagliflozin”. Please justify the choice of this source.

McMurray et al. presented a contemporary cost-effectiveness analysis in a HFrEF population in countries including the UK and was identified as the most appropriate evidence source identified reporting background costs associated with healthcare resource utilisation (14). Sensitivity analysis presented in the submission dossier (Figure 35 and Figure 36) show that cost-effectiveness is not sensitive to a 20% increase or decrease in background health state costs, with lower costs favouring dapagliflozin as a result of improved patient life expectancy in the dapagliflozin arm.

B15. Please clarify the extent that costs of specialist care (and potentially required training) related to dapagliflozin are incorporated for base case analyses #1, #2 and #3 and provide alternative scenarios where appropriate.

The use of dapagliflozin is not expected to be associated with any additional costs, other than the cost of dapagliflozin, in the specialist setting nor in the primary care setting. Dapagliflozin is a once daily oral treatment, without need for titration, with a well-established safety profile.

B16. Please justify the inclusion of costs related to CV-death events but no other causes of mortality in the economic model. Please provide scenario analyses that incorporate event costs related to other causes of death.

DAPA-HF demonstrated that dapagliflozin is associated with reduced risk of CV death, as such costs associated with CV death are relevant to the economic evaluation of dapagliflozin for the treatment of HFrEF. No appropriate costs associated with non-CV specific death in a UK setting were identified; as such, costs associated with non-CV death were not modelled. Sensitivity analysis was conducted to assess the impact of costs associated with non-CV death on cost-effectiveness results. The cost of non-CV death was assumed to be equivalent to that of CV death. Cost-effectiveness was not sensitive to the inclusion of costs associated with non-CV death, increasing the ICER by £7/QALY in analysis #2 and by £13/QALY in analysis #3 (Table 28 and Table 29).

Table 28. Scenario analysis for analysis #2 with costs of non-CV death assumed to be the same as costs of CV-death

	Dapagliflozin + SC (intervention)	Placebo + SC (comparator)	Incremental	ICER (£/QALY)
Life years	6.183	5.609	0.574	£5,842
QALYs	4.596	4.125	0.471	
Costs (£)	£15,302	£12,550	£2,752	

These results were generated using the updated version of the model, which incorporates the exponential distribution for treatment discontinuation (see response to question B8).
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years, SC, standard care.

Table 29. Scenario analysis for analysis #3 with costs of non-CV death assumed to be the same as costs of CV-death

	Dapagliflozin + SC (intervention)	Placebo + SC (comparator)	Incremental	ICER (£/QALY)
Life years	5.990	5.428	0.562	£5,885
QALYs	4.444	3.983	0.461	
Costs (£)	£15,903	£13,191	£2,712	

These results were generated using the updated version of the model, which incorporates the exponential distribution for treatment discontinuation (see response to question B8).
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years, SC, standard care.

Model analyses

B17. Based on the response to Priority question A1. If the population for base case #1 and #2 is the same:

a. **Please combine these two analyses into one full incremental analysis where dapagliflozin + SC is compared with both sacubitril valsartan + SC and SC alone.**

As explained in response to question A1 and B2, the populations in base case analysis #1 and base case analysis #2 are different, and as such a full incremental analysis is not relevant.

A full incremental analysis can be provided if the ERG would still find such an analysis useful, following the clarifications and explanations provided in response to questions A1 and B2.

b. **Please clarify why the life years, QALYS and costs for dapagliflozin + SC are different for base case #1 (Table 46 of the company submission) and #2 (Table 47 of the company submission.**

As explained in response to question A1 and B2, the populations in base case analysis #1 and base case analysis #2 are different, with different baseline characteristics, which lead to different event rates as estimated by the fully-adjusted survival equations and risk equations. This in turn leads to small differences in the total life years, QALYs and costs for the dapagliflozin arm of base case analysis #1 and base case analysis #2.

B18. Priority question: Please clarify and justify which input parameters are specific to base case analyses #1, #2 or #3 and which parameters are assumed to be identical.

The table below summarises and justifies the parameters that are specific to each of the base case analyses.

Table 30. Input parameters specific to base case analyses #1, #2 and #3

Input parameter	Justification	Reference to company submission
Baseline characteristics	The populations evaluated in base case analyses #1, #2 and #3 are different from each other (see response to A1 for details). The differences in patient characteristics in each of these populations are reflected in these base case specific baseline characteristics. The baseline characteristics for base case analysis #1 are based on the patients who have been matching adjusted to the PARADIGM-HF sacubitril valsartan trial. The baseline characteristics of base case analysis #2 are based on the subgroup of patients from DAPA-HF who did not receive sacubitril valsartan at baseline. The baseline characteristics of base case analysis #3 are based on the subgroup of patients from DAPA-HF who received sacubitril valsartan at baseline.	Section B.3.3.1.1 and Table 31 of company submission
Adjusted survival and risk equations	The adjusted survival equations for all-cause mortality and CV-mortality, and the risk equations for hHF were derived using the full analysis set from DAPA-HF to maximise use of data and to establish the relationship between covariates and the outcome variable. The baseline characteristics for each base case analysis (see row above) and time-updated KCCQ-TSS quartile are applied to the survival equations and risk equations in each cycle of the model, and as such the estimate risk of all-cause mortality, CV-mortality and hHF is specific for each base case analysis, and for each cycle.	Section B.3.3.1.3 and B.3.3.1.4
Background treatment costs	Annual cost of standard care differed between base case analysis #2 and #3 to reflect the differences in background therapy in the populations evaluated. Base case analysis #1 uses the same annual cost of standard care as base case analysis #2.	Section B.3.6.2 and Table 42 of company submission

Abbreviations: CV, cardiovascular; hHF, hospitalisation for heart failure; KCCQ-TSS; Kansas City Cardiomyopathy Questionnaire – Total Symptom Score.

B19. Please provide probabilistic sensitivity analyses (PSA) for base case #1.

Base case analysis #1 assumed equivalent outcomes for patients treated with dapagliflozin and sacubitril valsartan, as a result the only determinant of differences in results for each treatment arm is the drug acquisition costs associated with each treatment strategy which is not sampled in PSA. As such, a PSA is not relevant.

B20. For all three base cases please provide one-way sensitivity analyses with tornado diagrams that include all parameters that were implemented probabilistically in the PSA.

The one-way sensitivity analyses requested by the ERG would provide no more information about the decision uncertainty than the PSAs already presented in the company submission. The effect of varying single input parameters on the modelled outcomes is likely to be smaller, and less informative, than the effect of simultaneously varying all input parameters in a PSA (19). Additionally, the reference case in

the NICE Guide to the methods of technology appraisal 2013 Section 5.8.7 states that PSA is preferred for evaluating parameter uncertainty (20), and as such no additional one-way sensitivity analyses have been provided.

B21. The economic model provided allows subgroup analyses to be implemented.

a. Please confirm which parameters are adjusted in the “Europe” subgroup analysis.

In the Europe scenario analyses (scenarios #13.1 and #13.2), the baseline characteristics have been adjusted based on the baseline characteristics of the Europe subgroup of the DAPA-HF trial. These baseline characteristics are applied to the adjusted survival equations for all-cause mortality and CV-mortality, and the risk equations for hHF, resulting in differences in events rates and therefore differences in the LY, QALYs and costs accrued compared to base case analyses.

b. Consistent with clarification question A17, please provide scenario analyses that implement Europe-specific relative treatment effectiveness.

DAPA-HF was not powered to estimate the treatment effect of dapagliflozin in the Europe subgroup and therefore the treatment effect observed in this subgroup is associated with substantially reduced precision, and the results are not under type 1 error control given the large number of subgroups evaluated. There was no significant difference in treatment effect observed between regions included in the DAPA-HF clinical trial (p-value for interaction:0.3818) and as such incorporating the treatment effect from the Europe subgroup would not be appropriate. Instead, the results from the overall DAPA-HF trial population provides the best estimate of the treatment effect associated with dapagliflozin.

The most appropriate analysis for evaluating the cost-effectiveness of dapagliflozin in Europe is to apply the treatment effect and fully-adjusted risk equations from the overall population (for which the trial is powered) to the baseline characteristics associated with the Europe subgroup of DAPA-HF. This analysis is provided as scenario analyses #15.1 and #15.2 in the company submission, which show dapagliflozin to be highly cost-effective with ICERs of £5,819/QALY and £5,980/QALY, respectively.

A less appropriate scenario analysis based on unadjusted risk equations derived using data from the Europe subgroup only, can be implemented in the model. The results of these scenario analyses are shown in Table 31 and Table 32. Dapagliflozin remains cost-effective in this scenario analysis with ICERs of ~£17,000, even when the treatment effect from the Europe subgroup is applied (trial not designed to estimate the treatment effect in individual regions). Because the DAPA-HF trial was powered for the overall population and not for the Europe subgroup, the results of scenario #15.1 and #15.2 are more reliable (see Table 56 of company submission), as they are based on the treatment effect of dapagliflozin as determined by the overall population analysis.

Scenario analysis for base case analysis #1 is not relevant, as there was no interaction between treatment effect and region in the DAPA-HF trial nor in the PARADIGM-HF trial, and as such it is expected that the results from the MAIC of dapagliflozin versus sacubitril valsartan based on the overall PARADIGM-HF population is representative of the relative treatment effect in the European subgroup.

Table 31. Scenario analysis of base case analysis #2 using unadjusted risk-equations based on data from Europe subgroup (trial not powered for this analysis)

	Dapagliflozin + SC (intervention)	Placebo + SC (comparator)	Incremental	ICER (£/QALY)
Life years	6.233	6.119	0.114	£17,087
QALYs	4.582	4.453	0.129	
Costs (£)	£15,179	£12,974	£2,205	

These results were generated using the updated version of the model, which incorporates the exponential distribution for treatment discontinuation (see response to question B8).
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years, SC, standard care.

Table 32. Scenario analysis of base case analysis #3 using unadjusted risk-equations based on data from Europe subgroup (trial not powered for this analysis)

	Dapagliflozin + SC (intervention)	Placebo + SC (comparator)	Incremental	ICER (£/QALY)
Life years	6.233	6.119	0.114	£17,203
QALYs	4.582	4.453	0.129	
Costs (£)	£15,998	£13,777	£2,220	

These results were generated using the updated version of the model, which incorporates the exponential distribution for treatment discontinuation (see response to question B8).
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years, SC, standard care.

c. Consistent with clarification question A11, please provide scenario analyses that implement NYHA class III to IV specific input parameters, including relative treatment effectiveness.

As discussed above in response to questions B21c, cost-effectiveness analyses based on subgroup analysis from the DAPA-HF trial are not appropriate, as the trial was not powered for the subgroups and as such the observed treatment effects of subgroups are associated with substantially reduced precision, and the results are not under type 1 error control, given the large number of subgroups evaluated. Any differences in treatment effect for patients with NYHA class III/IV at baseline in comparison with NYHA class II at baseline are therefore believed to be a chance finding, given the shortcomings of the NYHA classification and the consistency of treatment effect observed across subgroups by other measures of HF disease severity (see details below and in Section B.2.7 in company submission). As such the overall DAPA-HF trial provides the best estimate of the treatment effect associated with dapagliflozin.

Additionally, it would not be appropriate to incorporate the treatment effect associated with the subgroup of patients with NYHA III/IV *at baseline*, and instead a valid analysis should apply the treatment effect associated with *time updated* NYHA class, given the progressive nature of HF. Such an analysis would need to also incorporate transition probabilities between NYHA classes, but the NYHA class transition probabilities derived from the DAPA-HF trial lack face-validity, as on average patients' NYHA class improved over time in DAPA-HF, which is at odds with the chronic progressive nature of HF. As such, KCCQ-TSS is seen as a more appropriate measure of disease severity in the DAPA-HF trial and cost-effectiveness model. Furthermore, cost-effectiveness has been demonstrated to be consistent in subgroups of patients with different underlying risk of worsening HF events and death (see Scenario analyses, including #9.1, #9.2, #10.1, #10.2, #11.1, #11.2, #12.1, #12.2, #13.1, #13.2, #13.2, #14.1 and #14.2 in company submission).

In the company submission, scenario analyses #9.1, #9.2, #10.1, and #10.2 were conducted to demonstrate the consistency in cost-effectiveness of dapagliflozin when fully adjusted risk equations are applied to the baseline characteristics of patient subgroups stratified by KCCQ-TSS. KCCQ-TSS is a validated, self-administered instrument that quantifies HF-related symptoms, in comparison, NYHA class is a more subjective, arbitrary, and non–patient-centric assessment of symptom burden.

The consistency in treatment effect of dapagliflozin by HF disease severity is supported by subgroup analyses stratified by KCCQ-TSS (Kosiborod et al. (21) and Figure 12 of company submission), LVEF, NT-proBNP and prior hHF (see Figure 11 of company submission) which do not support the presence of any interaction between treatment effect and HF disease severity. Additionally, the directionality of trends in treatment effect with disease severity are not consistent across the different disease severity measures, lending further support for the results by NYHA II and III/IV to be a chance finding. For example, when disease severity is approximated by prior hHF or LVEF, patients with more severe HF (prior hHF – yes; LVEF ≤ median) appear to benefit from a larger treatment effect, whereas the reverse is true when disease severity is approximated by KCCQ-TSS or NT-proBNP.

In summary, given the multiple testing and lack of type 1 error associated with subgroup analyses, and the consistency in treatment effect cross subgroups by disease severity as approximated by several measures, the difference in treatment effect between the two NYHA subgroups is thought to be a spurious finding, and the results from the powered overall population represent the most robust and appropriate estimate of the treatment effect.

Validation and transparency

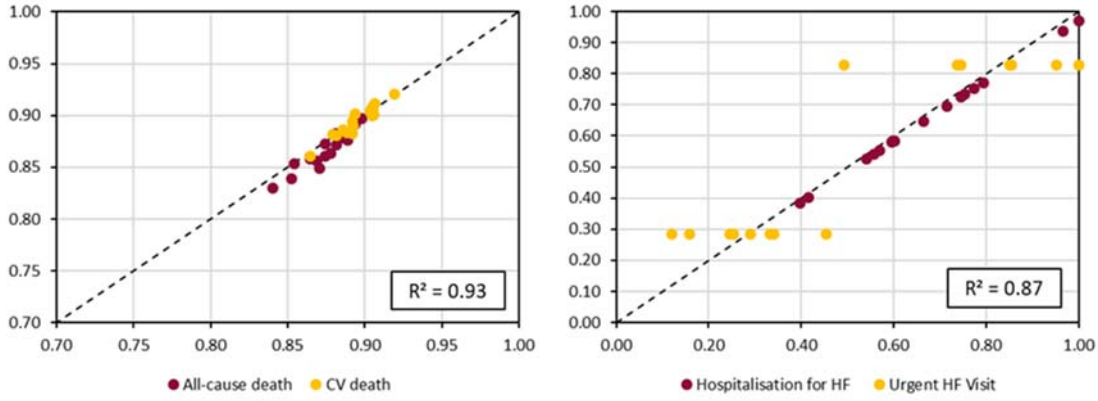
B22. Priority question: The following questions relate to model validation:

a. **Please provide details of the methods/steps performed for the validation exercise with the results.**

The cost-effectiveness model was developed in collaboration with [redacted], who provided expert guidance on the appropriateness of the proposed model structure and subsequently in the development of multivariable risk equations describing the incidence of all-cause mortality, CV-specific mortality and hHF event incidence and final model results and intermediate outcomes (see responses to B3f and B6b for more detail regarding expert validation of model outcomes, and comparisons with previously published estimates). Additionally, model output was validated back to data from DAPA-HF to ensure that predictions were aligned to the observed data, analysis of observed versus expected survival and incidence of worsening HF events can be seen in Figure 11. These analyses show that model output is in good agreement with the observed data, with an R^2 of 0.93 and mean absolute percentage error of 0.7% in predicting survival. The model also reproduced the observed incidence of hHF, however model fit to incidence of uHFv events was less good as no adjustments were made to the incidence of uHFv and it was not stratified by patient subgroup due to the limited number of events observed in the trial (39 including recurrent events). Further technical validation of the model functionality is presented in the attached TECH-VER checklist.

A B

Figure 11. Observed versus expected for mortality (A) and worsening HF events (B)



Abbreviations: CV, cardiovascular; HF, heart failure.

b. Please elaborate on the face validity (assessed by a clinical expert) of the:

i. model assumptions,

ii. model structure,

iii. model inputs,

iv. intermediate model outcomes (including model extrapolation),

v. final model results (including whether alternative assumptions, structure, and inputs are more plausible than those used in the base-case analyses).

Please see response to question B22a.

c. Please provide a cross-validation with NICE TA388 and TA267 regarding model structure, assumptions, inputs, intermediate outcomes (including extrapolation) and final results. Please elaborate on the identified differences.

The *de novo* model described in the submission dossier was developed following a review of NICE TA388 and TA267, a summary of key model characteristics for each submission is shown in Table 33. All submissions utilised Markov models, however, the models utilised in TA388 and TA267 utilised a simplified model framework with health states only describing patients as alive or dead. In order to capture patient heterogeneity, the models for both TA388 and TA267 were run for baseline patient characteristics describing each patient in the trial population and aggregated resulting in high model runtimes. The dapagliflozin model incorporated additional health state stratifications defined by KCCQ-TSS quartile (a measure of disease severity) and the presence of T2DM to capture important components of patient heterogeneity and thus enabling the model to be run a single time for each analysis using mean patient characteristics, reducing model run times. The dapagliflozin model and the model used in TA388 both assessed the impact of treatment on all-cause mortality, whereas TA267 considered CV-specific mortality only in their base case analysis. DAPA-HF demonstrated a significant reduction in all-cause mortality for patients treated with dapagliflozin, justifying a modelled treatment effect on all-cause mortality. Analysis for dapagliflozin also incorporate UK life table estimates of non-CV specific mortality in order to ensure non-CV specific mortality estimates derived from the DAPA-HF trial never dropped below general population levels. All three models captured the incidence of hospitalisation, the dapagliflozin model conservatively incorporated only hHF and uHFv aligned to the endpoints of DAPA-HF, whereas the models used in TA388 and TA267 captured all-cause hospitalisations. Time horizons and cycle lengths were aligned between the three models.

Table 33. Comparison of models used for evaluation of dapagliflozin, sacubitril valsartan (TA388) and ivabradine (TA267)

	Dapagliflozin	TA388	TA267
Model structure	Markov	Markov	Markov
Health states	KCCQ-TSS quartiles, with and without T2DM, Death	Alive, dead	Alive, dead
Cycle length	1 month	1 month	1 month
Time horizon	Lifetime	Lifetime	Lifetime
Mortality	All-cause mortality modelled through parametric survival analysis, supplemented with UK life tables	All-cause mortality modelled through parametric survival analysis	CV-specific mortality modelled through parametric survival analysis
Hospitalisation	Negative binomial regression model of hHF and uHFv	Negative binomial regression model of all-cause hospitalisation	Poisson regression model of all-cause hospitalisation

Abbreviations: CV: cardiovascular, hHF: hospitalisation for heart failure, KCCQ-TSS: Kansas City Cardiomyopathy Questionnaire Total Symptom Score, T2DM: type 2 diabetes mellitus, uHFv: urgent heart failure visit

Clinical and utility data from all three submissions were based on analysis of the respective clinical trials, DAPA-HF, PARADIGM-HF and SHIFT. Analysis methods were consistent across the three submissions with parametric survival analysis used to inform extrapolated patient survival and negative binomial or Poisson regression models used to extrapolate the incidence of hospitalisation events. Utility inputs were based on the coefficients of mixed effects regression models fit to individual patient data in all submissions. Utility estimates that could not be derived from DAPA-HF trial data were sourced from the published literature in line with previous appraisals of dapagliflozin in T2DM and T1DM (Table 44). Model estimates of patient survival and total costs in the control arms of each model were consistent, with estimated life years gained ranging from 5.61 to 6.03, QALYs ranging from 3.99 to 4.46 and total costs ranging from £9,445 to £13,286 (Table 34).

Table 34. Comparison of base case results in the control arms of dapagliflozin, sacubitril valsartan (TA388) and ivabradine (TA267)

	Dapagliflozin*	TA388	TA267
Total LYs	5.61	6.03	5.61
Total QALYs	4.13	4.46	3.99
Total costs (£)†	12,226	13,286	9,445

† costs as reported in TA388 and TA267
* based on analysis #2
Abbreviations: CV: cardiovascular, hHF: hospitalisation for heart failure, KCCQ-TSS: Kansas City Cardiomyopathy Questionnaire Total Symptom Score, T2DM: type 2 diabetes mellitus, uHFv: urgent heart failure visit

d. Please provide a detailed explanation of the technical verification of model implementation and fill out the TECH-VER checklist (Büyükkaramikli NC et al. Pharmacoeconomics 2019, https://doi.org/10.1007/s40273-019-00844-y).

Please find completed TECH-VER checklist in Appendix P submitted alongside this response document.

e. Please provide an updated version of company submission Figure 39 using smaller 'dots' and discuss the implications of differences between observed and modelled outcomes (e.g. for angiotensin receptor-neprilysin inhibitor (ARNi) and KCCQ.

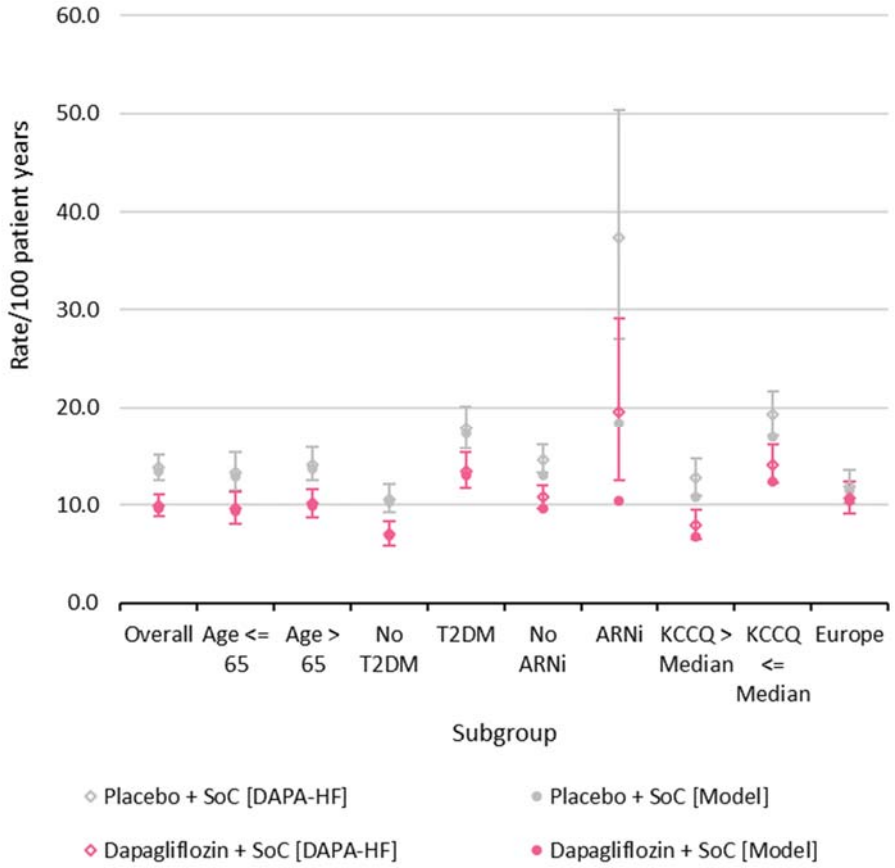
The modelled incidence rates for hHF for the overall DAPA-HF population and for most of the subgroups align well with the observed incidence rates for hHF in the DAPA-HF trial (Figure 12). When there are differences between the modelled incidence rate and the observed incidence rate, the modelled incidence rate is lower for both the dapagliflozin and the placebo arms, with a larger discrepancy for the placebo arm. As such, the modelled treatment effect is smaller than the observed treatment effect, which means that where there is a bias, the model is biased in favour of placebo.

Overall, the impact of the incidence of hHF on the cost-effectiveness result is limited. Table 92 and Table 94 in Appendix J of the company submission shows that hHF are associated with -0.018 to -

0.023 QALYs only over the life-time time horizon, resulting in a contribution of 0.003 to the total incremental QALYs.

In summary, the incidence of hHF is not a major driver of the model and any bias associated with the modelled incidence rate is in favour of the placebo arm.

Figure 12. Amended Figure 39 from company submission: Observed and predicted incidence of hHF events



Abbreviations: ARNi, angiotensin receptor neprilysin inhibitor; KCCQ, Kansas City Cardiomyopathy Questionnaire; SoC, standard care; T2DM, type 2 diabetes mellitus.

Section C: Textual clarification and additional points

C1. According to section B.2.1, “the search identified a total of five citations reporting on one unique trial”, however, only four references are reported. Please check and provide any missing references.

Kosiborod et al, 2019 (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), was mistakenly excluded from the citations; while the trial is listed in the complete reference list in Table 58, it has been mistakenly cited as reference 49. This study is included along with the responses to NICE questions.

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NICE National Institute for Health and Care Excellence

Professional organisation submission

Dapagliflozin for treating heart failure with reduced ejection fraction [ID1656]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

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- Your response should not be longer than 13 pages.

About you	
1. Your name	
2. Name of organisation	**British Society for Heart Failure**

3. Job title or position	
4. Are you (please tick all that apply):	☐ an employee or representative of a healthcare professional organisation that represents clinicians? ☐ a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☒ other (please specify): Charity
5a. Brief description of the organisation (including who funds it).	The British Society for Heart Failure is the national organisation representing heart failure professionals and patients. It is/We are charitable organisation whose aims are: • To increase knowledge and promote research about the diagnosis, causes, management and consequences of heart failure amongst healthcare professionals, with the intention of delaying or preventing the onset of heart failure and improving care for patients with heart failure; • To provide expert advice to healthcare professionals, patient or government organisations, including the National Health Service, when appropriate and as requested. The Society relies on grants and sponsorships to carry out its charitable objects.
4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the	The BSH has received the following funding from Astra Zeneca • £11,500 fee for exhibiting at BSH Autumn Meeting 2019 • 21 June 2019 - £10,000 sponsorship grant BSH for period from 1 Jan 2019 to 31 Dec 2019 • £1,000 donation towards the cost of running the UK Heart Failure Investigator meeting

appraisal matrix.] If so, please state the name of manufacturer, amount, and purpose of funding.	
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
The aim of treatment for this condition	
6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	The treatment of heart failure with reduced ejection fraction is two-fold. Firstly, aiming to reduce the symptom burden such as shortness of breath and fluid overload. Secondly, to improve mortality rates, prevent disease progression and reduce admission to hospital.
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by	Clinically significant treatment response would include: • Improved symptoms – reduction in NYHA class, improved exercise tolerance, improved quality of life • Reduced admission to hospital • Reduced mortality

x cm, or a reduction in disease activity by a certain amount.)	
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes. Despite treatment advances heart failure remains as malignant a condition as the most common cancers. (1) With the most recent data showing in-hospital mortality to be 10.1% and for those who survive to discharge, a 1-year mortality rate of 32%. (2) Heart failure accounts for 1 million bed days, 2% of the total NHS budget (3) and is the commonest reason for hospital re-admission among older adults. (4)
What is the expected place of the technology in current practice?	
9. How is the condition currently treated in the NHS?	Treatment includes • Medications • Device therapy • Cardiac rehabilitation • Lifestyle measure
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	National Institute of Clinical Excellence. Chronic heart failure in adults: diagnosis and management. NG106. National Cardiac Audit Programme; 2018
• Is the pathway of care well defined? Does it	Yes. The pathway of heart failure diagnosis and treatment is well defined within the current guidelines however, variation does occur depending of the availability of diagnostic tests with in localities and local

vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	guideline interpretation.
• What impact would the technology have on the current pathway of care?	The treatment in question, would add and additional treatment option to the pathway giving heart failure clinicians further treatment options to improve patient care.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Yes
• How does healthcare resource use differ between the technology and current care?	This treatment is already used in the treatment of diabetes mellitus. It would add an additional treatment option within the current treatment pathway for patients with heart failure and reduced ejection fraction (HFrEF). Existing services and resources would be used to implement the new treatment within the current care pathway. It will however, increase the current work load for heart failure specialist teams.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Dapagliflozin in heart failure patients without diabetes should be initiated by heart failure specialists. For patient with concomitant diabetes, treatment should be initiated by either a diabetes or heart failure specialist with collaborative working where appropriate to ensure patient safety with complex polypharmacy.
• What investment is	As this is a new class of medication within the area of heart failure, a significant training resource will need

needed to introduce the technology? (For example, for facilities, equipment, or training.)	to be implemented to ensure patient safety and upskill both diabetologists and heart failure specialists. In addition, education of primary care physicians in the monitoring of such patients will need to be considered.
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes
• Do you expect the technology to increase length of life more than current care?	Yes. Clinical trials have shown that treatment with dapagliflozin in addition to the already defined standard of care (ACEI/ARB/ARNI + BB + MRA) provided additional benefit to patients in terms of reduced admission to hospital and mortality. (5) Treatment with dapagliflozin showed a relative risk reduction of 18% for cardiovascular death and a 17% RRR in all-cause death. (5)
• Do you expect the technology to increase health-related quality of life more than current care?	Yes. Dapa-HF (5) showed an improvement in health-related quality of life when dapagliflozin was given in addition to current standard treatment.
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate)	No, the effect of dapagliflozin was generally consistent across pre-specified groups. This medication should be used in keeping with the evidence base – as provided by the inclusion criteria in the DAPA- HF study. (5)

than the general population?	
The use of the technology	
13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	Introduction of dapaglifozin to standard HFrEF care represents and extension of current therapy. It can be taken alongside pre-prescribed therapies but will require additional education for patients and their carers/heathcare professionals. As with other HFrEF therapies, more intense monitoring will be required in the initiation phase to assess for side effects and tolerability. This is likely to require: 1) More clinic appointments/reviews with the specialist teams. 2) Additional blood test and blood pressure monitoring 3) Education and training of healthcare professionals 4) Increased joint working between endocrinology for diabetic patients and ensuring robust protocols.
14. Will any rules (informal or formal) be used to start or stop treatment with the technology?	Criteria for starting treatment as per the clinical trial: • ≥18 years of age

Do these include any additional testing?	• With or without T2D • Diagnosis of symptomatic HFrEF (NYHA class II-IV) for ≥ 2 months • LVEF ≤40% within last 12 months • Elevated NT-proBNP • eGFR ≥30 ml/min/1.73 m^2 Stopping treatment in the event of any adverse event or contraindications.
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	No
16. Do you consider the technology to be innovative in its potential to make a significant and substantial	Dapagliflozin is a new class of medicine in the treatment of heart failure therefore is felt to be innovative.

impact on health-related benefits and how might it improve the way that current need is met?	
• Is the technology a 'step-change' in the management of the condition?	Yes. Dapagliflozin would be an additional step within the current management of heart failure
• Does the use of the technology address any particular unmet need of the patient population?	No
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Any adverse effects could result in discontinuation of the treatment, preventing benefit of the additional treatment. Common side effects include: Back pain; balanoposthitis; diabetic ketoacidosis (discontinue immediately); dizziness; dyslipidaemia; hypoglycaemia (in combination with insulin or sulfonylurea); increased risk of infection; rash; urinary disorders Uncommon side effects include: Constipation; dry mouth; genital pruritus; hypovolaemia; thirst; vulvovaginal pruritus; weight decreased Rare side effects include:

	Angioedema; Fournier's gangrene (discontinue and initiate treatment promptly) Fourniers gangrene – could significantly impact patient's quality of life, however, this is a rare side effect and patient should be counselled as to what to look out for to prevent it. .
Sources of evidence	
18. Do the clinical trials on the technology reflect current UK clinical practice?	Yes. Dapa-HF (5) compared dapagliflozin with placebo in addition to standard of care (ACEI/ARB + BB + MRA). This is reflective of data collected in the national HF audit (2).
• If not, how could the results be extrapolated to the UK setting?	N/A
• What, in your view, are the most important outcomes, and were they measured in the trials?	Important outcomes include: • Mortality • HF admissions • Quality of life All were measure within the clinical trial.

• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	N/A
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
20. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance TA388?	N/A
21. How do data on real-world experience compare with the	There is little UK data available. Data from other countries has shown that the treatment is well tolerated. As with all other heart failure clinical trials, recruited patients (mean age 66 years) were somewhat younger

trial data?	than the mean age of the heart failure population (mean 78 years at diagnosis).
Equality	
22a. Are there any potential equality issues that should be taken into account when considering this treatment?	No
22b. Consider whether these issues are different from issues with current care and why.	
Key messages	
23. In up to 5 bullet points, please summarise the key messages of your submission. • The BSH strongly supports the application. • Heart failure is an important area of need with associated high mortality, high hospital admission rate and reduced quality of life. • This is a novel use for a medication that is already licensed and in use for diabetic patients. • Type 2 diabetes is present in around 25% of heart failure patients so addition of this medication will have dual benefits. • This medication is straightforward to introduce for non-diabetic patients.	

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Patient organisation submission

Dapagliflozin for treating heart failure with reduced ejection fraction [ID1656]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

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- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.Your name	[redacted]

2. Name of organisation	Pumping Marvellous Foundation
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	The Pumping Marvellous Foundation is the UK's patient led heart failure charity. It represents all patients in the UK. It does not have a membership as is open to all people impacted by HF. The organisation has a broad base of funders including Life Science companies through hands off educational grants, the NHS, grant and company based funding and many different types of personal fundraisers across the UK.
4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] If so, please state the name of manufacturer, amount, and purpose of funding.	AZ - £15k – Hands off educational Grant to develop educational webinars AZ – A number of small Honorarium, paid directly to the charity for speaking at events.

4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	We run the largest patient communities on our social media platforms globally. We talk to patient, carers and their families constantly, aggregating their insights about living with heart failure.
Living with the condition	
6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Heart failure impacts people in different ways. The social/psychological aspects of living with heart failure impact patients greatly, quality of life is a key driver for patients. It rips their way of life, before diagnosis, away from them. The physical symptoms can be very debilitating including breathlessness, extreme fatigue and fluid accumulation. In many cases, carers and family members experience similar challenges to the patients where they feel and experience the debilitating attrition that heart failure is. Being told you have a condition that is life limiting doesn't set you up to win with heart failure
Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	They think the treatments are limited and options are constrained. Many times, we see the anguish around can't anything else be done? naïve patients are treated with widely available generics through triple therapy and only have two 2nd line guidelinebtreatments available to them if there is a deterioration in heart function, one of those is highly constrained with who can have it. Medical device therapy is available but doesn't play a big enough part in the treatment perception. The HF MDT as outlined in the

	NG106 guidelines are generally well respected, especially the heart failure nurse, however there is a general feeling that primary care/community care is not fully cognisant of the challenges or best care and treatments for people living with heart failure. Diagnosis is a primary concern and constant topic of discussion around mis-diagnosis and the failure to diagnosis and its impact on the patient and families.
8. Is there an unmet need for patients with this condition?	There is a significant unmet need for people living with HF. Historically there has not been enough investment or focus by many stakeholders on the importance of a quick and accurate diagnosis, treatment of, care of and helping patients live with HF which lives 99% of the time in their homes. Investment in new treatments and ways of delivering care is paramount to see HF as treatable and manageable in many many cases. The unmet need is matching the needs of patients and their families. New treatments are essential to drive better outcomes, not just mortality and readmission costs but most importantly, allowing people to live with their heart failure better.
Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	Patients and carers see HOPE. They are aware of the new technology for potentially treating heart failure and as soon as the trial results were published there was significant discussion in our communities, highlighting the reporting. People see an “ADVANTAGE” as, does it help me. Patients know how under resourced HF is and will support and advocate advancements in how we make life better with HF. Options in HF have been lacking, having more options that work are essential, both on a physical and mental level.
Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	We don’t see the patients talking about the disadvantages at the moment, not that they are not there, just that the overriding benefit of a new treatment that may alleviate their challenges is on the horizon.

Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	It seems that the new technology may offer better treatment for their heart failure, whether diabetic or not. Just like the newest treatment, with authorisation for broad deployment in the HF population, Sacubitril Valsartan (Entresto), this technology could have a profound impact across the whole population but only in the HFrEF population. This population is 60% of the whole population according to NICE. 40% of the population have HFpEF and these are the people who will not get access. This is a syndrome of HF where the HFpEF population are left with no prognostically available treatment. This is a major access issue.
Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	**I am not aware of any equality issues.**

Other issues	
13. Are there any other issues that you would like the committee to consider?	It is important for the committee to understand the importance of new treatments in HF. Too many times we have seen committees not fully understand the impact of new technologies other than the satisfaction of the health economics. The health economics does not access the macro economics of living with a condition like heart failure and the impact of getting it right. On a clinical and economic view-point, we can only pass educated comment on how we see it. We are the patient's eyes and ears. We see HF through their eyes and advocate for a better quality of life and a reduction in mortality.

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission:

- HF lacks treatment options
- New treatments are important to people impacted by HF
- More treatments are required as options are good
- QOL is more important to people living with HF
- With 24x7 access to media patients are eagerly awaiting the outcome of this appraisal

Thank you for your time.

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in collaboration with:

ERASMUS UNIVERSITEIT ROTTERDAM
INSTITUTE OF HEALTH POLICY & MANAGEMENT

Maastricht University

Dapagliflozin for treating heart failure with reduced ejection fraction

Produced by Kleijnen Systematic Reviews (KSR) Ltd. in collaboration with Erasmus University Rotterdam (EUR) and Maastricht University

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Date completed 29/07/2020

Source of funding: This report was commissioned by the NIHR HTA Programme as project number 13/16/82.

Declared competing interests of the authors
None.

Acknowledgements
None.

Commercial in confidence (CiC) data are highlighted in blue throughout the report.

Academic in confidence (AiC) data are highlighted in yellow throughout the report.

Rider on responsibility for report
The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

This report should be referenced as follows:

Wolff R, Ramaekers BLT, Brandts L, Witlox W, Ryczek E, Posadzki P, Ahmadu C, Armstrong N, Worthy G, Duffy S, Joore MA, Kleijnen J. Dapagliflozin for treating heart failure with reduced ejection fraction: a Single Technology Assessment. York: Kleijnen Systematic Reviews Ltd, 2020.

Contributions of authors
Robert Wolff acted as project lead and systematic reviewer on this assessment, critiqued the clinical effectiveness methods and evidence, and contributed to the writing of the report. Bram Ramaekers acted as health economic project lead, critiqued the company's economic evaluation, and contributed to the writing of the report. Lloyd Brandts, Willem Witlox, Charlotte Ahmadu and Nigel Armstrong acted as health economists on this assessment, critiqued the company's economic evaluation and contributed to the writing of the report. Edyta Ryczek and Pawel Posadzki acted as systematic reviewers, critiqued the clinical effectiveness methods and evidence, and contributed to the writing of the report. Gill Worthy acted as statistician, critiqued the analyses in the company's submission and contributed to the writing of the report. Steven Duffy critiqued the search methods in the submission and contributed to the writing of the report. Manuela Joore acted as health economist on this assessment, critiqued the company's economic evaluation, contributed to the writing of the report, and provided general guidance. Jos Kleijnen critiqued the company's definition of the decision problem and their description of the underlying health problem and current service provision, contributed to the writing of the report, and supervised the project.

Abbreviations

A&E	Accident and emergency
ACC	American College of Cardiology
ACEi	Angiotensin-converting enzyme inhibitor
ACP	American College of Physicians
AE	Adverse event
AF	Atrial fibrillation
AHA	American Heart Association
AiC	Academic in confidence
AIC	Akaike information criterion
AP	Asia or Pacific
ARB	Angiotensin II receptor blocker
ARNI	Angiotensin receptor–neprilysin inhibitor
BB	Beta blocker
BIC	Bayesian information criterion
bid	Twice daily
BMI	Body mass index
CABG	Coronary artery bypass grafting
CADTH	Canadian Agency for Drugs and Technologies in Health
CCA	Cochrane Clinical Answers
CCTR	Cochrane Central Register of Controlled Trials
CDSR	Cochrane Database of Systematic Reviews
CE	Cost effective
CEA	Cost effectiveness analysis
CHF	Chronic heart failure
CI	Confidence interval
CiC	Commercial in confidence
CMR	Cochrane Methodology Register
con.	Control
CRT	Cardiac resynchronisation therapy
CS	Company submission
CSR	Clinical study report
CV	Cardiovascular
CVD	Cardiovascular death
DARE	Database of Abstracts of Reviews of Effects
DKA	Diabetic ketoacidosis
DM	Diabetes mellitus
DPP-4	Dipeptidyl peptidase 4
DSA	Deterministic sensitivity analysis
EBM	Evidence-based medicine
ECG	Electrocardiogram
EED	Economic Evaluation Database
EF	Ejection fraction
eGFR	Estimated glomerular filtration rate
eMIT	Electronic Marketing Information Tool
EQ-5D-3L	European Quality of Life-5 Dimensions, three-level scale
ERG	Evidence Review Group
ESC	European Society of Cardiology
ESRD	End-stage renal disease
EUR	Erasmus University Rotterdam
FAS	Full analysis set
FDA	Food and Drug Administration
GCP	Good clinical practice
GEE	Generalised estimating equations

GP	General practitioner
HCHS	Hospital and Community Health Services
HF	Heart failure
hHF	Hospitalisation for heart failure
HFmrEF	Heart failure with mid-range or borderline ejection fraction
HFpEF	Heart failure with preserved ejection fraction
HFrEF	Heart failure with reduced ejection fraction
HR	Hazard ratio
HR	Heart rate
HRG	Healthcare Resource Group
HRQoL	Health-related quality of life
HSUV	Health state utility value
HTA	Health technology assessment
HTAi	Health Technology Assessment international
HTN	Hypertension
Hx	History of
ICD	Implantable cardioverter defibrillator
ICER	Incremental cost effectiveness ratio
ICTRP	International Clinical Trials Registry Platform
inv.	Intervention
IPD	Individual participant data
IQR	Interquartile range
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
ISSG	InterTASC Information Specialists' Sub-Group
ITC	Indirect treatment comparison
ITT	Intention to treat
KCCQ	Kansas City Cardiomyopathy Questionnaire
KCCQ-TSS	Kansas City Cardiomyopathy Questionnaire – Total Symptom Score
KM	Kaplan–Meier
KSR	Kleijnen Systematic Reviews
LVEF	Left ventricular ejection fraction
LYG	Life year gained
MAIC	Matched adjusted indirect comparison
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
MI	Myocardial infarction
ml	Millilitre
mmHg	Millimetre of mercury
MRA	Mineralocorticoid receptor antagonist
NA	North America
NA	Not applicable
NG	NICE guideline
NHS	National Health Service
NHSCII	NHS Cost Inflation Index
NICE	National Institute for Health and Care Excellence
NICOR	National Institute for Cardiovascular Outcomes Research
NIHR	National Institute for Health Research
NT-proBNP	N-terminal pro B-type natriuretic peptide
NYHA	New York Heart Association
od	Once daily
OR	Odds ratio
PACD	Primary analysis censoring date
PBAC	Pharmaceutical Benefits Advisory Committee
PCI	Percutaneous coronary intervention
pg	Picogram

PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSA	Probabilistic sensitivity analyses
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
QALY	Quality-adjusted life year
QIC	Quasi-likelihood under the independence model criterion
RCT	Randomised controlled trial
SA	South America
SAE	Serious adverse events
SAS	Safety analysis set
SBP	Systolic blood pressure
SC	Standard care
ScHARRHUD	School of Health and Related Research Health Utility Database
SD	Standard deviation
SE	Standard error
SGLT2i	Sodium glucose cotransporter 2 inhibitor
SLR	Systematic literature review
SMC	Scottish Medicines Consortium
SMDM	Society for Medical Decision Making
SmPC	Summary of product characteristics
T1DM	Type 1 diabetes mellitus
T2DM	Type 2 diabetes mellitus
TA	Technology appraisal
TECH-VER	TECHnical VERification
TSD	Technical support document
UK	United Kingdom
UMC+	Maastricht University Medical Center+
US NIH	United States National Institutes of Health
uHFv	Urgent heart failure visit
UTI	Urinary tract infection
WCC	World Congress of Cardiology and Cardiovascular Health
WHO	World Health Organization
WTP	Willingness-to-pay

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1. Executive summary

1.1 Critique of the decision problem in the company's submission

1.1.1 Population

The final scope issued by the National Institute for Health and Care Excellence (NICE) defined the population of interest as adults with chronic heart failure with reduced ejection fraction (HFrEF). The population presented in the company submission (CS) is as per the NICE scope.

In the cost effectiveness analysis (CEA), there were three populations, defined effectively by the line of therapy and comparator:

1. Population #1: patients not previously treated with sacubitril valsartan, dapagliflozin as an add-on therapy to angiotensin-converting enzyme inhibitor/ angiotensin II receptor blocker (ACEi/ARB), beta blocker (BB) ±mineralocorticoid receptor antagonist (MRA) was compared to ACEi/ARB, BB ±MRA with sacubitril valsartan,
2. Population #2: patients not previously treated with sacubitril valsartan, dapagliflozin, as an add-on therapy to ACEi/ARB, BB ±MRA was compared to ACEi/ARB, BB ±MRA without sacubitril valsartan,
3. Population #3: patients previously treated with sacubitril valsartan, dapagliflozin, as an add-on therapy to sacubitril valsartan, BB ±MRA, was compared to sacubitril valsartan, BB ±MRA

The difference between populations #1 and #2 was unclear given that the line of therapy appeared to be the same. In response to request for clarification, the company stated that the difference lay in eligibility for sacubitril, i.e. population #1 is eligible for sacubitril valsartan in accordance with the marketing authorisation of sacubitril valsartan (patients need to have ejection fraction (EF) ≤35% and must not have hyperkalaemia (serum potassium >5.4 mmol/l) and/or hypotension), but population #2 is ineligible for sacubitril valsartan. However, the company also stated that population #2 might include patients who do not progress to receiving sacubitril valsartan due to other reasons, e.g. due to the complexity associated with sacubitril valsartan initiation and titration.

1.1.2 Intervention

The NICE scope defined the intervention of interest as: "*dapagliflozin in combination with SC* [standard care] *(including treatment with an ACEi* [angiotensin-converting enzyme inhibitor], *ARB* [angiotensin II receptor blocker], *mineralocorticoid receptor antagonist* [MRA], *beta blocker* [BB], *sacubitril valsartan and/or an aldosterone antagonist)"*.

The intervention addressed in the CS was described as *"dapagliflozin in combination with SC, where SC is defined as:*

1. *ACEi or ARB, in combination with beta-blocker, ±MRA (according to patient's tolerance of MRA)*
2. *Sacubitril valsartan, in combination with beta-blocker, ±MRA (according to patient's tolerance of MRA)"*

In the proposed treatment pathway, population #1 was compared to sacubitril valsartan after first-line treatment and positioned in the primary setting, before specialist reassessment. However, according to the recommendation in NICE technology appraisal (TA) 388, treatment with sacubitril valsartan should be started by a heart failure specialist with access to a multidisciplinary heart failure team. In response to request for clarification, the company proposed that this population "*would not need to wait for a*

specialist appointment to initiate treatment with dapagliflozin, as initiation could be undertaken in primary care, given the extensive clinical experience primary care clinicians have accumulated in initiating dapagliflozin for type 2 diabetes patients, over more than 7 years". However, it should be noted that the professional organisation submission by the British Society for Heart Failure indicated that dapagliflozin treatment should be initiated by either heart failure (in case of heart failure with/ without diabetes) or diabetes (in case of heart failure with diabetes) specialists.

1.1.3 Comparator

According to the NICE scope, the comparator of interest is *"individually optimised SC without dapagliflozin"* where *"standard care is defined as:*

- *ACEi in combination with beta-blockers, and/or mineralocorticoid receptor antagonists*
- *ARBs in combination with beta-blockers, and/or mineralocorticoid receptor antagonists*
- *Sacubitril valsartan in combination with beta-blockers, and/or mineralocorticoid receptor antagonists"*

The comparator treatments defined in the CS differed for the treatment of HFrEF patients on ACEi or ARB, in combination with beta-blocker, ±MRA (sacubitril valsartan, placebo) and HFrEF patients on sacubitril valsartan, in combination with beta-blocker, ±MRA (placebo). This was in line with TA 388 and NICE guideline 106. Background therapy (SC) will be the same in both the dapagliflozin arm and the comparator arm.

1.1.4 Outcomes

The final NICE scope listed these outcomes as relevant:

- symptoms of heart failure
- hospitalisation for heart failure
- all-cause hospitalisation
- mortality
- cardiovascular mortality
- adverse effects of treatment (including diabetic ketoacidosis, genital infections, Fournier's gangrene, amputations, and fractures) and
- health-related quality of life.

The outcomes reported in the CS mostly reflect this list with the exception of all-cause hospitalisation which has not been reported and adverse event (AE) incidences of genital infection and urinary tract infection which were not routinely collected in the DAPA-HF trial, the main source of evidence.

1.1.5 Other relevant factors

According to the National Institute for Cardiovascular Outcomes Research 2019 Heart Failure Audit, there is substantial inter-hospital variation of specialist input for heart failure admissions. Only 59% of hospitals achieved specialist review rates of over 80%, whilst specialist review rates were less than 80% of patients in 41% of hospitals. This should be noted, especially when considering the issue described in section 1.1.2.

1.2 Summary of the key issues in the clinical effectiveness evidence

The company submission and response to clarification provided enough details for the Evidence Review Group (ERG) to appraise the literature searches conducted as part of the systematic review to identify randomised controlled trial (RCT) evidence reporting on efficacy and safety. A broad range of

databases and resources, including clinical trial registries, conference proceedings and health technology assessment (HTA) organisation websites, was searched and the searches were transparent and reproducible. The searches included RCT study design filters to identify clinical efficacy but did not include search terms to identify safety evidence. Searches were conducted between November and December 2019.

The ERG was concerned with some aspects of the searches, including the search terms used in the HFrEF population facet, and the limit used to remove studies about children. Overall, however, the searches were satisfactory, and given the comprehensive list of interventions included and the range of resources searched, it was unlikely that any relevant studies meeting the NICE scope were missed.

However, there are some issues regarding the conduct of the systematic literature review (SLR):

- Non-English language studies were excluded which means that potentially relevant studies might have been missed. The company did not provide the list of all references excluded using this criterion as requested by the ERG.
- It is unclear whether data extraction followed best practice as relevant details were not reported, e.g. how many people were involved in data extraction and how any discrepancies were resolved.
- Similarly, it is unclear whether the risk of bias assessment followed best practice as relevant details were not reported, e.g. how many people were involved in risk of bias assessment, how any discrepancies were resolved, and which tool was used to assess the included studies.

The evidence for the effectiveness of dapagliflozin came from the DAPA-HF trial. This was a randomised, double-blind, multicentre, placebo-controlled, phase III trial which compared dapagliflozin 10 mg once daily with placebo in patients aged 18 years or over with HFrEF (New York Heart Association (NYHA) class ≥II with left ventricular ejection fraction (LVEF) ≤40%). Concomitant treatment with standard care was allowed in both trial arms according to local guidelines. The primary outcome was the time to the first occurrence of cardiovascular (CV) death, hospitalisation for heart failure (HF) or an urgent hospital visit for HF (a composite outcome). The trial comprised 410 centres worldwide with 10 centres in the United Kingdom (UK) recruiting 62 participants. The median follow-up period was 18.2 months (range 0 to 27.8 months) and a total of 4,744 participants were randomised.

It should be noted that patients with type 1 diabetes mellitus (T1DM) were excluded from the trial (see section 4.2.1 for details), i.e. any recommendation needs to consider this limitation. Furthermore, the ERG wants to highlight differences regarding both efficacy as well as safety in the European subgroup compared to the overall trial population (see section 4.2.1 for details). Despite higher uncertainty (as *"the subgroup analyses were not powered to detect statistically significant differences between treatment groups"*), the European population seems more relevant to the UK setting and has therefore been used in the ERG base-case, see section 1.4. Table 1.1 includes results for the primary outcome (as well as for components of this composite endpoint) for both the overall population as well as the population recruited/treated in Europe.

Table 1.1: Time to first occurrence of any of the composite components: CV death or hHF or an urgent HF visit

Outcome	Dapagliflozin	Placebo	HR (95% CI) dapagliflozin vs placebo
Whole study population	**N=2,373**	**N=2,371**	
Primary outcome*	386 (16.3%)	502 (21.2%)	0.74 (95% CI 0.65 to 0.85) P<0.001
hHF or an urgent visit for HF	237 (10.0%)	326 (13.7%)	0.70 (95% CI 0.59, 0.83) P<0.0001
hHF	231 (9.7%)	318 (13.4%)	0.70 (95% CI 0.59, 0.83) P<0.0001
Urgent heart failure visit	10 (0.4%)	23 (1.0%)	0.43 (95% CI 0.20, 0.90) P=0.0213
CV death	227 (9.6%)	273 (11.5%)	0.82 (95% CI 0.69, 0.98) P=0.0294
European subgroup	**N=1094#**	**n=1060#**	
Primary outcome*	[redacted]	[redacted]	[redacted]
hHF or an urgent visit for HF	[redacted]	[redacted]	[redacted]
hHF	[redacted]	[redacted]	[redacted]
Urgent heart failure visit	[redacted]	[redacted]	[redacted]
CV death	[redacted]	[redacted]	[redacted]

* Time to first occurrence of any of the composite components: CV death or hHF or an urgent HF visit; # Number of participants with event calculated based on reported percentage

CI = confidence interval; CS = company submission; CV = cardiovascular; HF = heart failure; hHF = hospitalisation for heart failure; HR = hazard ratio

All-cause mortality showed a statistically significant difference between dapagliflozin and placebo in favour of the active treatment (hazard ratio (HR) 0.83, 95% confidence interval (CI) 0.71 to 0.97). Results of other secondary endpoints are presented in section 4.2.2.2.

The CS included EQ-5D-5L (European Quality of Life-5 Dimensions, three-level scale) as an exploratory endpoint. There was no significant difference in change from baseline for EQ-5D-5L score between dapagliflozin and placebo at 24 months (least squares mean [redacted] least squares mean difference [redacted]).

The most commonly experienced serious adverse events (SAEs) in both dapagliflozin and placebo trial arms respectively were, pneumonia 3.2% and 3.5%, ischaemic stroke 1.0% and 1.1%, cardiac failure 11.1% and 14.8%, congestive cardiac failure 2.7% and 3.0%, acute cardiac failure 1.8% and 2.5%, acute myocardial infarction 1.6% and 1.6%, ventricular tachycardia 1.4% and 2.3%, chronic cardiac failure

1.1% and 1.4%, atrial fibrillation 1.1% and 1.6%, unstable angina 0.9% and 1.3%, acute kidney injury 1.0% and 1.9%, and death 2.0% and 2.0%. Table 1.2 presents results on adverse events for both the overall population as well as the population recruited/treated in Europe. It should be noted that the proportion of European participants with any AE or any SAE was typically [redacted] than in the overall study population. Further details on adverse events are presented in section 4.2.3.

Table 1.2: Adverse events of interest

AE, n(%)	Dapagliflozin 10 mg		Placebo	
	Overall (N=2,368)	European subgroup (N=1,094)	Overall (N=2,368)	European subgroup (N=1,059)
On treatment (SAS)†				
Any AE with an outcome of death	227 (9.6)	[redacted]	250 (10.6)	[redacted]
Any SAE (including events with an outcome of death)	846 (35.7)	[redacted]	951 (40.2)	[redacted]
AE leading to discontinuation	111 (4.7)	[redacted]	116 (4.9)	[redacted]
AE leading to dose interruption	284 (12.0)	[redacted]	349 (14.7)	[redacted]
AE leading to dose reduction	43 (1.8)	[redacted]	25 (1.1)	[redacted]
On and off treatment (SAS)‡				
Any AE with an outcome of death	286 (12.1)	[redacted]	333 (14.1)	[redacted]
Any SAE (including events with an outcome of death)	895 (37.8)	[redacted]	994 (42.0)	[redacted]
AE leading to discontinuation	111 (4.7)	[redacted]	116 (4.9)	[redacted]
AE leading to dose interruption	284 (12.0)	[redacted]	349 (14.7)	[redacted]
AE leading to dose reduction	43 (1.8)	[redacted]	25 (1.1)	[redacted]

† On treatment includes AEs with an onset date on or after date of first dose and up to and including 30 days following last dose of study drug; ‡ On and off treatment includes AEs with an onset date on or after date of first dose of study drug
AE = adverse effect; CS = company submission; SAE = serious adverse event; SAS = safety analysis set

In the absence of trials directly comparing dapagliflozin with sacubitril valsartan, the company performed an anchored matched adjusted indirect comparison (MAIC). This used results from DAPA-HF and PARADIGM-HF. These trials were the only two trials identified though the SLR.

PARADIGM-HF was an international, randomised, double-blind, parallel-group, active control trial in patients with chronic HFrEF comparing sacubitril valsartan 200 mg twice daily (bid) to enalapril 10 mg bid both given in conjunction with standard care. The primary outcome was a composite of the time to CV death or the first hospitalisation for heart failure (hHF) and the median duration of follow-up was 27 months. The trial recruited across 47 countries.

The ERG asked the company to justify the use of MAIC based on the two criteria specified in NICE technical support document (TSD) 18. As the response did not provide sufficient details regarding the two criteria, the results of the Bucher method *("unadjusted analysis based on a common anchor"* in the CS) were used as the main indirect treatment comparison (ITC) supporting the economic model, see section 4.4.2. In addition, results of the MAICs are presented in section 4.4.3 for illustration. Overall, similar effect estimates were reported for both methods with narrower 95% CIs for the Bucher method. Results for time to hHF or CV death using the Bucher method are presented in Table 1.3.

Table 1.3: Bucher results: Time to hHF or CV death (secondary endpoint)

Population	Effect estimate
Subgroup 1: Dapagliflozin plus ACEi vs. sacubitril valsartan	[redacted]
Subgroup 2: Dapagliflozin plus ARB vs. sacubitril valsartan	[redacted]
Subgroup 3: Dapagliflozin plus ACEi and/or ARB vs. sacubitril valsartan	[redacted]
ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor blocker; CI = confidence interval; CS = company submission; hHF = hospitalisation for heart failure; HR = hazard ratio	

1.3 Summary of cost effectiveness evidence submitted by the company

The company submission provided enough details for the ERG to appraise the literature searches. A good range of resources was searched, and the searches were transparent and reproducible. One set of searches was conducted to identify cost effectiveness evidence, health state utility values (HSUVs), and healthcare cost and resource data. The searches included study design filters to identify cost effectiveness studies, HSUVs and healthcare resource use data. Searches were conducted in December 2019.

The ERG was concerned with some aspects of the searches conducted, including the search terms used in the HFrEF population facet. Overall, the searches were satisfactory, and given the comprehensive list of interventions included, the study design filters used, and the range of resources searched, it was unlikely that any relevant studies were missed.

In line with its anticipated marketing authorisation and the final scope issued by NICE, dapagliflozin was considered in the cost effectiveness model for the treatment of adult patients with symptomatic HFrEF. In the model, populations #1 and #2 considered patients not previously treated with sacubitril valsartan while population #3 considered patients that were previously treated with sacubitril valsartan. Based on the CS, the overlap/differences between populations #1 and #2 (both not previously treated with sacubitril valsartan) is unclear.

Dapagliflozin was considered within the economic evaluation as per the anticipated licensed indication in HFrEF. Dapagliflozin was, in line with the dosage used in DAPA-HF, modelled as an add-on therapy with a once daily dose of 10 mg administered orally.

For population #1, dapagliflozin, as an add-on therapy to ACEi/ARB, BB ±MRA was compared to ACEi/ARB, BB ±MRA with sacubitril valsartan while for population #2 dapagliflozin, as an add-on therapy to ACEi/ARB, BB ±MRA was compared to ACEi/ARB, BB ±MRA without sacubitril valsartan. Also, dapagliflozin, as an add-on therapy to sacubitril valsartan, BB ±MRA, was compared to sacubitril valsartan, BB ±MRA for population #3.

The company developed a cohort state transition model in Microsoft Excel. The model comprised disease progression states based on Kansas City Cardiomyopathy Questionnaire – Total Symptom Score (KCCQ-TSS) quartile scores, stratified by the presence of type 2 diabetes mellitus (T2DM), and death. Patients could transition across disease progression health states that were divided in KCCQ-TSS scores of 0–<58, 58–<77, 77–<92, 92–100 (higher = better) with health state-specific costs and utility values. Furthermore, the impact of hHF, urgent heart failure visit (uHFv), as well as adverse events on quality of life and cost were incorporated.

The analysis takes a National Health Service (NHS) and Personal Social Services (PSS) perspective. Discount rates of 3.5% are applied to both costs and benefits. The model cycle length is one month with a lifetime time horizon (upon reaching an age of 100 years) and a half-cycle correction is applied.

The main source of evidence on treatment effectiveness used for the economic model was the DAPA-HF trial. Moreover, the treatment effect of sacubitril valsartan (population #1) was assumed to be equivalent to dapagliflozin.

Parametric survival models were used to estimate all-cause and CV mortality as well as time to treatment discontinuation (for the latter a constant discontinuation probability over time was assumed). Moreover, transition probabilities between health states defined by KCCQ-TSS quartiles were derived using monthly transition count data assuming last observation carried forward for imputing missing values. The incidence of hHF and uHFv events were modelled using generalised estimating equations (GEE).

The company included the most common serious AEs reported in the DAPA-HF trial in the economic model. AE incidences of genital infection and urinary tract infection were not routinely collected in the DAPA-HF trial and were therefore based on dapagliflozin and placebo arms of the cardiovascular outcomes trial of dapagliflozin in T2DM patients (DECLARE).

The company used health state utility values and disutilities derived from the DAPA-HF clinical trial. To estimate patient reported utility values derived from EQ-5D-5L questionnaires, linear mixed effects regression models were fitted using data collected at trial randomisation, day 120, day 240, day 360, and every 12 months thereafter.

The cost categories included in the model were treatment costs, health state costs and costs related to adverse events. All costs applied in the model were inflated to a 2018/19 cost-year.

For population #1, the CS base-case indicated that dapagliflozin was dominant compared with sacubitril valsartan. Moreover, for populations #2 and #3, the CS base-case resulted in probabilistic incremental cost effectiveness ratios (ICERs) of £5,701 and £5,757 per quality-adjusted life year (QALY) respectively for dapagliflozin versus standard care.

1.4 Summary of the ERG's critique of cost effectiveness evidence submitted

The company developed a de novo model. The economic model described in the CS is considered by the ERG to partly meet the NICE reference case. The main deviation from the NICE reference case was the type of economic evaluation for population #1, where the company assumed equal effectiveness and thus effectively performed a cost-minimisation analysis. Notably, during the clarification phase, the company provided cost effectiveness analyses for population #1 relaxing the equal effectiveness assumption through informing the relative effectiveness by indirect treatment comparisons (used in the ERG base-case). Also, the sensitivity analyses performed by the company are not fully consistent with the NICE reference case given probabilistic sensitivity analyses are not performed for population #1. Related to this, the company did not perform one-way sensitivity analyses for all parameters that are implemented probabilistically in the probabilistic sensitivity analyses (PSAs), limiting the ability to identify impactful parameters.

The adopted model structure is more sophisticated than for instance the two-state model structure used in TA388 in terms of adding disease progression states based on KCCQ-TSS quartile scores (stratified by the presence of T2DM). It is unclear why the company used KCCQ-TSS rather than the KCCQ quality of life domain, the KCCQ clinical summary score or the overall summary score to

characterise/define the health states. The company justified this choice by indicating that KCCQ-TSS encompasses HF symptoms only while the Kansas City Cardiomyopathy Questionnaire (KCCQ) quality of life score, clinical summary score or overall summary scores also encompass other aspects of HF disease. It is unclear to the ERG why a metric encompassing HF symptoms only would be preferred compared to metrics that (also) consider other domains/aspects. The impact of this assumption is unclear. Nevertheless, the ERG considers that the model structure is appropriate to reflect this condition and treatment pathway,

Based on the CS, the definitions of populations #1 and #2 were initially unclear to the ERG, specifically whether both analyses reflected the same population, i.e. patients not previously treated with sacubitril valsartan. It was clarified by the company that populations #1 and #2 are different with respect to eligibility for sacubitril valsartan. Population #1 is eligible for sacubitril valsartan and is in accordance with the marketing authorisation of sacubitril valsartan, i.e. patients need to have ejection fraction (EF) ≤35% and must not have hyperkalaemia (serum potassium >5.4 mmol/l) and/or hypotension. Population #2 is ineligible for sacubitril valsartan or does not progress to receiving sacubitril valsartan due to other reasons, e.g. due to the complexity associated with sacubitril valsartan initiation and titration. Also, it can be debated whether the full DAPA-HF population or the predefined European subgroup should be used to inform the cost effectiveness analyses. The ERG considered the European subgroup to be more representative to the UK setting than the overall population (as elaborated above in section 1.2) and adopted relative effectiveness based on the European subgroup in its base-case. Because the DAPA-HF was originally not powered to find a treatment effect in the European sub-population, the ERG acknowledges that these effect estimates might be accompanied with a higher statistical uncertainty compared to the full DAPA-HF population.

The exact position of dapagliflozin is uncertain, particularly whether dapagliflozin can be initiated in the primary setting. In population #1, dapagliflozin was positioned in the primary setting, before specialist reassessment (see section 1.1.2 for details).

The main concerns of the ERG relate to the estimation of treatment effectiveness were 1) the assumption of equal effectiveness between dapagliflozin and sacubitril valsartan, 2) the selection of the Weibull distribution to estimate survival, 3) methods and population to calculate the transition probabilities between health states defined by KCCQ-TSS quartiles, 4) extrapolating treatment effectiveness and, 5) estimation of treatment discontinuation over time. Notably, the cost effectiveness results were robust to adopting different assumptions/approaches related to these issues when explored conditional on the CS base-case. However, when explored conditional on the ERG base-cases and worst-case analyses, the cost effectiveness results are potentially less robust. In particular, selecting a Gompertz distribution to estimate survival did have a substantial impact on the estimated ICERs for the ERG base-cases and worst-case analyses. According to the CS, clinical expert opinion suggested that predictions made using the Gompertz distribution were likely to underestimate patient survival. It is however unclear to the ERG how this expert opinion was exactly derived, what the exact results of the expert elicitation were and thus whether the Gompertz distribution is a plausible option or not.

Regarding estimated health state utilities, the main concern of the ERG relate to the relatively high utility values for patients with HFrEF, e.g. when considering the general population utility of people, the utility values associated with KCCQ TSS Q4: 92-100 and Q3 77 to <92 in the economic model (0.833 and 0.773 respectively) appear to be relatively high for patients with HFrEF. Therefore, the ERG adopted the scenario provided by the company, using general population health state utilities for KCCQ TSS Q4: 92-100 and applying relative differences to obtain health state utilities for the health states KCCQ TSS Q1-Q3 (Q4=0.774, Q3=0.714, Q2=0.646, Q1=0.541).

The ERG considered the internal, face validity, cross and external validity of the economic model. The ERG was able to reproduce the trace and QALY calculation and the company's assessment using TECHnical VERification checklist (TECH-VER) also supports the internal validity of the economic model. According to the company, the cost effectiveness model was developed in collaboration with clinical experts, who provided guidance on the appropriateness of the proposed model structure and subsequently on the estimation of input parameters. However, no details were provided regarding exact methods used and results produced for the face validity assessment, making it challenging for the ERG to confirm the face validity. The ERG's cross-validity assessment revealed a discrepancy between the sacubitril valsartan results from TA388 and the current TA. The reason for and thus the potential impact of this discrepancy are unclear to the ERG. The external validity assessment indicated that the observed (DAPA-HF) and predicted outcomes were for the main part consistent and the identified differences do not seem to be main drivers of cost effectiveness.

1.5 Summary of exploratory and sensitivity analyses undertaken by the ERG

The ERG has incorporated various adjustments to the company base-cases. This resulted in ERG base-cases in which dapagliflozin remained dominant for population #1 while for populations #2 and #3 the probabilistic ICERs increased to £18,037 and £18,159 per QALY gained, respectively. The most influential ERG adjustment was the use of the European subgroup relative effectiveness. The ERG performed exploratory scenario analyses using treatment independent transition probabilities between KCCQ-TSS health states (given the uncertainty related to the estimation of these probabilities) as well as assuming complete waning of the dapagliflozin treatment effect after three years (the maximum follow-up in the DAPA-HF trial was 28 months according to Table 14.3.1.1 of the clinical study report), both increasing the estimated ICERs for populations #2 and #3. When combined, these exploratory scenario analyses resulted in a worst-case scenario with probabilistic ICERs of £34,858 and £35,048 per QALY gained for populations #2 and #3 respectively. For population #1, dapagliflozin remained dominant.

At a £20,000 per QALY threshold, the probability that dapagliflozin is cost effective in the ERG base-cases is 100%, 88%, and 88% for population #1, #2 and #3 respectively while this is 100%, 96%, and 96% for a £30,000 per QALY threshold. For the worst-case scenarios this is 97%, 13%, and 13% (£20,000 per QALY threshold) and 94%, 49%, and 48% (£30,000 per QALY threshold), for population #1, #2 and #3 respectively.

2. Background

In this report, the Evidence Review Group (ERG) provides a review of the evidence submitted by AstraZeneca in support of dapagliflozin (Forxiga®) for the treatment of adults with chronic heart failure (HF) with reduced ejection fraction.

In the section below, the ERG will critique the company's description of the underlying health problem and the overview of current service provision. For additional information on epidemiology, disease burden, diagnosis, and management of the disease, please see pages 17 to 24 of document B of the company submission (CS).[1]

2.1 Introduction

HF is a complex clinical syndrome that results from any structural or functional impairment of ventricular filling or ejection of blood into the arteries. This may result in fatigue, difficulty breathing, or fluid retention which could lead to pulmonary and/or splanchnic congestion and/or peripheral oedema.[2] The prognosis for patients with diagnosed HF remains poor, and 30% of them die within one year and up to 60% within five years of diagnosis.[3]

There are three different subtypes of HF depending on left ventricular ejection fraction, natriuretic peptide levels, the presence of structural heart disease and diastolic dysfunction:

1. HF with reduced ejection fraction (HFrEF) of <40%,
2. HF with preserved ejection fraction (HFpEF) of >50%,
3. HF mid-range or borderline ejection fraction (HFmrEF) between 40% and 50%.

As of 2018, there were approximately 920,000 individuals diagnosed with the disease in the United Kingdom (UK); and there are around 200,000 new diagnoses every year in the country. The incidence rates vary between genders i.e., 4.4 per 1,000 population per year in men and 3.9 per 1,000 in women, with rates doubling every five years after the age of 55. Estimates show that the number of people living with heart failure grew by 23% between 2002 and 2014.[4] There are several known risk factors for the disease including hypertension, diabetes, and obesity.

The underlying health problem in this appraisal is chronic heart failure with reduced ejection fraction (HFrEF).

2.2 Background

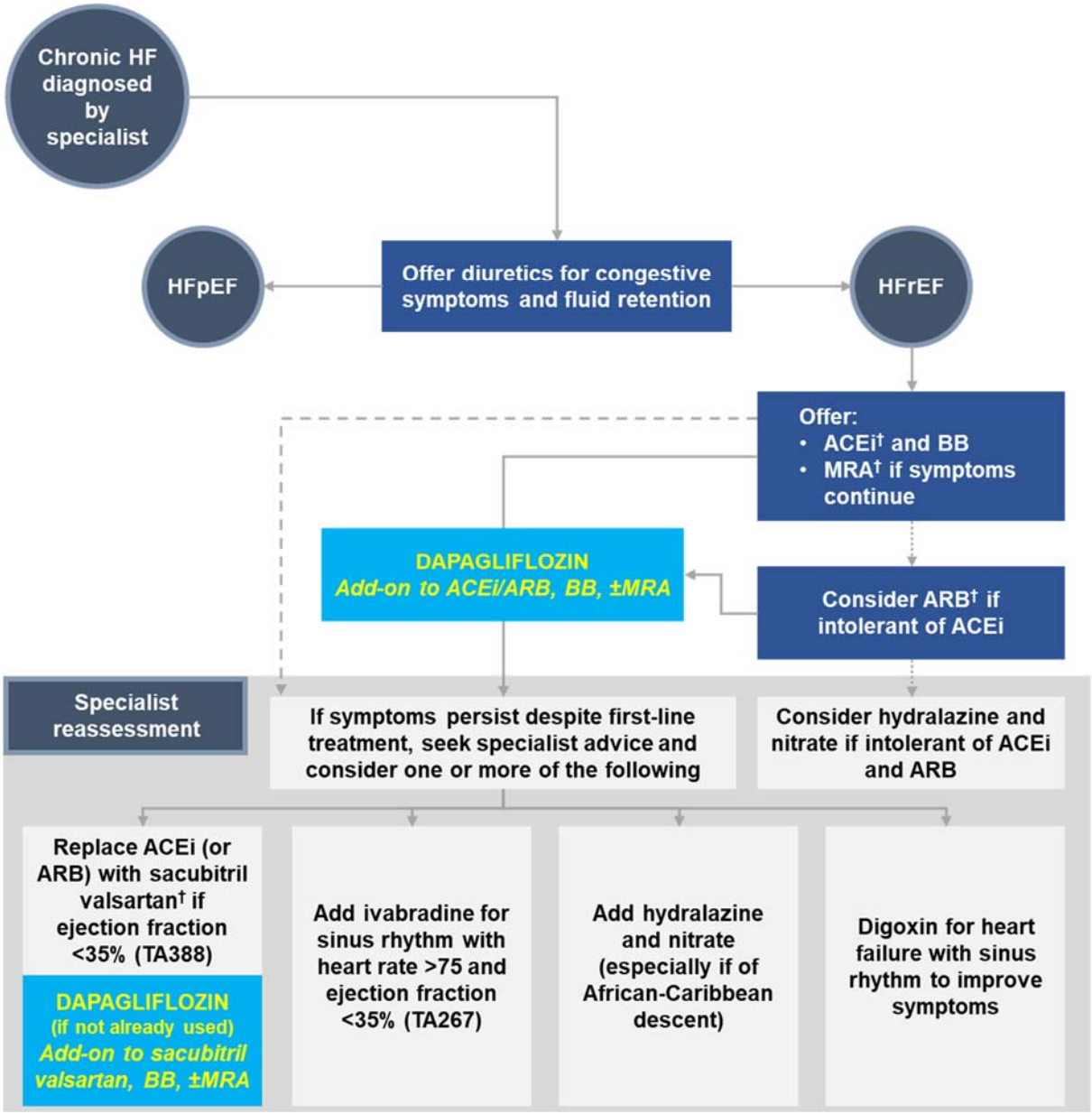
Dapagliflozin is a sodium glucose cotransporter 2 inhibitor (SGLT2i). The drug exerts haemodynamic effects, potently reducing intravascular volume through osmotic diuresis, alleviating cardiac workload, and improving left ventricular function. Furthermore, it reduces the glucose reabsorption in the renal proximal tubules leading to urinary excretion of glucose; and reduces glycated haemoglobin levels in patients with type 2 diabetic mellitus (T2DM). In 2014, the US Food and Drug Administration (FDA) approved dapagliflozin for the treatment of people with T2DM.[5]

Section B.1.3.6. of the CS list the current treatment options for HF and distinguishes between fist-line treatments and specialist treatments.[1] However, Figure 2 of the CS, omits specialist treatments. Although the CS refers to National Institute for Health and Care Excellence (NICE) guideline (NG) 106 when managing of HF patients, the role of a personalised, exercise-based cardiac rehabilitation programme, is underemphasised.[6]

The intervention is largely in line with the NICE scope, however the use of aldosterone antagonists appears unclear in the CS. Similarly, the threshold of tolerability of mineralocorticoid receptor

antagonists is missing. The proposed positioning of dapagliflozin in HFrEF with respect to the treatment pathway recommended by NICE NG106 is only based on anecdotal evidence, i.e. the favourable tolerability profile of dapagliflozin (reference 42 of the CS) or interviews with experts (UK clinical advisory board).[6] It is largely unclear what the specialist reassessment involves (Figure 2.1). Therein, the pathway for patients intolerant of angiotensin II receptor blocker (ARB) is missing.

Figure 2.1: Current treatment pathway for HFrEF (NG106) and proposed place in therapy of dapagliflozin



Based on Figure 3 of the CS[1]

† Measure serum sodium, potassium and assess renal function before and after starting and after each dose increment. If eGFR is 30 to 45 ml/min/1.73 m^2, consider lower doses or slower titration of ACEI or ARBs, MRAs, sacubitril valsartan and digoxin.

ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor blocker; BB = beta blocker; CS = company submission; HF = heart failure; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; MRA = mineralocorticoid-receptor antagonist; NG = NICE guideline; TA = technology appraisal

3. Critique of company's definition of decision problem

Table 3.1: Decision problem defined in the CS

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG comment
Population	Adults with chronic heart failure with reduced ejection fraction.	As per scope.	NA	No comment
Intervention	Dapagliflozin in combination with SC (including treatment with an ACEi, ARB, mineralocorticoid receptor antagonist, beta blocker, sacubitril valsartan and/or an aldosterone antagonist).	Dapagliflozin in combination with SC, where SC is defined as: • ACEi or ARB, in combination with beta-blocker, ±MRA (according to patient's tolerance of MRA) • Sacubitril valsartan, in combination with beta-blocker, ±MRA (according to patient's tolerance of MRA)	The intervention is in line with the scope, with SC defined more clearly to reflect the two distinct places of therapy relevant for dapagliflozin in the treatment pathway for HFrEF patients.	Concern regarding the first population and the position in the treatment pathway, see section 3.2.
Comparator(s)	Individually optimised SC without dapagliflozin. Standard care is defined as: • ACEi in combination with beta-blockers, and/or mineralocorticoid receptor antagonists • ARBs in combination with beta-blockers, and/or mineralocorticoid receptor antagonists • Sacubitril valsartan in combination with beta-	For the treatment of HFrEF patients on ACEi or ARB, in combination with beta-blocker, ±MRA, the comparators will be: • Sacubitril valsartan • Placebo For the treatment of HFrEF patients on sacubitril valsartan, in combination with beta-blocker, ±MRA, the comparators will be: • Placebo	In line with NICE TA388 and NG106, the relevant comparators at the two distinct places of therapy relevant for dapagliflozin in the treatment pathway for HFrEF patients (see 'intervention') are sacubitril valsartan and placebo. Background therapy (SC) will be the same in both the dapagliflozin arm and the comparator arm.	No comment

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG comment
	blockers, and/or mineralocorticoid receptor antagonists			
Outcomes	The outcome measures to be considered include: • symptoms of heart failure • hospitalisation for heart failure • all-cause hospitalisation • mortality • cardiovascular mortality • adverse effects of treatment (including diabetic ketoacidosis, genital infections, Fournier's gangrene, amputations, and fractures) • health-related quality of life.	As per scope.	NA	No comment
Economic analysis	Health economic analysis.	As per scope.	NA	No comment
Special considerations including issues related to equity or equality	None stated.	Equality issues related to current use and availability of dapagliflozin in T2DM patients.	Dapagliflozin is currently available across primary and secondary treatment settings for T2DM patients, including T2DM patients with comorbid HFrEF. A positive recommendation for dapagliflozin in HFrEF is expected to improve equality by extending the benefits of dapagliflozin for the treatment of all eligible HFrEF patients with	No comment

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG comment
			and without comorbid T2DM. Similarly, initiation of dapagliflozin for the treatment of HFrEF in the primary care setting would improve equality of access without relying on access to specialist care, which currently varies by geography.	

Based on Table 1 of the CS[1]

ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor blocker; CS = company submission; ERG = Evidence Review Group; HFrEF = Heart failure with reduced ejection fraction; MRA = mineralocorticoid receptor antagonist; NA = not applicable; NICE = National Institute for Health and Care Excellence; SC = standard care; T2DM = type 2 diabetes mellitus

3.1 Population

The population in the CS is in line with the NICE scope.

In the cost effectiveness analysis (CEA), there were three populations, defined effectively by the line of therapy and comparator:

1. Population #1: patients not previously treated with sacubitril valsartan, dapagliflozin as an add-on therapy to angiotensin-converting enzyme inhibitor/ angiotensin II receptor blocker (ACEi/ARB), beta blocker (BB) ±mineralocorticoid receptor antagonist (MRA) was compared to ACEi/ARB, BB ±MRA with sacubitril valsartan,
2. Population #2: patients not previously treated with sacubitril valsartan, dapagliflozin, as an add-on therapy to ACEi/ARB, BB ±MRA was compared to ACEi/ARB, BB ±MRA without sacubitril valsartan,
3. Population #3: patients previously treated with sacubitril valsartan, dapagliflozin, as an add-on therapy to sacubitril valsartan, BB ±MRA, was compared to sacubitril valsartan, BB ±MRA

The difference between populations #1 and #2 was unclear given that the line of therapy appeared to be the same. In response to request for clarification, the company stated that the difference lay in eligibility for sacubitril, i.e. population #1 is eligible for sacubitril valsartan in accordance with the marketing authorisation of sacubitril valsartan (patients need to have ejection fraction (EF) ≤35% and must not have hyperkalaemia (serum potassium >5.4 mmol/l) and/or hypotension), but population #2 is ineligible for sacubitril valsartan. However, the company also stated that population #2 might include patients who do not progress to receiving sacubitril valsartan due to other reasons, e.g. due to the complexity associated with sacubitril valsartan initiation and titration.

3.2 Intervention

In the proposed treatment pathway (see Figure 2.1), population #1 (angiotensin-converting enzyme inhibitor (ACEi) or angiotensin II receptor blocker (ARB), in combination with beta-blocker (BB), ± mineralocorticoid receptor antagonists (MRA; according to patient's tolerance of MRA)) was compared to sacubitril valsartan after first-line treatment and positioned in the primary setting, before specialist reassessment. However, according to recommendation in NICE technology appraisal (TA) 388, treatment with sacubitril valsartan should be started by a heart failure specialist with access to a multidisciplinary heart failure team.[7]

In response to request for clarification, the company proposed that this population *"would not need to wait for a specialist appointment to initiate treatment with dapagliflozin, as initiation could be undertaken in primary care, given the extensive clinical experience primary care clinicians have accumulated in initiating dapagliflozin for type 2 diabetes patients, over more than 7 years"*.[8] However, it should be noted that the professional organisation submission by the British Society for Heart Failure indicated that dapagliflozin treatment should be initiated by either heart failure (in case of heart failure with/ without diabetes) or diabetes (in case of heart failure with diabetes) specialists.[9]

3.3 Comparators

The comparator treatments defined in the CS differed for the treatment of HFrEF patients on ACEi or ARB, in combination with beta-blocker, ±MRA (sacubitril valsartan, placebo) and HFrEF patients on sacubitril valsartan, in combination with beta-blocker, ±MRA (placebo).[1] This was in line with TA388 and NICE guideline 106.[6, 7] Background therapy (SC) will be the same in both the dapagliflozin arm and the comparator arm.

3.4 Outcomes

The outcomes reported in the CS mostly reflect this list with the exception of all-cause hospitalisation which has not been reported and adverse event (AE) incidences of genital infection and urinary tract infection which were not routinely collected in the DAPA-HF trial, the main source of evidence. Results are reported in section 4.2.

3.5 Other relevant factors

According to the National Institute for Cardiovascular Outcomes Research (NICOR) 2019 Heart Failure Audit, there is substantial inter-hospital variation of specialist input for heart failure admissions. Only 59% of hospitals achieved specialist review rates of over 80%, whilst specialist review rates were less than 80% of patients in 41% of hospitals. This should be noted, especially when considering the issue described in section 3.2.[10]

4. Clinical effectiveness

4.1 Critique of the methods of review(s)

4.1.1 Searches

Appendix D of the CS provided details of the systematic literature search used to identify clinical efficacy and safety evidence.[11] Database searches were conducted on 11 November 2019. Conference and HTA organisation website searches were conducted between 27 November 2019 and 13 December 2019. A summary of the resources searched is provided in Table 4.1.

Table 4.1: Resources searched for clinical efficacy and safety

Resource	Host/source	Date range	Date searched
Electronic databases			
Embase	Ovid	1974 to 8 November 2019	11 November 2019
MEDLINE and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily Update	Ovid	1946 to 8 November 2019	11 November 2019
EBM Reviews: CDSR, ACP Journal Club, DARE, CCA, CCTR, CMR, HTA database, and NHSEED	Ovid	Not reported	11 November 2019
Conference proceedings			
AHA	https://www.ahajournals.org/toc/circ/136/suppl_1 https://www.ahajournals.org/toc/circ/138/Suppl_1 https://www.ahajournals.org/toc/circ/140/Suppl_1	2017, 2018, 2019	27 November 2019
ESC	ESC Congress online library: https://esc365.escardio.org/	2017, 2018, 2019	28 November 2019
WCC	2017 searched through ACC supplement 2018 abstracts online links broken: unable to access 2019 searched through ESC congress online library	2017, 2019	29 November 2019
ACC	http://www.onlinejacc.org/content/meeting-abstract-supplements	2017, 2018, 2019	29 November 2019
ESC Heart Failure congress	https://spo.escardio.org	2017, 2018, 2019	2 December 2019

Resource	Host/source	Date range	Date searched
ISPOR International & European meetings	https://www.ispor.org/heor-resources/presentations-database/search	2017, 2018, 2019	13 December 2019
HTAi	https://htai.org/annual-meetings/htai	2017, 2018, 2019	2 December 2019
SMDM	https://smdm.confex.com/smdm/17bec/meetingapp.cgi/ https://smdm.confex.com/smdm/2019/meetingapp.cgi/	2018, 2019	2 December 2019
HTA websites			
NICE	https://www.nice.org.uk/	All years	3 December 2019
SMC	https://www.scottishmedicines.org.uk/		
CADTH	https://www.cadth.ca/		
PBAC	www.pbs.gov.au/info/industry/listing/participants/pbac		
Clinical trial registries			
US NIH registry & results database	https://clinicaltrials.gov	All years	27 November 2019
WHO ICTRP registry	http://apps.who.int/trialsearch	All years	28 November 2019
Other sources			
Reference lists of included studies were searched			

ACC = American College of Cardiology; ACP = American College of Physicians; AHA = American Heart Association; CADTH = Canadian Agency for Drugs and Technologies in Health; CCA = Cochrane Clinical Answers; CCTR = Cochrane Central Register of Controlled Trials; CDSR = Cochrane Database of Systematic Reviews; CMR = Cochrane Methodology Register; DARE = Database of Abstracts of Reviews of Effects; EBM = evidence-based medicine; EED = Economic Evaluation Database; ESC = European Society of Cardiology; HTA = Health Technology Assessment; HTAi = Health Technology Assessment international; ICTRP = International Clinical Trials Registry Platform; ISPOR = International Society for Pharmacoeconomics and Outcomes Research; NHS = National Health Service; NICE = National Institute for Health and Care Excellence; PBAC = Pharmaceutical Benefits Advisory Committee; SMC = Scottish Medicines Consortium; SMDM = Society for Medical Decision Making; US NIH = United States National Institutes of Health; WCC = World Congress of Cardiology and Cardiovascular Health; WHO = World Health Organization

ERG comment:

- The selection of databases searched was satisfactory, and searches were clearly reported and reproducible. The database name, host, date range and date searched were provided.
- The search strategies were designed to be sensitive as they included a comprehensive list of intervention search terms; beyond that of the NICE scope.
- The ERG was concerned about the quality of the population facet used in the searches. The combination of terms for heart failure with terms for reduced ejection fraction was unusual. The CS population facet appeared to be searching for 'reduced heart failure' OR 'heart failure with reduced ejection fraction' OR 'heart failure AND 'left ventricular systolic dysfunction' OR 'less than ejection fraction'. A better approach might have been to search for 'heart failure'

AND 'ejection fraction'. There was a lack of synonyms: terms such as cardiac, coronary, myocardial, and decompensation were not included. Truncation was used for 'reduced*' and for numbers (4*, 3*), but not for 'failure', 'dysfunction' or 'fraction'. Numbers, symbols (<) and stop words (no, than) were included in search line 5, and although the search line produced results, it is not clear if this search line retrieved the results intended.

- Study design filters were included for RCTs. It is not clear if the study design filters were based on validated search filters, such as those published on the ISSG Search Filters Resource website: https://sites.google.com/a/york.ac.uk/issg-search-filters-resource/. It is good practice to provide citation details of any study design filters used.
- There were no search terms for safety included in the search strategies. Guidance by the Centre for Reviews and Dissemination recommends that if searches have been limited by inclusion of a study design filter, additional searches should be undertaken to ensure that adverse events that are long-term, rare or unanticipated are not missed.[12] Ideally, this would entail searching without any study design terms, or would include generic and specific adverse event and safety search terms.
- The population of interest was adults only, so the search strategy included a limit attempting to remove studies with children. The ERG felt that this limit was inappropriate, as potentially relevant studies could have been missed. Studies investigating both adults and children would not have been identified, nor would studies reporting that they had excluded children. NB: The children limit was inadvertently redundant in the Embase search strategy.
- Search terms used to limit the search to retrieve human only studies appeared twice in the search strategy.
- Truncation and proximity operators were inconsistently used throughout.
- The EBM reviews resource, including the Cochrane Library databases, did not report the date ranges or database issue searched. The search results were reported for all databases in total. It would have been more useful and transparent to have reported the search results from each database separately.
- The EBM reviews search included a study design filter to identify RCTs. As the databases included in EBM reviews are pre-filtered to include trials and systematic reviews, a study design filter was not necessary and may have adversely affected the results.

4.1.2 Inclusion criteria

The eligibility criteria for the review are described in Table 4.2.

Table 4.2: Eligibility criteria used in the efficacy and safety studies

	Inclusion criteria	Exclusion criteria
Population	Adult patients with symptomatic chronic HFrEF in line with the populations enrolled in the DAPA-HF clinical trial: • Adults ≥18 years • Ejection fraction ≤40% • NYHA class II, III, IV Also: • Patients with chronic kidney disease • Mixed CHF populations[a]	Studies including 100% patient populations with the following characteristics will be excluded: • Patients with heart failure with preserved ejection fraction (HFpEF) • Patients with type 1 diabetes mellitus

	Inclusion criteria	Exclusion criteria
Intervention	Interventions in full SLR, pharmacological interventions recommended in relevant clinical guidelines for HFrEF, to include: • Sodium glucose cotransporter 2 inhibitors (SGLT2i) • Angiotensin-converting-enzyme inhibitors (ACEi) • Angiotensin II receptor blockers (ARB) • Beta blockers (BB) • Angiotensin receptor-neprilysin inhibitors (ARNI) • Mineralocorticoid receptor antagonists (MRA) • Ivabradine • Cardiac resynchronisation therapy (CRT) • Implantable cardioverter defibrillator (ICD) Interventions in the current submission: • Sodium glucose cotransporter 2 inhibitors (SGLT2i) • Angiotensin receptor-neprilysin inhibitors (ARNI)	Other
Outcomes	• Symptoms of heart failure • Hospitalisation for heart failure • All-cause hospitalisation • All-cause mortality • Cardiovascular mortality • Composite measures of mortality and hospitalisation • Adverse effects of treatment • Health-related quality of life (HRQoL)	Other outcomes[b]
Study design	Randomised controlled trials (RCTs) of any phase and design	Sub studies of RCTs providing only prognostic data
Territory	No restriction	NA
Date of publication	No restriction	NA
Language	English language publications or non-English publications with an English-language abstract	Full non-English publications

Based on Table 57 of Appendix D of the CS[11]

[a] Mixed populations were included at the title and abstract screening stage, however at the full publication stage they were excluded if they did not report HFrEF data separately; b In response to the request for clarification, the company clarified that *"'other outcomes' refer to outcomes not listed in the inclusion criteria column, i.e. trials which did not report an outcome listed in the inclusion criteria column were excluded"*.[8]

ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor blocker; ARNI = angiotensin receptor–neprilysin inhibitor; BB = beta-blocker; CHF = chronic heart failure; CRT = cardiac resynchronisation therapy; CS = company submission; HF = heart failure; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; HRQoL = health-related quality of life; ICD = implantable cardioverter defibrillator; MRA = mineralocorticoid receptor antagonist; NA = not applicable; NYHA = New York Heart Association; RCT = randomised controlled trial; SGLT2i = sodium glucose cotransporter 2 inhibitor; SLR = systematic literature review

ERG comment: In response to the request for clarification, the company provided further details on the exclusion criteria used in the systematic literature review (SLR).[8] The ERG mostly agrees with the company's chosen approach.

However, it should be noted that the company argued that exclusion of full text manuscripts in non-English is common practice but provide no references in support of this statement.[8] Furthermore, the company did not provide the list of all references excluded using this criterion as requested by the ERG.[13] Overall, the ERG does not agree that this approach is correct as potentially relevant studies might have been missed.

With regard to study selection, the company stated that two reviewers independently assessed study eligibility with a third reviewer resolving any discrepancies.[8] The ERG considers this approach to be adequate. The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) diagram as well as complete reference lists of included and excluded studies are provided in Appendix D of the CS.[11]

4.1.3 Critique of data extraction

In response to request for clarification, the company stated that *"data from relevant publications were extracted into tables within the submission"* but did not provide information on other aspects, e.g. how many people were involved in data extraction and how any discrepancies were resolved.[8]

ERG comment: It is unclear whether methods used for data extraction followed best practice.[12, 14]

4.1.4 Quality assessment

In response to request for clarification, the company stated that *"risk of bias was assessed using the relevant validated tool appropriate to the study design"* but did not provide information on other aspects, e.g. how many people were involved in risk of bias assessment, how any discrepancies were resolved, and which tool was used to assess the included studies.[8]

ERG comment: It is unclear whether methods used for risk of bias assessment followed best practice.[12, 14]

4.1.5 Evidence synthesis

According to the response to request for clarification, *"no evidence synthesis was conducted as part of the SLRs"*.[8]

4.2 Critique of trials of the technology of interest, the company's analysis and interpretation (and any standard meta-analyses of these)

4.2.1 DAPA-HF trial

The evidence for the effectiveness of dapagliflozin came from the DAPA-HF trial. This was a randomised, double-blind, multicentre, placebo-controlled, phase III trial which compared dapagliflozin 10 mg once daily with placebo in patients aged 18 years or over with heart failure with reduced ejection fraction (HFrEF; New York Heart Association (NYHA) class ≥II with left ventricular ejection fraction (LVEF) ≤40%). Concomitant treatment with standard care was allowed in both trial arms according to local guidelines.

DAPA-HF was an event-driven trial with the sample size governed by the planned number of primary outcome events.[15-17] The primary outcome was the time to the first occurrence of cardiovascular (CV) death, hospitalisation for HF or an urgent hospital visit for HF (a composite outcome). The trial

comprised 410 centres worldwide with 10 centres in the UK recruiting 62 participants. The median follow-up period was 18.2 months (range 0 to 27.8 months) and a total of 4,744 participants were randomised. Further details of the trial methods, inclusion criteria and outcomes are provided in Table 4.3.

Table 4.3: DAPA-HF trial design and methodology

Parameter	Description
Study objective	To determine whether dapagliflozin is superior to placebo, when added to standard care, in reducing the incidence of a worsening HF episode (hospitalisation or the equivalent, i.e. an urgent HF visit) or CV death, analysed as time-to-first event.
Trial design	Randomised, double-blind, placebo-controlled, international, multicentre phase III trial.
Duration of study	This was an event driven trial; median follow-up 18.2 months (range 0 to 27.8 months).
Method of randomisation	Fixed-randomisation schedule using balanced blocks and interactive voice- or web-response system.
Method of blinding (care provider, patient, and outcome assessor)	Patients, investigators, and adjudication committee were blind to the assignment of treatment.
Eligibility criteria for participants	Inclusion criteria: • Men and women ≥18 years of age, with or without T2DM • Documented diagnosis of symptomatic HFrEF for ≥2 months (NYHA class II-IV) • LVEF ≤40% within the last 12 months • Elevated NT-proBNP (≥600 pg/ml or ≥400 pg/ml if hHF within 12 months or ≥900 pg/ml if atrial fibrillation/flutter irrespective of hHF history) • Optimal and stable (≥4 weeks) background standard care for HFrEF as per local guidelines including (unless contraindicated or not tolerated): ACEI, ARB, or sacubitril valsartan; beta-blocker; and if appropriate an MRA • eGFR ≥30 ml/min/1.73 m^2 Key exclusion criteria: • T1D • Recent treatment with or unacceptable side effects associated with an SGLT2i, or concomitant use of open-label SGLT2i • Symptomatic hypotension or SBP <95 mmHg • Current acute decompensated HF or hospitalisation within last 4 weeks due to decompensated HF • Coronary revascularisation (PCI or CABG), valve repair/replacement, or CRT device implantation within last 12 weeks or planned after randomisation • HF due to restrictive cardiomyopathy, active myocarditis, constrictive pericarditis, hypertrophic cardiomyopathy, or uncorrected primary valvular disease

Parameter	Description
Settings and locations where the data were collected	410 centres across 20 countries in Asia Pacific, Europe, Latin America, North America, and Russia, including 10 UK sites
Trial drugs	Dapagliflozin 10 mg oral od plus standard care (N=2,373) Placebo plus standard care (N=2,371)
Permitted and disallowed concomitant medications	Disallowed medications: • SGLT2 inhibitors other than dapagliflozin as study medication. Permitted medications: • HF medications based on local guidelines (ACEi, ARB, sacubitril valsartan, beta-blocker, MRA) • Antidiabetic medications other than SGLT2 inhibitors
Primary outcomes*	Time to first occurrence of any of the composite components: CV death or hHF or an urgent HF visit
Other outcomes used in the economic model/specified in the scope	• Time to first occurrence of either of: CV death or hHF • Total number of (first and recurrent) hHF and CV death • Change from baseline to 8 months in the total symptom score of the KCCQ • Time to first occurrence of: ≥50% sustained decline in eGFR or reaching ESRD or renal death • Time to death from any cause
Safety	Safety data were collected for all SAEs, AEs leading to discontinuation, interruption, or dose reduction of study drug, and AEs of special interest: • Volume depletion • Renal AEs • Diabetic ketoacidosis • Major hypoglycaemic events • Fractures • AEs leading to amputation • AEs leading to a risk of lower limb amputation Data on other AEs were not routinely collected due to the extensive safety data which already exist for dapagliflozin in other indications.
Pre-planned subgroups	Pre-specified: • T2D status at baseline (established diabetes or glycated haemoglobin level ≥6.5% at both visit 1 and visit 2) (yes/no) • Baseline eGFR (≥60 ml/min/1.73 m^2 / <60 ml/min/1.73 m^2) • MRA at baseline (yes/no) • NYHA class (II/III or IV) • LVEF (≤median/>median) • NT-proBNP (≤median/>median) • Atrial fibrillation or flutter at enrolment ECG (yes/no) • Age (≤65 years/>65 years) • Sex (male/female) • Race (white/black/Asian/other)

Parameter	Description
	• Geographic region (Asia/Europe [including Russia]/North America/South America) • Prior hospitalisation for HF (yes/no) • Main aetiology of HF (ischaemic/non-ischaemic or unknown) • BMI (<30 kg/m^2/≥30 kg/m^2) Post-hoc: • KCCQ-TSS (≤median/>median) • NO use of MRA and sacubitril valsartan at baseline (yes/no) • Use of MRA but NO use of sacubitril valsartan at baseline (yes/no) • Use of sacubitril valsartan at baseline (yes/no)
Based on Table 7 of the CS[1] * Definition of all outcomes reported in Table 8 of the CS ACEi = angiotensin-converting enzyme inhibitor; AE = adverse event; ARB = angiotensin-receptor blocker; BMI = body mass index; CABG = coronary artery bypass grafting; CRT = cardiac resynchronisation therapy; CS = company submission; CV = cardiovascular; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; ESRD = end-stage renal disease; hHF = hospitalisation for heart failure; HF = heart failure; HFrEF = heart failure with reduced ejection fraction; KCCQ = Kansas City Cardiomyopathy Questionnaire; KCCQ-TSS = Kansas City Cardiomyopathy Questionnaire – Total Symptom Score; LVEF = left ventricular ejection fraction; ml = millilitre; mmHg = millimetre of mercury; MRA = mineralocorticoid-receptor antagonist; NT-proBNP = N-terminal pro B-type natriuretic peptide; NYHA = New York Heart Association; od = once daily; PCI = percutaneous coronary intervention; pg = picogram; SBP = systolic blood pressure; SGLT2i = sodium-glucose transport protein 2 inhibitor; T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus; UK = United Kingdom	

Further details of the statistical methods of the DAPA-HF trial are provided in Table 4.4. This was an event-driven trial with the analysis of the primary outcome planned after 844 events had occurred in approximately 4,500 participants.

Table 4.4: DAPA-HF statistical methods

DAPA-HF	Description
Hypothesis	That dapagliflozin is superior to placebo, when added to SC, in reducing the incidence of a worsening HF episode (hospitalisation or the equivalent, i.e. an urgent HF visit) or CV death, analysed as time-to-first event.
Statistical analysis	A closed testing procedure was used with pre-specified hierarchical testing of the primary and secondary outcomes. Type I error was controlled at a two-sided α level of 0.0499 for multiple comparisons across primary and secondary outcomes, with one interim efficacy analysis taken into account. Time-to-event data were evaluated using Kaplan-Meier estimates and Cox proportional hazards models, stratified according to diabetes status, with history of hHF and treatment-group assignment as fixed-effect factors; for the renal outcome, baseline eGFR was included instead of history of hHF. Cox models were used to calculate HRs, 95% CIs, and two-sided p values. A semiparametric proportional-rates model was used to calculate total number of (first and recurrent) hHF and CV death events. Total symptom score on the KCCQ was analysed as a composite, rank-based outcome, incorporating patient vital status at 8 months along with change in score from baseline to 8 months in surviving patients, using the rank analysis of covariance method with a corresponding win ratio used to estimate the magnitude of treatment effect.

DAPA-HF	Description
Sample size, power calculation	It was calculated that 844 primary outcome events would provide 90% power to detect an HR of 0.80 for dapagliflozin vs placebo with a two-sided α level of 0.05. The expected annual event incidence for primary outcome events was expected to be 11%, resulting in an estimate of approximately 4,500 patients based on an anticipated recruitment period of 18 months and an average follow-up period of approximately 24 months.
Patient withdrawals and dataset definition	All patients who underwent randomisation were included in the analyses of the primary and secondary outcomes The full analysis set (FAS) included all patients who were randomised and who were analysed according to their randomised treatment The safety analysis set included all randomised patients who received at least one dose of randomised treatment

Based on Table 11 of the CS[1]

CS = company submission; CV = cardiovascular; FAS = full analysis set; hHF = hospitalisation for heart failure; HF = heart failure; HR = hazard ratio; KCCQ = Kansas City Cardiomyopathy Questionnaire; SC = standard care

The baseline patient characteristics of the two treatment groups in the DAPA-HF trial are shown in Table 4.5. Most patients were male (76.2% and 77.0%) and the largest region represented was Europe (46.1% and 44.7%). Most patients (67.6%) had NYHA II heart failure, an ischaemic aetiology (55.5% and 57.3%) and 41.8% had type 2 diabetes mellitus. The two groups were well-balanced at baseline and the overall population was similar to those in the European Union (EU) subgroup and age over 65 years subgroup (data not shown).

In the request for clarification (question A13a), the company was asked to clarify how many patients in the DAPA-HF trial had a LVEF ≥35% and <40% due to concerns that technology appraisal (TA) 388 recommended sacubitril valsartan only in people with a LVEF <35%.[1, 7] The numbers reported are [redacted] of patients in the dapagliflozin arm and the placebo arm, respectively.[8]

Table 4.5: DAPA-HF baseline patient characteristics

Baseline characteristics	Dapagliflozin (N=2,373)	Placebo (N=2,371)
Age, years, mean (SD)	66.2 (11.0)	66.5 (10.8)
Female sex, n (%)	564 (23.8)	545 (23.0)
BMI, kg/m^2, mean (SD)	28.2 (6.0)	28.1 (5.9)
Race, n (%)		
White	1,662 (70.0)	1,671 (70.5)
Black	122 (5.1)	104 (4.4)
Asian	552 (23.3)	564 (23.8)
Other	37 (1.6)	32 (1.3)
Region, n (%)		
North America	335 (14.1)	342 (14.4)
South America	401 (16.9)	416 (17.5)
Europe	1,094 (46.1)	1,060 (44.7)
Asia-Pacific	543 (22.9)	553 (23.3)

Baseline characteristics	Dapagliflozin (N=2,373)	Placebo (N=2,371)
NYHA functional classification, n (%)		
II	1,606 (67.7)	1,597 (67.4)
III	747 (31.5)	751 (31.7)
IV	20 (0.8)	23 (1.0)
Heart rate, beats per min, mean (SD)	71.5 (11.6)	71.5 (11.8)
Systolic blood pressure, mm Hg, mean (SD)	122.0 (16.3)	121.6 (16.3)
LVEF, %, mean (SD)	31.2 (6.7)	30.9 (6.9)
Median NT-proBNP, pg/ml (IQR)	1,428 (857, 2,655)	1,446 (857, 2,641)
Principal cause of HF, n (%)		
Ischaemic	1,316 (55.5)	1,358 (57.3)
Non-ischaemic	857 (36.1)	830 (35.0)
Unknown	200 (8.4)	183 (7.7)
Medical history, n (%)		
Hospitalisation for HF	1,124 (47.4)	1,127 (47.5)
Atrial fibrillation	916 (38.6)	902 (38.0)
Type 2 diabetes mellitus[†]	993 (41.8)	990 (41.8)
eGFR		
Mean (SD), ml/min/1.73 m^2	66.0 (19.6)	65.5 (19.3)
<60 ml/min/1.73 m^2, n (%)	962/2,372 (40.6)	964 (40.7)
Heart failure medication, n (%)		
Diuretic	2,216 (93.4)	2,217 (93.5)
ACEI	1,332 (56.1)	1,329 (56.1)
ARB	675 (28.4)	632 (26.7)
Sacubitril-valsartan	250 (10.5)	258 (10.9)
Beta-blocker	2,278 (96.0)	2,280 (96.2)
MRA	1,696 (71.5)	1,674 (70.6)
Digitalis	445 (18.8)	442 (18.6)
Glucose-lowering medication, n/N (%) for patients with history if diabetes at baseline		
Biguanide	504/993 (50.8)	512/990 (51.7)
Sulfonylurea	228/993 (23.0)	210/990 (21.2)
DPP-4 inhibitor	161/993 (16.2)	149/990 (15.1)
GLP-1 receptor agonist	11/993 (1.1)	10/990 (1.0)
Insulin	274/993 (27.6)	266/990 (26.9)

Based on Table 9 of the CS[1]

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin-receptor blocker; BMI = body mass index; CS = company submission; DPP-4 = dipeptidyl peptidase 4; eGFR = estimated glomerular filtration rate; GLP-1 = glucagon-like peptide-1; HF = heart failure; LVEF = left ventricular ejection fraction; MRA = mineralocorticoid-receptor antagonist; NT-proBNP = N-terminal pro B-type natriuretic peptide; NYHA = New York Heart Association; SD = standard deviation

The quality assessment of the DAPA-HF trial is reported in Table 4.6.

Table 4.6: Quality assessment results

Criteria	Rating and justification
Was randomisation carried out appropriately?	Yes. Patients were randomised in a 1:1 ratio stratified by diabetes status at baseline based on a computer-generated randomisation schedule prepared before the study by or under the supervision of the sponsor.
Was the concealment of treatment allocation adequate?	Yes. An interactive voice/web-response system was used to determine treatment assignment and matching placebo was used.
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes. Demographics and disease characteristics were balanced between the groups and patients were stratified according to baseline diabetes status.
Were the care providers, participants, and outcome assessors blind to treatment allocation?	Yes. This was a double-blind study. The interactive voice/web-response system was used to manage study agent inventory while ensuring that no one at the sites had to be unblinded. The investigator was not provided with the treatment randomisation codes. The investigators and the site personnel were blinded to the treatment assignment.
Were there any unexpected imbalances in drop-outs between groups?	No. Discontinuations of study medication were low and well-balanced between treatment arms.
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No. Based on the clinical study report all outcomes are reported in detail.
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes. Efficacy analyses were performed on the full analysis set.
Based on Table 12 of the CS[1]	

ERG comment: In the request for clarification, the ERG noted that "[redacted]" and asked *"please provide all results for efficacy and safety outcomes for the subgroup of participants recruited/treated in Europe"*.[13] In response, the company stated that *"while the effect size in the European subgroup was slightly less than in the overall population,* [redacted] *the subgroup analyses were not powered to detect statistically significant differences between treatment groups, and geographic location was not identified as a treatment effect modifier. The ITT data from DAPA-HF are therefore most relevant in the current assessment"*.[8] Additional results by region subgroup have been provided in Tables 4 and 5 of the response to request for clarification[8] and incorporated in relevant Tables of this report. Overall, the ERG wants to highlight differences regarding both efficacy as well as safety in the European subgroup compared to the overall trial population.

Furthermore, the company stated that at the time of designing the DAPA-HF trial there was no information regarding the safety profile of dapagliflozin in type 1 diabetes mellitus (T1DM) and, in order to avoid extra monitoring and higher frequency of visits in this group of patients, T1DM patients were excluded from the trial.[8] The ERG is concerned with this approach as dapagliflozin in indicated for patients with T1DM as specified in the summary of product characteristics (SmPC).[18]

The ERG does not have any concerns regarding the quality assessment of DAPA-HF other than those highlighted in section 4.1.3.

4.2.2 Clinical effectiveness results of DAPA-HF

4.2.2.1 Primary outcome

The primary outcome was a composite outcome of the time to the first occurrence of CV death, hospitalisation for HF (hHF) or an urgent visit resulting in intravenous therapy for HF. Treatment with dapagliflozin significantly reduced the proportion of patients experiencing the primary outcome compared to placebo (hazard ratio [HR] 0.75, 95% confidence interval [CI] 0.65 to 0.85, P<0.001). The Kaplan-Meier (KM) survival curve is shown in Figure 4.1. Results for the individual components of the primary outcome are provided in Table 4.7 and show that dapagliflozin significantly reduced the risk of hospitalisation for HF, an urgent hospital visit and cardiovascular death compared to placebo.

The company performed subgroup analysis for pre-planned subgroups specified in Table 4.3. The results are shown in Figures 11 and 12 of the CS.[1] Overall, [redacted]. The company states, following further investigation, that this may be due [redacted].[8]

However, as discussed in section 4.2.1, there are differences in the primary efficacy outcome depending on geographical region. According to Figure 11 of the CS, treatment with dapagliflozin did not statistical significantly reduce the proportion of patients experiencing the primary outcome compared to placebo in the subgroup of participants recruited/treated in Europe (HR 0.84, 95% CI 0.69 to 1.01, P not reported, N=2,154).1 Results for the components of the primary outcome in this subgroup are presented in Table 4.7.

Table 4.7: Time to first occurrence of any of the composite components: CV death or hHF or an urgent HF visit

Outcome	Dapagliflozin	Placebo	HR (95% CI) dapagliflozin vs placebo
Whole study population	**N=2,373**	**N=2,371**	
Primary outcome*	386 (16.3%)	502 (21.2%)	0.74 (95% CI 0.65 to 0.85) P<0.001
hHF or an urgent visit for HF	237 (10.0%)	326 (13.7%)	0.70 (95% CI 0.59, 0.83) P<0.0001
hHF	231 (9.7%)	318 (13.4%)	0.70 (95% CI 0.59, 0.83) P<0.0001
Urgent heart failure visit	10 (0.4%)	23 (1.0%)	0.43 (95% CI 0.20, 0.90) P=0.0213
CV death	227 (9.6%)	273 (11.5%)	0.82 (95% CI 0.69, 0.98) P=0.0294

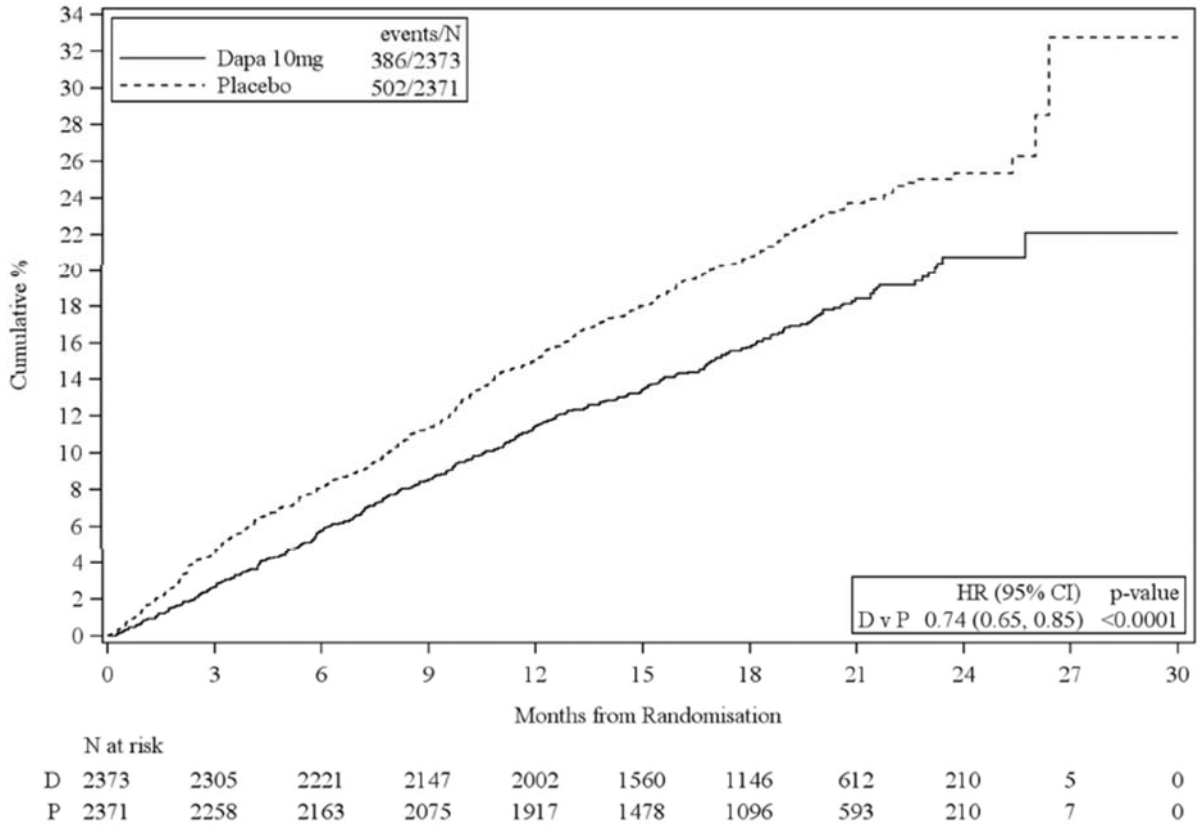
Outcome	Dapagliflozin	Placebo	HR (95% CI) dapagliflozin vs placebo
European subgroup	**N=1,094[#]**	**n=1,060[#]**	
Primary outcome[*]	[redacted]	[redacted]	[redacted]
hHF or an urgent visit for HF	[redacted]	[redacted]	[redacted]
hHF	[redacted]	[redacted]	[redacted]
Urgent heart failure visit	[redacted]	[redacted]	[redacted]
CV death	[redacted]	[redacted]	[redacted]

Based on Figure 11 and Table 15 of the CS[1] as well as Table 4 of the response to request for clarification[8]

[*] Time to first occurrence of any of the composite components: CV death or hHF or an urgent HF visit; [#] Number of participants with event calculated based on reported percentage

CI = confidence interval; CS = company submission; CV = cardiovascular; HF = heart failure; hHF = hospitalisation for heart failure; HR = hazard ratio

Figure 4.1: DAPA-HF time to the first occurrence of the composite primary outcome



Based on Figure 7 of the CS[1]

CI = confidence interval; CS = company submission; HF = heart failure; HR = hazard ratio

The company performed a sensitivity analysis of primary outcome where death adjudicated as 'undetermined' were not included as endpoint events but were treated as censoring events. The results were consistent with the primary analysis (14.4% vs 19.2%, HR 0.72 [95% CI 0.63, 0.83]; P<0.0001). The results of a 'worst case scenario', where patients in the dapagliflozin group (censored before primary analysis censoring date (PACD) and using their censoring time as the time of the imputed event) were considered having experienced the composite endpoint and patients in the placebo group before PACD were considered censored and event free, remained statistically significant (HR 0.85, 95% CI 0.74 to 0.96, P=0.0103).[1]

4.2.2.2 Secondary outcomes

The secondary outcomes included: the composite of CV death or hHF; total number for (first and recurrent) hospitalisations for HF and CV; Kansas City Cardiomyopathy Questionnaire – Total Symptom Score (KCCQ-TTS); composite of worsening renal function (sustained decline in eGFR ≥50%), end-stage renal disease (sustained [≥28 days] eGFR <15 ml/min/1.73 m^2, sustained dialysis, or renal transplantation), or renal death; all-cause death.

The results for secondary endpoints of DAPA-HF (excluding KCCQ-TSS) are presented in Table 4:8. The Kaplan-Meier curves for composite of CV death or hHF and composite of worsening renal function are available in the CS (Figures 8 and 9).[1]

The results for KCCQ-TSS are presented in Table 4.9. In response to the request for clarification, the company provided results to match the data included in the DAPA-HF clinical study report (CSR).[8, 15] Note that higher KCCQ-TSS indicated a lower symptom burden.

Table 4.8: Results of secondary endpoints for DAPA-HF

Secondary outcome	Dapagliflozin	Placebo	Effect estimate (95% CI)
Composite of CV death or hHF	16.1%	20.9%	HR 0.75 (0.65 to 0.85) P<0.001
Total number for hospitalisations for HF and CV death	567	742	Rate ratio 0.75 (0.65 to 0.88)
Composite of worsening renal function	1.2%	1.6%	HR 0.71 (0.44 to 1.16)
All-cause death	11.6%	13.9%	HR 0.83 (0.71 to 0.97)

Based on section B.2.6.3 of the CS[1]
CI = confidence interval; CS = company submission; CV = cardiovascular; HF = heart failure; hHF = hospitalisation for heart failure; HR = hazard ratio

Table 4.9:Results of secondary endpoint of DAPA-HF: KCCQ-TSS

Outcome	Dapagliflozin (N=2,373)	Placebo (N=2,371)
Change in KCCQ-TSS at 8 months, mean±SD	6.1±18.6	3.3±19.2
Win ratio vs placebo (95% CI)†	1.18 (1.11, 1.26; P<0.001)	
Increases in KCCQ-TSS at 8 months		
≥5-point increase %	57.4%	50.0%
OR‡ (95% CI) vs placebo	1.15 (1.08, 1.23; P<0.0001)	
≥10-point increase %	53.9%	46.9%
OR‡ (95% CI) vs placebo	1.15 (1.08, 1.22; P<0.0001)	
≥15-point increase %	53.7%	47.7%

Outcome	Dapagliflozin (N=2,373)	Placebo (N=2,371)
OR‡ (95% CI) vs placebo	1.14 (1.07, 1.22; P<0.0001)	
Reductions in KCCQ-TSS at 8 months		
≥5-point reduction, n (%)	25.1%	33.1%
OR§ (95% CI) vs placebo	0.84 (0.78, 0.90; P<0.001)	
Based on Table 6 of the response to request for clarification[8] † Win ratio >1 indicates superiority of dapagliflozin over placebo. ‡ OR >1 for ≥5-point increase in KCCQ-TSS indicates superiority of dapagliflozin over placebo. § OR <1 for ≥5-point reduction in KCCQ-TSS indicates superiority of dapagliflozin over placebo CI = confidence interval; KCCQ-TSS = Kansas City Cardiomyopathy Questionnaire – Total Symptom Score; OR = odds ratio; SD = standard deviation		

4.2.2.3 Exploratory endpoints

The CS included the results of analysis of exploratory endpoints (EQ-5D-5L (European Quality of Life-5 Dimensions, three-level scale) and change in NYHA class from baseline).[1] There was [redacted] in change from baseline for EQ-5D-5L score between dapagliflozin and placebo at 24 months (least squares mean [redacted]; least squares mean difference [redacted]). The proportion of patients with no worsening of NYHA class from baseline was only [redacted].

ERG comment: The ERG does not have any major concerns regarding the analysis of primary, secondary, and exploratory outcomes as well as any sensitivity and subgroup analysis.

However, there are a number of minor points that should be noted:

- Results provided in response to question A17 of the request for clarification were incomplete, i.e. the company did not *"provide all results for efficacy and safety outcomes for the subgroup of participants recruited/treated in Europe"*.[8]
- The committee should consider the differences in results between the whole trial population and the participants recruited/treated in Europe.
- Although health-related quality of life (HRQoL) was included in the NICE scope, results of EQ-5D-5L were only included as exploratory endpoint.
- While quality of life is part of the overall summary score of the KCCQ, DAPA-HF only presented results for KCCQ-TSS which excluded the quality of life domain (see Table 4 of the CS and section 5.2.2 of this report).[1] The ERG noticed that [redacted]. In response to the request for clarification, [redacted].[8]

4.2.3 Adverse effects

In the DAPA-HF trial, safety data was collected for all serious adverse events (SAEs), adverse effects (AEs) leading to discontinuation, interruption or dose reduction of study drug, and AEs of special interest (see Tables 4.9 and 4.10). The CS concludes that dapagliflozin is well-tolerated in

patients with HFrEF as SAEs were numerically less frequent with dapagliflozin (35.7%) than with placebo (40.2%).[1]

The most commonly experienced SAEs in both dapagliflozin and placebo trial arms respectively were, pneumonia 3.2% and 3.5%, ischaemic stroke 1.0% and 1.1%, cardiac failure 11.1% and 14.8%, congestive cardiac failure 2.7% and 3.0%, acute cardiac failure 1.8% and 2.5%, acute myocardial infarction 1.6% and 1.6%, ventricular tachycardia 1.4% and 2.3%, chronic cardiac failure 1.1% and 1.4%, atrial fibrillation 1.1% and 1.6%, unstable angina 0.9% and 1.3%, acute kidney injury 1.0% and 1.9%, and death 2.0% and 2.0%.[16] These SAEs were experienced on or after the date of the first dose of the study drug in the trial (on and off treatment SAS) and a summary of these SAEs by system organ class is listed in Table 4.11.

The company emphasised that the AEs of special interest (volume depletion, renal AEs, diabetic ketoacidosis, major hypoglycaemic events, fractures, AEs leading to amputation and AEs leading to a risk of lower limb amputation) collected in the DAPA-HF trial were generally balanced between treatment groups, or less frequently experienced in the dapagliflozin arm than in the placebo arm.[1] This is demonstrated in Table 4.12. Adverse effects highlighted in the NICE scope such as genital infections and Fournier's gangrene were not considered in the CS table of adverse effects as genital and urinary tract infection (UTI) AEs were not routinely collected in the DAPA-HF trial, and only one case of Fournier's gangrene was identified in the trial, and on the placebo arm.[1, 19]

Additionally, placebo-administered patients had an increased incidence of adverse effects leading to death when compared to patients administered 10 mg dapagliflozin, 286 participants and 333 participants in the on and off treatment SAS for placebo and dapagliflozin, respectively.[16]

Table 4.10: Adverse events of interest

AE, n(%)	Dapagliflozin 10 mg		Placebo	
	Overall (N=2,368)	European subgroup (N=1,094)	Overall (N=2,368)	European subgroup (N=1,059)
On treatment (SAS)†				
Any AE with an outcome of death	227 (9.6)	[redacted]	250 (10.6)	[redacted]
Any SAE (including events with an outcome of death)	846 (35.7)	[redacted]	951 (40.2)	[redacted]
AE leading to discontinuation	111 (4.7)	[redacted]	116 (4.9)	[redacted]
AE leading to dose interruption	284 (12.0)	[redacted]	349 (14.7)	[redacted]
AE leading to dose reduction	43 (1.8)	[redacted]	25 (1.1)	[redacted]
On and off treatment (SAS)‡				
Any AE with an outcome of death	286 (12.1)	[redacted]	333 (14.1)	[redacted]
Any SAE (including events with an outcome of death)	895 (37.8)	[redacted]	994 (42.0)	[redacted]
AE leading to discontinuation	111 (4.7)	[redacted]	116 (4.9)	[redacted]
AE leading to dose interruption	284 (12.0)	[redacted]	349 (14.7)	[redacted]
AE leading to dose reduction	43 (1.8)	[redacted]	25 (1.1)	[redacted]

Based on Table 25 of the CS[1] as well as Table 5 of the response to request for clarification[8]
† On treatment includes AEs with an onset date on or after date of first dose and up to and including 30 days following last dose of study drug; ‡ On and off treatment includes AEs with an onset date on or after date of first dose of study drug

AE, n(%)	Dapagliflozin 10 mg		Placebo	
	Overall (N=2,368)	European subgroup (N=1,094)	Overall (N=2,368)	European subgroup (N=1,059)

AE = adverse effect; CS = company submission; SAE = serious adverse event; SAS = safety analysis set

Table 4.11: SAEs with on and off treatment (SAS) by system organ class

AE, n(%)	Dapagliflozin 10 mg (N=2,368)	Placebo (N=2,368)
Patients with any SAE	895 (37.8)	994 (42.0)
Infections and infestations	185 (7.8)	199 (8.4)
Neoplasms benign, malignant, and unspecified (including cysts and polyps)	55 (2.3)	52 (2.2)
Blood and lymphatic system disorders	9 (0.4)	16 (0.7)
Immune system disorders	1 (0.0)	0
Endocrine disorders	2 (0.1)	2 (0.1)
Metabolism and nutrition disorders	44 (1.9)	43 (1.8)
Psychiatric disorders	5 (0.2)	7 (0.3)
Nervous system disorders	81 (3.4)	87 (3.7)
Eye disorders	8 (0.3)	13 (0.5)
Ear and labyrinth disorders	2 (0.1)	5 (0.2)
Cardiac disorders	520 (22.0)	634 (26.8)
Vascular disorders	47 (2.0)	60 (2.5)
Respiratory, thoracic, and mediastinal disorders	57 (2.4)	88 (3.7)
Gastrointestinal disorders	65 (2.7)	65 (2.7)
Hepatobiliary disorders	21 (0.9)	23 (1.0)
Skin and subcutaneous tissue disorders	11 (0.5)	8 (0.3)
Musculoskeletal and connective tissue disorders	28 (1.2)	32 (1.4)
Renal and urinary disorders	54 (2.3)	82 (3.5)
Reproductive system and breast disorders	7 (0.3)	9 (0.4)
General disorders and administration site conditions	102 (4.3)	115 (4.9)
Investigations	10 (0.4)	11 (0.5)
Injury, poisoning and procedural complications	52 (2.2)	44 (1.9)
Product issues	2 (0.1)	7 (0.3)

Based on Supplementary Table S1 of McMurray et al. 2019[16]

Notes: On and off treatment includes AEs with an onset date on or after date of first dose of study drug; MedDRA version 22.0 was used to classify SAEs by system organ class and preferred terms.[20]

AE = adverse effect; MedDRA = Medical Dictionary for Regulatory Affairs; SAE = serious adverse event; SAS = safety analysis set

Table 4.12: Adverse events of special interest

AE, n(%)	Dapagliflozin 10 mg (N=2,368)	Placebo (N=2,368)
On treatment (SAS)†		
Any definite or probable diabetic ketoacidosis	3 (0.1)	0
Any major hypoglycaemic event	4 (0.2)	4 (0.2)
Any event of symptoms of volume depletion	170 (7.2)	153 (6.5)
Any fracture	48 (2.0)	47 (2.0)
Any renal AE	141 (6.0)	158 (6.7)
Any amputation	11 (0.5)	11 (0.5)
On and off treatment (SAS)‡		
Any definite or probable diabetic ketoacidosis	3 (0.1)	0
Any major hypoglycaemic event	4 (0.2)	4 (0.2)
Any event of symptoms of volume depletion	178 (7.5)	162 (6.8)
Any fracture	49 (2.1)	50 (2.1)
Any renal AE	153 (6.5)	170 (7.2)
Any amputation	13 (0.5)	12 (0.5)

Based on Table 25 of the CS
† On treatment includes AEs with an onset date on or after date of first dose and up to and including 30 days following last dose of study drug; ‡ On and off treatment includes AEs with an onset date on or after date of first dose of study drug
AE = adverse effect; CS = company submission; SAE = serious adverse event; SAS = safety analysis set

ERG comment: Overall, the company noted that no SAE occurred more frequently with dapagliflozin than with placebo, this is also acknowledged in the DAPA-HF trial.[16] A perusal of SAEs published in the Supplementary Table S1 of McMurray et al. 2019 shows that this is mostly true with the exception of slightly higher SAE incidence rates in dapagliflozin 10 mg in skin and subcutaneous tissue disorders, prostate cancer, diabetic metabolic decompensation, transient ischaemic attack, atrial flutter, peripheral ischaemia, inguinal hernia, sudden death, and hip fractures, when compared to placebo.[16]

It should be noted that the proportion of European participants with any AE or any SAE was typically [redacted] than in the overall study population (see Table 4.10).

Although genital infection AEs were not routinely collected in the DAPA-HF trial, in justifying the modelling assumption that there was no AE-associated with mortality, the company identifies that based on data modelled from DECLARE TIMI-58, genital infections have a higher incidence rate in the dapagliflozin arm than the standard care arm.[19]. Genital infections are also reported as a common adverse drug reaction for in the summary of product characteristics of dapagliflozin for use in T1DM and T2DM.[1]

4.3 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

In the absence of trials directly comparing dapagliflozin with sacubitril valsartan, the company performed an anchored matched adjusted indirect comparison (MAIC). This used results from DAPA-HF and PARADIGM-HF.[16, 21] These trials were the only two trials identified though the SLR.

PARADIGM-HF was an international, randomised, double-blind, parallel-group, active control trial in patients with chronic HFrEF comparing sacubitril valsartan 200 mg twice daily (bid) to enalapril 10 mg bid both given in conjunction with standard care. The primary outcome was a composite of the time to CV death or the first hHF and the median duration of follow-up was 27 months. The trial recruited across 47 countries.[21]

There was a run-in period of up to 10 months where all patients received enalapril 10 mg bid followed by sacubitril valsartan 100 mg BID (titrated to 200 mg) as well as a matched placebo to establish whether they could tolerate the trial treatments. Patients were then randomised 1:1 to receive either treatment, other background HF treatments remained the same during the trial but use of an ACEi or an ARB after randomisation was prohibited. A total of 8,442 participants were randomised but 43 were excluded from the analysis due randomisation and Good Clinical Practice (GCP) violations. Of the analysed intention-to-treat (ITT) dataset, following randomisation, 4,187 patients were randomised to receive sacubitril valsartan and 4,212 patients were randomised to receive enalapril.[21]

Results for the primary composite outcome in PARADIGM-HF and its individual components are presented in Table 4.13. All results favoured sacubitril valsartan over enalapril with a HR for the primary outcome of time to CV death or hHF of 0.80 (95% CI 0.73 to 0.87).

Table 4.13: Primary outcome results for PARADIGM-HF

Outcome	Sacubitril valsartan	Enalapril	HR (95% CI)
Primary outcome (CV death or hHF)†	21.8%	26.5%	0.80 (0.73–0.87)
hHF	12.8%	15.6%	0.79 (0.71–0.89)
CV death	13.3%	16.5%	0.80 (0.71–0.89)
All cause death	17.0%	19.8%	0.84 (0.76–0.93)

Based on Table 65 of Appendix F of the CS[22]

† Primary outcome in PARADIGM-HF was CV death, hHF, or urgent HF visit.

CI = confidence interval; CS = company submission; CV = cardiovascular; hHF = hospitalisation for heart failure; HF = heart failure; HR = hazard ratio

ERG comment: The ERG has no comments regarding the inclusion of PARADIGM-HF.

4.4 Critique of the indirect comparison and/or multiple treatment comparison

The DAPA-HF trial compared dapagliflozin plus standard care to placebo plus standard care.[16] As this was the only trial of these interventions, no meta-analysis was performed. However, as there was no direct evidence comparing dapagliflozin with sacubitril valsartan, a MAIC was performed. This was used to compare outcomes from the dapagliflozin plus standard care arm from DAPA-HF with the sacubitril valsartan plus standard care arm from the PARADIGM-HF trial. The MAIC adjusted the individual participant data (IPD) from DAPA-HF so the reweighted baseline patient characteristics matched those of the patients from the PARADIGM-HF trial. Outcomes were then compared between the two treatment arms using the reweighted data. Further details of the MAIC methods are provided in section 4.4.1.

4.4.1 MAIC methods

The MAIC used IPD from DAPA-HF trial and aggregate data from trial publications for PARADIGM-HF. The IPD from DAPA-HF was reweighted to match the published summary statistics for baseline patient characteristics from PARADIGM-HF. Standard care used in DAPA-HF varied and consisted of

combinations of ACEi/ARB, beta-blockers, MRA with or without sacubitril valsartan, so contained different subgroups of patients based on their standard care. PARADIGM-HF had a five to 10 weeks run-in period where patients received enalapril followed by sacubitril valsartan prior to randomisation. A subgroup of the placebo arm from DAPA-HF and the enalapril arm of PARADIGM-HF trial were used as the anchor in the MAIC. The subgroups used from the dapagliflozin arm of DAPA-HF in the MAIC were as follows:

1. Dapagliflozin plus an ACEi (from standard care) vs. sacubitril valsartan plus standard care. This was the primary analysis as it was most comparable to PARADIGM-HF patients as all those patents were known to be tolerant of ACEi (trial eligibility criteria)
2. Dapagliflozin plus an ARB (from standard care) vs. sacubitril valsartan plus standard care.
3. Dapagliflozin plus an ACEi or ARB (from standard care) vs. sacubitril valsartan plus standard care.
4. Dapagliflozin plus sacubitril valsartan (from standard care) vs. sacubitril valsartan plus standard care.

These outcomes which were measured in both trials, i.e. where results were available for both, dapagliflozin and sacubitril valsartan, have been considered in the cost effectiveness model:

1. Time to CV death or first hHF (whichever occurred first)
2. Time to CV death
3. Time to first hHF
4. Time to all-cause death
5. Incidence of AEs of special interest
6. Incidence of SAEs

In order to ensure that the two trial populations were similar, patients from DAPA-HF who would not have satisfied the patient exclusion criteria for PARADIGM-HF, were excluded from the analysis. The ERG asked for further details of how these patients were identified but no further details were provided other than that patients who did not receive ACEi as part of their background therapy were excluded.[8] Patients with type 1 diabetes and who received treatment with an SGLT2 inhibitor within eight weeks of trial enrolment or who were intolerant to an SGLT2 inhibitor were also excluded from the DAPA-HF dataset.

The placebo arm of DAPA-HF was split into the subgroup of patients receiving an ACEi as part of their standard care in order to provide a better match to PARADIGM-HF for the purposes of obtaining a common anchor. However, several potential sources of bias remained, of which the run-in period in PARADIGM-HF was considered to be the most concerning:

- Presence of ACEi treatment other than enalapril in the DAPA-HF placebo subgroup
- Differences between enalapril dosing in PARADIGM-HF and background regional standard care
- Presence of placebo in the DAPA-HF control arm, whilst patients in the PARADIGM-HF active control arm were treated with enalapril
- Potential presence of ARNI or ARB intolerant patients in the DAPA-HF subset placebo arm (removed from PARADIGM-HF by active run-in period and by exclusion criteria, respectively)
- Presence of a single-blind run-in period in PARADIGM-HF during which patients were treated with enalapril and sacubitril valsartan

In order to identify baseline variables to use in the matching of the two trial populations and the reweighting of the DAPA-HF IPD, generalised linear models with forward stepwise variable selection were used to analyse the DAPA-HF data. The potential variables included all baseline variables, treatment (dapagliflozin or placebo) and all interactions between variables including treatment. A single set of aggregate data was not available for both arms of PARADIGM-HF. Forward variable selection was performed once for each arm of PARADIGM-HF and the final outcome-specific matched sets were taken from the treatment interaction terms in both models. The outcome-specific matching sets were used to inform the overall pooled matching sets. Details of the variables included in the matching sets for each outcome are provided in Table 4.14.

Details of baseline data for both trials before and after the matching are provided in Table 4.15. Results for subgroup 4 were not presented as this analysis was not performed due to too few patients being available to achieve matching to the primary matching set (250 with dapagliflozin). After matching the effective sample sizes were reduced to less than half of the original sample size. Histograms of patient weights showed a continuous distribution with most cases having weights <2 and less than [redacted] had weights >5.

Table 4.14: Variables included in matching sets

		Matching Set																
Variable	**Aggregate Data**	**Primary**	**hHF/CVD**	**All-cause mortality**	**hHF**	**CVD**	**Hypotension**	**Cardiac Failure**	**Hyperkalaemia**	**Renal Impairment**	**Dizziness**	**Pneumonia**	**Oedema Peripheral**	**Dyspnoea**	**SAE cardiac failure**	**SAE cardiac failure**	**SAE cardiac failure (acute)**	**SAE ventricular tachycardia**
Age	Mean, SD	✓							✓									
Sex	Proportion	✓														✓		
Race (white)	Proportion	✓	✓															
Race (black)	Proportion	✓	✓															
Race (Asian)	Proportion	✓	✓															
Region (NA)	Proportion	✓			✓	✓	✓			✓								
Region (SA)	Proportion	✓			✓	✓	✓			✓								
Region (AP)	Proportion	✓			✓	✓	✓			✓								
SBP	Mean, SD	✓				✓								✓				
HR	Mean, SD	✓												✓				
BMI	Mean, SD																	
Creatinine	Mean, SD																	
Ischaemic HF	Proportion	✓											✓	✓		✓		✓
LVEF	Mean, SD	✓					✓				✓	✓						✓
NT-proBNP	Median, IQR	✓				✓												
NYHA III	Proportion	✓	✓	✓					✓									
NYHA IV	Proportion	✓	✓	✓					✓									
Hx HTN	Proportion	✓						✓							✓			
Hx DM	Proportion	✓	✓							✓								

		Matching Set																
Variable	**Aggregate Data**	**Primary**	**hHF/CVD**	**All-cause mortality**	**hHF**	**CVD**	**Hypotension**	**Cardiac Failure**	**Hyperkalaemia**	**Renal Impairment**	**Dizziness**	**Pneumonia**	**Oedema Peripheral**	**Dyspnoea**	**SAE cardiac failure**	**SAE cardiac failure**	**SAE cardiac failure (acute)**	**SAE ventricular tachycardia**
Hx AF	Proportion	✓									✓					✓	✓	
Hx hHF	Proportion	✓	✓					✓									✓	✓
Hx MI	Proportion	✓										✓					✓	
Hx Stroke	Proportion	✓		✓					✓									

Based on Table 68 of Appendix F of the CS[22]

Note: Safety outcomes not associated with any treatment effects not shown.

AF = atrial fibrillation; AP = Asia or Pacific; BMI = body mass index; CS = company submission; CVD = cardiovascular death; DM = diabetes mellitus; hHF = hospitalisation for heart failure; HF = heart failure; HR = heart rate; HTN = hypertension; Hx = history of; IQR = inter-quartile range; LVEF = left ventricular ejection fraction; MI = myocardial infarction; NA = North America; NT-proBNP = N-terminal pro B-type natriuretic peptide; NYHA = New York Heart Association; SA = South America; SAE = serious adverse event; SBP = systolic blood pressure; SD = standard deviation

Table 4.15: Baseline variables before and after matching: primary matching set

Variable	**PARADIGM-HF enalapril**	**DAPA-HF placebo + ACEi (anchor)**		**DAPA-HF dapagliflozin + ACEi (subgroup 1)**		**DAPA-HF dapagliflozin + ARB (subgroup 2)**		**DAPA-HF dapagliflozin + ACEi or ARB (subgroup 3)**	
		Raw	**Adjusted**	**Raw**	**Adjusted**	**Raw**	**Adjusted**	**Raw**	**Adjusted**
N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sex (female)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Race (white)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Race (black)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Race (Asian)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Variable	PARADIGM-HF enalapril	DAPA-HF placebo + ACEi (anchor)		DAPA-HF dapagliflozin + ACEi (subgroup 1)		DAPA-HF dapagliflozin + ARB (subgroup 2)		DAPA-HF dapagliflozin + ACEi or ARB (subgroup 3)	
		Raw	Adjusted	Raw	Adjusted	Raw	Adjusted	Raw	Adjusted
Region (NA)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Region (SA)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Region (AP)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SBP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Heart rate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BMI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Creatinine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ischaemic HF	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LVEF	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
NT-proBNP[†]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
NYHA Class III	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
NYHA Class IV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hx HTN	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hx DM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hx AF	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hx hHF	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hx MI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hx stroke	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Based on Table 16 of the CS[1]

[†] Median (lower quartile, upper quartile); [‡] The sacubitril valsartan subgroup had too few patients (250 receiving dapagliflozin) to achieve matching to the primary matching set, and so analysis was not performed using this matching set on that subpopulation.

Variable	PARADIGM-HF enalapril	DAPA-HF placebo + ACEi (anchor)		DAPA-HF dapagliflozin + ACEi (subgroup 1)		DAPA-HF dapagliflozin + ARB (subgroup 2)		DAPA-HF dapagliflozin + ACEi or ARB (subgroup 3)	
		Raw	Adjusted	Raw	Adjusted	Raw	Adjusted	Raw	Adjusted
ACEi = angiotensin-converting enzyme inhibitor; AF = atrial fibrillation; AP = Asia or Pacific; ARB = Angiotensin II receptor blocker, BMI = body mass index; CS = company submission; DM = diabetes mellitus; hHF = hospitalisation for heart failure; HF = heart failure; HTN = hypertension; Hx = history of; LVEF = left ventricular ejection fraction; MI = myocardial infarction; NA = North America; NT-proBNP = N-terminal pro B-type natriuretic peptide; NYHA = New York Heart Association; SA = South America; SBP = systolic blood pressure									

Differences in outcomes between the matched datasets were analysed using a Cox proportional hazards model. As well as performing an anchored MAIC, indirect comparisons directly comparing the two treatment arms from the two trials were also performed, without using any matching, these have been reported as a "naïve comparison".

ERG comment: As detailed in question A21 of the request for clarification, the company provided no justification for choosing a MAIC to compare dapagliflozin and sacubitril over the more established Bucher method.[13] Page 61 of NICE technical support document (TSD) 18 recommends that a MAIC for an anchored ITC (using RCTs with a common comparator) should be fulfil two criteria:[23]

1. "*Evidence must be presented that there are grounds for considering one or more variables as effect modifiers on the appropriate transformed scale. This can be empirical evidence, or an argument based on biological plausibility"*,
2. "*Quantitative evidence must be presented that population adjustment would have a material impact on relative effect estimates due to the removal of substantial bias"*.

The ERG asked the company to justify the use of MAIC based on these criteria (question A21.b of the request for clarification).[13] The response did not provide sufficient details regarding the two criteria specified in TSD18.[8, 23] Therefore, the results of the Bucher method *("unadjusted analysis based on a common anchor"* in the CS) were used as the main ITC supporting the economic model, see section 4.4.2. In addition, results of the MAICs are presented in section 4.4.3 for illustration. Overall, similar effect estimates were reported for both methods with narrower 95% CIs for the Bucher method.

In addition, Table 69 in Appendix F of the company submission reported the *"expected bias reduction"* by adjustment on the log hazard ratio scale.[22] However, this has not been performed for all characteristics. In response to the request for clarification, the company stated that it had only been performed for characteristics which *"were found to be treatment effect modifying covariates for each individual endpoint in question"*.[8]

4.4.2 Bucher results

Results for time to hHF or CV death using the Bucher method are presented in Table 4.16.

Table 4.16: Bucher results: Time to hHF or CV death (secondary endpoint)

Population	Effect estimate
Subgroup 1: Dapagliflozin plus ACEi vs. sacubitril valsartan	[redacted]
Subgroup 2: Dapagliflozin plus ARB vs. sacubitril valsartan	[redacted]
Subgroup 3: Dapagliflozin plus ACEi and/or ARB vs. sacubitril valsartan	[redacted]
Based on Figures 16, 18, and 20 of the CS[1] ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor blocker; CI = confidence interval; CS = company submission; hHF = hospitalisation for heart failure; HR = hazard ratio	

ERG comment: Results were reported for time to hHF or CV death (see Table 4.16) as well as death, hHF, or CV death. However, no results were reported for the primary outcome of the DAPA-HF trial (Time to first occurrence of any of the composite components: CV death or hHF or an urgent HF visit).

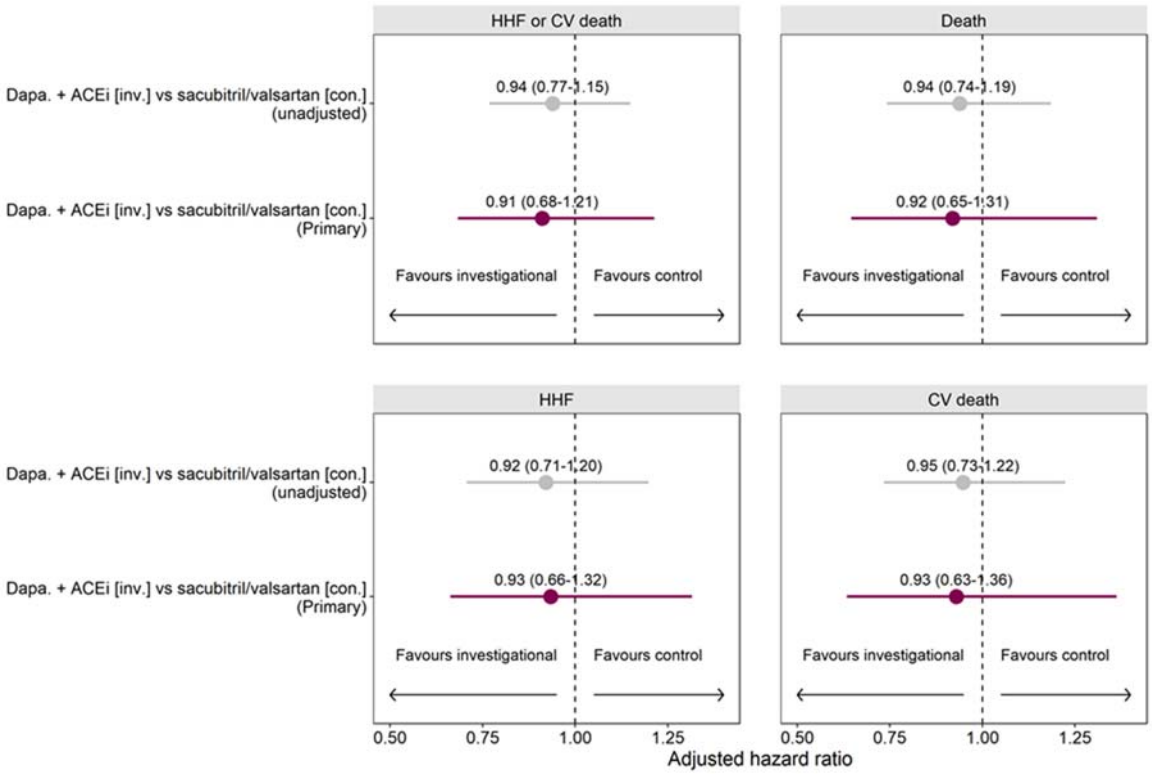
4.4.3 MAIC results

In line with its anticipated marketing authorisation and the final scope issued by NICE, dapagliflozin was considered in the cost effectiveness model for the treatment of adult patients with symptomatic HFrEF.[24] Populations #1 and #2 considered patients not previously treated with sacubitril valsartan while population #3 considered patients that were previously treated with sacubitril valsartan.

4.4.3.1 Subgroup 1: Dapagliflozin plus ACEi vs. sacubitril valsartan

Results from the MAIC comparing dapagliflozin plus ACEi with sacubitril valsartan for time to hHF or CV death are shown in Figure 4.2. This showed that there was no statistically significant difference between treatments for time to hHF or CV death in adjusted MAIC (HR 0.91, 95% CI 0.68 to 1.21) or the naïve indirect treatment comparison (ITC; HR 0.94, 95% CI 0.77 to 1.15).

Figure 4.2: MAIC results: Dapagliflozin plus ACEi vs. sacubitril valsartan (subgroup 1)



Based on Figure 16 of the CS[1]
Grey = unadjusted; purple = matching-adjusted
ACEi, angiotensin converting enzyme inhibitor; con. = control; CS = company submission; CV = cardiovascular; hHF = hospitalisation for heart failure; inv. = intervention.

4.4.3.2 Subgroup 2: Dapagliflozin plus ARB vs. sacubitril valsartan

Results from the MAIC comparing dapagliflozin plus ARB with sacubitril valsartan for time to hHF or CV death are shown in Figure 4.3. This showed that there was no statistically significant difference between treatments for time to hHF or CV death in adjusted MAIC [redacted] or the naïve ITC [redacted].

Figure 4.3: MAIC results: Dapagliflozin plus ARB vs. sacubitril valsartan (subgroup 2)

Based on Figure 18 of the CS[1]
Grey = unadjusted; purple = matching-adjusted
ACEi, angiotensin converting enzyme inhibitor; con. = control; CS = company submission; CV = cardiovascular; hHF = hospitalisation for heart failure; inv. = intervention.

4.4.3.3 Subgroup 3: Dapagliflozin plus ACEi and/or ARB vs. sacubitril valsartan

Results from the MAIC comparing dapagliflozin plus ACEi and/or ARB with sacubitril valsartan for time to hHF or CV death are shown in Figure 4.4. This showed that there was no statistically significant difference between treatments for time to hHF or CV death in adjusted MAIC) or the naïve ITC .

Figure 4.4: MAIC results: Dapagliflozin plus ACEi and/or ARB vs. sacubitril valsartan (subgroup 3)

Based on Figure 20 of the CS [1]
Grey = unadjusted; purple = matching-adjusted
ACEi, angiotensin converting enzyme inhibitor; con. = control; CS = company submission; CV = cardiovascular; hHF = hospitalisation for heart failure; inv. = intervention.

4.4.3.4 Safety outcomes for all subgroups

The CS included the results of comparison of all SAEs between the two trials. Other adverse events were not analysed as PARADIGM-HF did not have similar criteria for recording AEs. The results are presented in Tables 19 to 24 of the CS.[1]

Considering the results of the naïve ITC only, the odds ratios significantly different from 1 at the α = 5% are reported).

4.5 Additional work on clinical effectiveness undertaken by the ERG

The ERG did not undertake any additional work on clinical effectiveness.

4.6 Conclusions of the clinical effectiveness section

The company submission and response to clarification provided enough details for the ERG to appraise the literature searches conducted as part of the systematic review to identify RCT evidence reporting on efficacy and safety. A broad range of databases and resources, including clinical trial registries, conference proceedings and HTA organisation websites, was searched and the searches were transparent and reproducible. The searches included RCT study design filters to identify clinical efficacy but did not include search terms to identify safety evidence. Searches were conducted between November and December 2019.

The ERG was concerned with some aspects of the searches, including the search terms used in the HFrEF population facet, and the limit used to remove studies about children. Overall, however, the searches were satisfactory, and given the comprehensive list of interventions included and the range of resources searched, it was unlikely that any relevant studies meeting the NICE scope were missed.

However, there are some issues regarding the conduct of the SLR:

- Non-English language studies were excluded which means that potentially relevant studies might have been missed. The company did not provide the list of all references excluded using this criterion as requested by the ERG.
- It is unclear whether data extraction followed best practice as relevant details were not reported, e.g. how many people were involved in data extraction and how any discrepancies were resolved.
- Similarly, it is unclear whether the risk of bias assessment followed best practice as relevant details were not reported, e.g. how many people were involved in risk of bias assessment, how any discrepancies were resolved, and which tool was used to assess the included studies.

The evidence for the effectiveness of dapagliflozin came from the DAPA-HF trial. This was a randomised, double-blind, multicentre, placebo-controlled, phase III trial which compared dapagliflozin 10 mg once daily with placebo in patients aged 18 years or over with HFrEF (New York Heart Association (NYHA) class ≥II with left ventricular ejection fraction (LVEF) ≤40%). Concomitant treatment with standard care was allowed in both trial arms according to local guidelines. The primary outcome was the time to the first occurrence of cardiovascular (CV) death, hospitalisation for heart failure (HF) or an urgent hospital visit for HF (a composite outcome). The trial comprised 410 centres worldwide with 10 centres in the United Kingdom (UK) recruiting 62 participants. The median follow-up period was 18.2 months (range 0 to 27.8 months) and a total of 4,744 participants were randomised.

It should be noted that patients with type 1 diabetes mellitus (T1DM) were excluded from the trial (see section 4.2.1 for details), i.e. any recommendation needs to consider this limitation. Furthermore, the ERG wants to highlight differences regarding both efficacy as well as safety in the European subgroup compared to the overall trial population (see section 4.2.1 for details). Despite higher uncertainty (as *"the subgroup analyses were not powered to detect statistically significant differences between treatment groups"*), the European population seems more relevant to the UK setting and has therefore been used in the ERG base-case, see section 5.[8] Table 4.7 includes results for the primary outcome (as well as for components of this composite endpoint) for both the overall population as well as the population recruited/treated in Europe.

All-cause mortality showed a statistically significant difference between dapagliflozin and placebo in favour of the active treatment (hazard ratio (HR) 0.83, 95% confidence interval (CI) 0.71 to 0.97). Results of other secondary endpoints are presented in section 4.2.2.2.

The CS included EQ-5D-5L (European Quality of Life-5 Dimensions, three-level scale) as an exploratory endpoint. There was [redacted] in change from baseline for EQ-5D-5L score between dapagliflozin and placebo at 24 months (least squares mean [redacted] least squares mean difference [redacted]).

The most commonly experienced serious adverse events (SAEs) in both dapagliflozin and placebo trial arms respectively were, pneumonia 3.2% and 3.5%, ischaemic stroke 1.0% and 1.1%, cardiac failure

11.1% and 14.8%, congestive cardiac failure 2.7% and 3.0%, acute cardiac failure 1.8% and 2.5%, acute myocardial infarction 1.6% and 1.6%, ventricular tachycardia 1.4% and 2.3%, chronic cardiac failure 1.1% and 1.4%, atrial fibrillation 1.1% and 1.6%, unstable angina 0.9% and 1.3%, acute kidney injury 1.0% and 1.9%, and death 2.0% and 2.0%. Table 4.10 presents results on adverse events for both the overall population as well as the population recruited/treated in Europe. It should be noted that the proportion of European participants with any AE or any SAE was typically [redacted] than in the overall study population. Further details on adverse events are presented in section 4.2.3.

In the absence of trials directly comparing dapagliflozin with sacubitril valsartan, the company performed an anchored matched adjusted indirect comparison (MAIC). This used results from DAPA-HF and PARADIGM-HF. These trials were the only two trials identified though the SLR.

PARADIGM-HF was an international, randomised, double-blind, parallel-group, active control trial in patients with chronic HFrEF comparing sacubitril valsartan 200 mg twice bid to enalapril 10 mg bid both given in conjunction with standard care. The primary outcome was a composite of the time to CV death or the first hHF and the median duration of follow-up was 27 months. The trial recruited across 47 countries.

The ERG asked the company to justify the use of MAIC based on the two criteria specified in NICE TSD 18. As the response did not provide sufficient details regarding the two criteria, the results of the Bucher method *("unadjusted analysis based on a common anchor"* in the CS) were used as the main indirect treatment comparison (ITC) supporting the economic model, see section 4.4.2.[1] In addition, results of the MAICs are presented in section 4.4.3 for illustration. Overall, similar effect estimates were reported for both methods with narrower 95% CIs for the MAIC. Results for time to hHF or CV death using the Bucher method are presented in Table 4.16.

5. Cost effectiveness

5.1 ERG comment on company's review of cost effectiveness evidence

The company conducted searches for cost effectiveness evidence, health state utility values (HSUVs), and healthcare cost and resource data. A broad range of databases was searched. The CS provided enough detail for the ERG to be able to appraise the searches conducted.

An SLR was performed with the objectives to identify and select relevant economic evaluations of relevant interventions for the management of HF. This search was also designed to identify studies reporting on health state utility values (HSUVs) and cost and resource data (CS Appendix G).

5.1.1 Searches performed for cost effectiveness section

The following paragraphs contain summaries and critiques of all searches related to cost effectiveness presented in the CS.

Appendices G, H and I of the CS reported the literature searches used to identify cost effectiveness evidence, HSUVs, and healthcare cost and resource data: one overarching search strategy was used to identify all cost related evidence.[25-27] Searches were conducted on 11 December 2019 (NB: the CS misreports the date as 11 December 2020). A summary of the resources searched is provided in Table 5.1.

Table 5.1: Resources searched for cost effectiveness, HSUV and healthcare resource use

Resource	Host/source	Date range	Date searched
Electronic databases			
Embase	Ovid	1974 to 10 December 2019	11 December 2019
MEDLINE and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily Update	Ovid	1946 to 11 December 2019	11 December 2019
EBM Reviews: CDSR, ACP Journal Club, DARE, CCA, CCTR, CMR, HTA, and NHS EED	Ovid	Not reported	11 December 2019

Resource	Host/source	Date range	Date searched
EconLit	Ovid	1886 to present	11 December 2019
Conference proceedings			
AHA	https://www.ahajournals.org/toc/circ/136/suppl_1 https://www.ahajournals.org/toc/circ/138/Suppl_1 https://www.ahajournals.org/toc/circ/140/Suppl_1	2017, 2018, 2019	27 November 2019
ESC	ESC Congress online library: https://esc365.escardio.org/	2017, 2018, 2019	28 November 2019
WCC	2017 searched through ACC supplement 2018 abstracts online links broken: unable to access 2019 searched through ESC congress online library	2017, 2019	29 November 2019
ACC	http://www.onlinejacc.org/content/meeting-abstract-supplements	2017, 2018, 2019	29 November 2019
ESC Heart Failure congress	https://spo.escardio.org	2017, 2018, 2019	2 December 2019
ISPOR International & European meetings	https://www.ispor.org/heor-resources/presentations-database/search	2017, 2018, 2019	13 December 2019
HTAi	https://htai.org/annual-meetings/htai	2017, 2018, 2019	2 December 2019
SMDM	https://smdm.confex.com/smdm/17bec/meetingapp.cgi/ https://smdm.confex.com/smdm/2019/meetingapp.cgi/	2018, 2019	2 December 2019
HTA websites			
NICE	https://www.nice.org.uk/	All years	3 December 2019
SMC	https://www.scottishmedicines.org.uk/		
CADTH	https://www.cadth.ca/		
PBAC	www.pbs.gov.au/info/industry/listing/participants/pbac		
Clinical Trial Registries			
US NIH registry & results database	https://clinicaltrials.gov	All years	27 November 2019
WHO ICTRP registry	http://apps.who.int/trialsearch	All years	28 November 2019
Other sources			
Reference lists of included studies were searched			

Resource	Host/source	Date range	Date searched
ACC = American College of Cardiology; ACP = American College of Physicians; AHA = American Heart Association; CADTH = Canadian Agency for Drugs and Technologies in Health; CCA = Cochrane Clinical Answers; CCTR = Cochrane Central Register of Controlled Trials; CDSR = Cochrane Database of Systematic Reviews; CMR = Cochrane Methodology Register; DARE = Database of Abstracts of Reviews of Effects; EBM = evidence-based medicine; EED = Economic Evaluation Database; ESC = European Society of Cardiology; HSUV = health state utility value; HTA = Health Technology Assessment; HTAi = Health Technology Assessment international; ICTRP = International Clinical Trials Registry Platform; ISPOR = International Society for Pharmacoeconomics and Outcomes Research; NHS = National Health Service; NICE = National Institute for Health and Care Excellence; PBAC = Pharmaceutical Benefits Advisory Committee; SMC = Scottish Medicines Consortium; SMDM = Society for Medical Decision Making; US NIH = United States National Institutes of Health; WCC = World Congress of Cardiology and Cardiovascular Health; WHO = World Health Organization			

ERG comment:

- The selection of databases searched was satisfactory, and searches were clearly reported and reproducible. The database name, host, date range and date searched were provided.
- It is not clear if the search facets used to identify cost effectiveness, HSUVs and healthcare resource use were based on validated search filters, such as those published on the ISSG Search Filters Resource website: https://sites.google.com/a/york.ac.uk/issg-search-filters-resource/. It is good practice to provide citation details of any study design filters used.
- Truncation and proximity operators were inconsistently used throughout.
- The EBM reviews resource, including the Cochrane Library databases, did not report the date ranges or database issue searched. The search results were reported for all databases in total. It would have been more useful and transparent to have reported the search results from each database separately.
- The EBM reviews resource search included study design filters to identify cost effectiveness evidence, HSUVs, and healthcare cost and resource data. As the databases included in EBM reviews are pre-filtered to include trials, systematic reviews, HTA reports and economic evaluations, study design filters were not necessary and may have adversely affected the results.
- A search of health economic databases, such as the Cost Effectiveness Analysis (CEA) Registry (www.cearegistry.org) and ScHARRHUD (School of Health and Related Research Health Utility Database; http://www.scharrhud.org/), might have been a useful addition to the literature searches.

5.1.2 Inclusion/exclusion criteria used in the study selection

In- and exclusion criteria for the review are presented in Table 5.2.

Table 5.2: Eligibility criteria for the systematic literature reviews

PICOS	Inclusion criteria	Exclusion criteria
Patient population	Adult patients with symptomatic chronic HFrEF in line with the populations enrolled in the DAPA-HF clinical trial: • Adults ≥18 years • Ejection fraction ≤40% • NYHA class II, III, IV Also: • Patients with chronic kidney disease • Mixed CHF populations	Studies including 100% patient populations with the following characteristics will be excluded: • Patients with heart failure with preserved ejection fraction (HFpEF) • Patients with type 1 diabetes mellitus

PICOS	Inclusion criteria	Exclusion criteria
Intervention	Pharmacological interventions recommended in relevant clinical guidelines for HFrEF, to include: • Sodium glucose cotransporter 2 inhibitors (SGLT2i) • Angiotensin-converting-enzyme inhibitors (ACEi) • Angiotensin receptor blockers (ARB) • Beta blockers (BB) • Angiotensin receptor-neprilysin inhibitors (ARNI) • Mineralocorticoid receptor antagonists (MRA) • Ivabradine • Cardiac resynchronisation therapy (CRT) • Implantable cardioverter defibrillator (ICD)	
Outcomes(s)	• Summary costs and health outcomes (e.g. QALYs, LYG) • Cost-effectiveness estimates (e.g. ICERs) • Cost drivers • Assumptions underpinning resource use • Model structure and summary	
Study design	• Cost-utility analyses • Cost-effectiveness analyses • Cost-minimisation analyses • Cost-benefit analyses	
Language	English language publications or non-English publications with an English-language abstract	

Based on Appendix G of the CS25

ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor blocker; ARNI = angiotensin receptor–neprilysin inhibitor; BB = beta blocker; CHF = chronic heart failure; CRT = cardiac resynchronisation therapy; CS = company submission; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; ICD = implantable cardioverter defibrillator; ICER = incremental cost effectiveness ratio; LYG = life year gained; MRA = mineralocorticoid receptor antagonists; NYHA = New York Heart Association; QALY = quality-adjusted life year; SGLT2i = sodium glucose cotransporter 2 inhibitor

ERG comment: The ERG agrees that the eligibility criteria are suitable to fulfil the company's objective to identify cost effectiveness studies. However, language criteria might be too restrictive, potentially resulting in relevant studies being missed.

5.1.3 Included/excluded studies in the cost effectiveness review

The company identified 120 economic evaluations in the SLR of which 12 (including two prior single technology appraisals (STAs)), reporting on drug-based interventions from a UK perspective, were extracted (see Tables 72 and 73 of the CS).[1]

ERG comment: Although the PRISMA diagram (see Figure 21 of the CS) provides information on the exclusion of studies, details were lacking here as well as in Table 76 of Appendix G of the CS.[1, 25] Therefore the rationale for excluding CE studies was not completely clear. Moreover, some criteria, such as publication date, were listed in the PRISMA diagram as reason for exclusion but not listed as exclusion criteria.

5.1.4 Conclusions of the cost effectiveness review

The CS provided an overview of the included cost effectiveness, utility and resource use and costs studies. It concluded that none of the identified studies evaluated the cost effectiveness of dapagliflozin in patients with HF and therefore were not directly generalisable to the NICE decision problem.

ERG comment: The company submission provided enough details for the ERG to appraise the literature searches. A good range of resources was searched, and the searches were transparent and reproducible.

Although the eligibility criteria were largely suitable for the SLR performed, some criteria were potentially too restrictive and the PRISMA diagram highlighted reasons for exclusion that were not listed as exclusion criteria.

5.2 Summary and critique of company's submitted economic evaluation by the ERG

Table 5.3: Summary of the company's economic evaluation (with signposts to CS)

	Approach	Source/Justification	Signpost (location in CS)
Model	Cohort state transition model		B.3.2.2
States and events	The model comprised disease progression states based on KCCQ-TSS quartile scores, stratified by the presence of T2DM, and death.		B.3.2.2
Comparators	Care as usual with or without sacubitril valsartan.		B.3.2.3
Population	Adult patients with symptomatic HFrEF. Populations #1 and #2 consisted of patients not previously treated with sacubitril valsartan while population #3 consisted of patients that were previously treated with sacubitril valsartan.	In line with anticipated marketing authorisation and the final scope issued by NICE	B.3.2.1 and B.1.3.8.1

	Approach	Source/Justification	Signpost (location in CS)
Treatment effectiveness	Treatment effectiveness in terms of time to death, time to treatment discontinuation, hHF and uHFv incidence as well as transition probabilities between health states defined by KCCQ-TSS quartiles was estimated based on the DAPA-HF trial.	DAPA-HF trial	B.3.3.1
Adverse events	The company included the most common serious AEs reported in the DAPA-HF trial.	DAPA-HF trial	B.3.3.1.5
Health related QoL	The company used health state utility values and disutilities derived from the DAPA-HF trial.	DAPA-HF trial	B.3.4
Resource utilisation and costs	The cost categories included in the model were treatment costs, health state costs and costs related to adverse events.	Costs applied in the model were based on the Hospital and Community Health Services (HCHS) pay and the relevant Personal Social Services Research Unit (PSSRU) publications (Unit Costs of Health and Social Care).	B.3.5
Discount rates	Discount of 3.5% for utilities and costs.	As per NICE reference case.	B.3.2.2
Subgroups	No subgroup analyses are specifically reported in CS section 3.9. However, scenario analyses explored the impact of varying baseline characteristics (based on baseline KCCQ-TSS score, age, T2DM status and geographical region)		B.3.9
Sensitivity analysis	Both DSA and PSA were performed as well as scenario analyses.		B.3.8

CS = company submission; DSA = deterministic sensitivity analysis; HFrEF = heart failure with reduced ejection fraction; hHF = hospitalisation for heart failure; KCCQ-TSS = Kansas City Cardiomyopathy Questionnaire – Total Symptom Score; NICE = National Institute for Health and Care Excellence; T2DM = type 2 diabetes mellitus; PSA = probabilistic sensitivity analysis; uHFv = urgent heart failure visit

5.2.1 NICE reference case checklist (TABLE ONLY)

Table 5.4: NICE reference case checklist

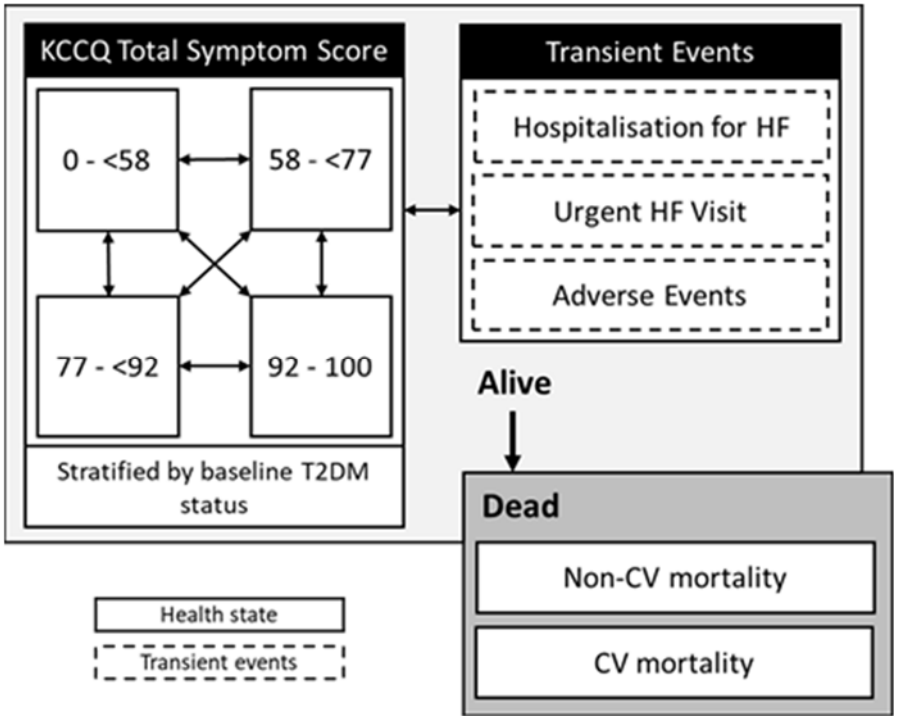
Elements of the economic evaluation	Reference Case	Included in submission	Comment on whether *de novo* evaluation meets requirements of NICE reference case
Population	As per NICE scope	Yes	
Comparator(s)	Therapies routinely used in the National Health Service (NHS), including technologies regarded as current best practice	Yes	
Type of economic evaluation	Cost effectiveness analysis	Partly	CS base-case for population #1 is a cost-minimisation analysis
Perspective on costs	NHS and Personal Social Services (PSS)	Yes	
Perspective on outcomes	All health effects on individuals	Yes	
Time horizon	Sufficient to capture differences in costs and outcomes	Yes	
Synthesis of evidence in outcomes	Systematic review (SLR)	Yes	
Measure of health effects	Quality adjusted life years (QALYs)	Yes	
Source of data for measurement HRQoL	Described using a standardised and validated instrument	Yes	
Source of preference data for valuation of changes in HRQoL	Time-trade off or standard gamble	Yes	
Discount rate	An annual rate of 3.5% on both costs and health effects	Yes	
Equity weighting	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes	
Sensitivity analysis	Probabilistic modelling	Partly	Probabilistic sensitivity analyses are not performed for population #1.

Elements of the economic evaluation	Reference Case	Included in submission	Comment on whether *de novo* evaluation meets requirements of NICE reference case
NHS = National Health Service; NICE = National Institute for Health and Care Excellence; PSS = Personal Social Services; QALY = quality-adjusted life year; SLR = systematic literature review			

5.2.2 Model structure

The company developed a cohort state transition model in Microsoft Excel. The model comprised disease progression states based on KCCQ-TSS quartile scores, stratified by the presence of T2DM, and death. Patients could transition between disease progression health states that were divided in KCCQ-TSS scores of 0 to <58, 58 to <77, 77 to <92, 92 to 100 (higher = better) with health state-specific costs and utility values. Furthermore, the impact of hHF, urgent heart failure visit (uHFv), as well as adverse events on quality of life and cost was incorporated. Parametric survival models for CV mortality and all-cause mortality were applied to estimate transitions to the absorbing death state. Moreover, a constant dapagliflozin discontinuation probability was applied, and input parameters for patients who discontinued treatment were assumed equal to those receiving placebo.

Figure 5.1: Model structure



Based on Figure 22 of the CS[1]
CS = company submission; CV = cardiovascular; HF = heart failure; KCCQ = Kansas City Cardiomyopathy Questionnaire; T2DM = type 2 diabetes mellitus.

ERG comment: The main concern of the ERG relates to the use of the KCCQ-TSS quartiles to characterise/define the health states.

a) KCCQ-TSS was used rather than the KCCQ quality of life domain, the KCCQ clinical summary score or the overall summary score to characterise/define the health states. The company justified this choice (clarification response B1) by indicating that KCCQ-TSS encompasses HF symptoms only while the KCCQ quality of life score, clinical summary score or overall summary scores also

encompass other aspects of HF disease.[8] The company also stated in clarification response A18c that the Food and Drug Administration (FDA) questioned the interpretability of the clinical summary score and agreed that the TSS is sufficiently established to capture the most relevant symptoms of heart failure. It is unclear to the ERG why a metric encompassing HF symptoms only would be preferred compared to metrics that (also) consider other domains/aspects. The impact of this assumption is unclear.

b) KCCQ-TSS quartiles rather than other grouping approaches (e.g. quintiles or equally sized quarters i.e. 0-25, 25-50, 50-75, 75-100) were used by the company. In response to clarification response B1 the company justified this approach as it was found to provide a better fit to the observed data while still containing enough data to produce stable estimates.[8] This justification was, however, not supported by evidence (indicating the observed fit and/or data per category for other grouping approaches) nor did the company elaborate on the potential impact of this approach. Moreover, homogeneity regarding transition probabilities, health-related quality of life (HRQoL), resource use and costs, an important aspect of the definition of health states, was not considered.

5.2.3 Population

In line with its anticipated marketing authorisation and the final scope issued by NICE, dapagliflozin was considered in the cost effectiveness model for the treatment of adult patients with symptomatic HFrEF.[24] Populations #1 and #2 considered patients not previously treated with sacubitril valsartan while population #3 considered patients previously treated with sacubitril valsartan. Based on the CS, the overlap/differences between populations #1 and #2 (both not previously treated with sacubitril valsartan) is unclear.

ERG comment: The main concern of the ERG relates to a lack of clarity regarding the definition of populations #1 and #2. In response to clarification response A1, the company clarified that populations #1 and #2 were different with respect to eligibility for sacubitril valsartan. Population #1 is eligible for sacubitril valsartan and is in accordance with the marketing authorisation of sacubitril valsartan (i.e. patients need to have ejection fraction (EF) ≤35% and must not have hyperkalaemia (serum potassium >5.4 mmol/l) and/or hypotension). Population #2 is ineligible for sacubitril valsartan or do not progress to receiving sacubitril valsartan due to other reasons (e.g. due to the complexity associated with sacubitril valsartan initiation and titration).

5.2.4 Interventions and comparators

Dapagliflozin was considered within the economic evaluation as per the anticipated licensed indication in HFrEF. Dapagliflozin was, in line with the dosage used in DAPA-HF, modelled as an add-on therapy with a once daily dose of 10 mg administered orally.

Dapagliflozin, as an add-on therapy to ACEi/ARB, BB ±MRA (with or without MRA, according to the patient's suitability for MRA) was compared to ACEi/ARB, BB ±MRA with sacubitril valsartan (population #1) as well as to ACEi/ARB, BB ±MRA without sacubitril valsartan (population #2) for patients not previously treated with sacubitril valsartan. Moreover, dapagliflozin, as an add-on therapy to sacubitril valsartan, BB ±MRA, was compared to sacubitril valsartan, BB ±MRA (population #3) for patients previously treated with sacubitril valsartan (see Table 5.5 and Figure 2.1).[1]

ERG comment: The main concern of the ERG relates to the positioning of dapagliflozin and sacubitril valsartan in the primary setting. For population #1, dapagliflozin after first-line treatment (ACEi/ARB, BB, ±MRA) was compared to sacubitril valsartan after first-line treatment. In the NICE

recommendations of TA388, it was stated that treatment with sacubitril valsartan should be started by a heart failure specialist with access to a multidisciplinary heart failure team.[28]

However, in CS Figure 3 (see Figure 2.1), population #1 was positioned in the primary setting, before specialist reassessment.[1] In response to clarification question A1, the company stated that *"it is proposed that the population in base-case analysis #1 would not need to wait for a specialist appointment to initiate treatment with dapagliflozin, as initiation could be undertaken in primary care, given the extensive clinical experience primary care clinicians have accumulated in initiating dapagliflozin for type 2 diabetes patients, over more than 7 years. Sacubitril valsartan would remain as a specialist initiation treatment for this patient population"*.[8] However, it should be noted that the professional organisation submission by the British Society for Heart Failure indicated that dapagliflozin treatment should be initiated by either heart failure (in case of heart failure with/without diabetes) or diabetes (in case of heart failure with diabetes) specialists.[9] This could potentially increase the cost of dapagliflozin treatment for population #1, but not the incremental costs, as the same applies to sacubitril valsartan.

Table 5.5: Overview of the population, intervention and comparators considered

	Population	Intervention	Comparator
Population #1	Patients not previously treated with and eligible for sacubitril valsartan (i.e. patients need to have EF ≤35% and must not have hyperkalaemia and/or hypotension).	ACEi/ARB, BB, ±MRA, dapagliflozin	ACEi/ARB, BB, ±MRA, sacubitril valsartan
Population #2	Patients not previously treated with and ineligible for sacubitril valsartan or not progressing to receiving sacubitril valsartan due to other reasons.	ACEi/ARB, BB, ±MRA, dapagliflozin	ACEi/ARB, BB, ±MRA
Population #3	Patients that were previously treated with sacubitril valsartan.	BB ±MRA, sacubitril valsartan, dapagliflozin	BB ±MRA, sacubitril valsartan

ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor blocker; BB = beta blocker; MRA = mineralocorticoid receptor antagonists

5.2.5 Perspective, time horizon and discounting

The analysis takes an NHS and Personal Social Services (PSS) perspective. Discount rates of 3.5% are applied to both costs and benefits. The model cycle length is one month with a lifetime time horizon (upon reaching an age of 100 years) and a half-cycle correction is applied.

ERG comment: The ERG agrees that the perspective, time horizon and discounting were in line with the NICE reference case.

5.2.6 Treatment effectiveness and extrapolation

The main source of evidence on treatment effectiveness used for the economic model was the DAPA-HF trial.[29] In population #1 the treatment effect of sacubitril valsartan was assumed to be equivalent to dapagliflozin.

5.2.6.1 Estimation of all-cause and CV mortality

Both all-cause and CV mortality were estimated using parametric survival models. All-cause mortality was used to estimate transitions to the death health state (CV mortality was used to calculate non-CV mortality as well as to incorporate costs related to CV deaths). Notably, the parametric survival models for all three populations were estimated based on the DAPA-HF ITT population. The use of the ITT population was justified by the company to *"maximise use of available data"*.[8] Non-CV mortality (difference between all-cause mortality and CV mortality) was calculated per model cycle and informed by UK life tables in case non-CV mortality based on DAPA-HF was lower than the non-CV mortality rate from the UK life tables (Appendix O of the CS).[30]

The company considered Weibull, log-logistic, log-normal, and Gompertz distributions for the estimation of parametric survival models.[1] The exponential and generalised gamma distributions were not considered, because constant mortality over time (exponential) was not considered plausible and to reduce the risk of overfitting within trial data (generalised gamma). The company stated that the Weibull distribution resulted in the most plausible estimates of long-term survival based on clinical expert opinion and when compared with previously published estimates.[31] Therefore, the Weibull distribution was used in the CS base-case analyses (see Figures 24 and 25 of the CS).[1] Moreover, the Akaike information criterion (AIC) and Bayesian information criterion (BIC) evaluated for the survival curves also supported the use of the Weibull distribution (see Table 35 of the CS).[1]

To add covariables to the parametric survival models, the company tested predefined candidate covariables using 1) univariate analyses to identify covariables that were likely to be predictive of CV mortality and all-cause mortality and 2) multivariable analyses based on covariables selected in step 1 using stepwise backward elimination based on AIC and P-values (Table 34 of the CS lists the selected covariables and more details regarding selection procedure and candidate variables are provided in response to clarification question B3).[1, 8]

Moreover, dapagliflozin was added as a covariable to estimate CV mortality (P=0.054) and all-cause mortality (P=0.053), implicitly assuming proportional hazards while this is not justified in the CS. For extrapolation purposes, it was assumed that the dapagliflozin treatment effect would be maintained while on treatment, i.e. no treatment waning was considered (neither was this explicitly considered in scenario analyses). Given the median follow-up time in study until last visit was 18.7 months (range 0-28 months, CSR Table 14.1.10) and the estimated life years-saved (by the economic model) for dapagliflozin were approximately six years, extensive extrapolation was required (see also Figures 26 and 27 of the CS).[1, 15]

5.2.6.2 Estimation of the transition probabilities between health states defined by KCCQ-TSS quartiles

Transition probabilities between health states defined by KCCQ-TSS quartiles were derived using monthly transition count data (using KCCQ-TSS measurements at baseline, 4, 8, 12 and 24 months) assuming last observation carried forward for imputing missing values.[1] These transition probabilities were assumed to differ for treatment with and without dapagliflozin (for populations #2 and #3) as well as for the first four months and thereafter. The four months cut-off point assumption was based on Figure 23 of the CS.[1] Additionally, for extrapolation purposes, it was assumed that the dapagliflozin treatment effect would be maintained while on treatment.

5.2.6.3 Treatment discontinuation

The probability of dapagliflozin discontinuation was estimated assuming a constant probability over time. The annual dapagliflozin discontinuation probability was estimated to be 0.07 (standard error: 0.01) for all three populations. Based on Figure 3 in the CSR, it can be derived that the [redacted][15]

5.2.6.4 Estimation of hospitalisation for heart failure and urgent heart failure visit

The incidence of hospitalisation for heart failure (hHF) and urgent heart failure visit (uHFv) events were modelled using generalised estimating equations (GEE), assuming that events are Poisson-distributed in order to capture first and recurrent hHF and uHFv events.

To add covariables to the GEE model, the company tested predefined candidate covariables using:

1. univariate analyses to identify covariables that were likely to be predictive of hHF and uHFv,
2. multivariable analyses checking the effect size of each covariable and the clinical face validity of the directionality of the effects, and
3. based on covariables selected in step 1 and using stepwise backward elimination based on QIC (quasi-likelihood under the independence model criterion) and P-values (Table 36 of the CS lists the selected covariables and more details regarding selection procedure, candidate variables and validation of estimated GEE models are provided in response to clarification question B6).[1, 8]

For uHFv only 39 events were observed within DAPA-HF and therefore the incidence of uHFv events was not adjusted by covariates (Table 37 of the CS).[1] Moreover, dapagliflozin was added as a covariable to estimate hHF ($P<0.001$) and uHFv ($P=0.006$). For extrapolation purposes, it was assumed that the dapagliflozin treatment effect would be maintained while on treatment.

ERG comment: The main concerns of the ERG relate to: a) assuming equal effectiveness between dapagliflozin + standard care (SC) and sacubitril valsartan + SC in population #1, b) the selection of the Weibull distribution to estimate survival, c) methods and d) population to calculate the transition probabilities between health states defined by KCCQ-TSS quartiles, e) extrapolating treatment effectiveness, f) estimation of treatment discontinuation over time and, g) the European subgroup of DAPA-HF being more representative to the UK setting than the overall population.

a) For population #1, equal effectiveness was assumed (i.e. a cost minimisation analysis is performed) between dapagliflozin + SC and sacubitril valsartan + SC. However, equal effectiveness has not been established. In response to clarification question B2, the company preformed this analysis while using the MAIC to inform relative treatment effectiveness (rather than assuming equal effectiveness).[8] This analysis indicated that dapagliflozin would be more effective (0.17 QALYs gained) and cheaper (£2,701 savings), thus dominant, compared with sacubitril valsartan. Comparable results were obtained when implementing the standard indirect treatment comparison (i.e. Bucher) method as well as the MAIC subgroups (see section B.2.9.1.2 of the CS).[1]

b) Based on additional clarification provided by the company in response to clarification question B3, the selection of the Weibull distribution as well as assuming proportional hazards seems reasonable based on the observed data.[8] Nevertheless, the results of validating the clinical plausibility of long-term survival (based on expert opinion of [redacted]) remains unclear.[8] It is therefore uncertain whether different distributions than the selected Weibull distributions would be preferred based on the clinical plausibility of long-term survival. It is however reassuring that scenario analyses performed reported by the company (see both CS and clarification responses) indicate that the cost effectiveness (for populations #2 and #3) is robust to the choice of survival distribution.[1, 8] This is however only fully applicable to the CS base-case. For instance, selecting a Gompertz distribution to estimate survival could have a substantial impact on the estimated ICERs for the ERG analyses. According to the CS, clinical expert opinion suggested that predictions made using the Gompertz distribution were likely to underestimate patient survival.[1] It is however unclear to the ERG how this expert opinion was exactly derived, what the exact results were and thus whether the Gompertz distributions is a plausible option or not. For the committee to assess the plausibility of extrapolated all-cause mortality using the Gompertz and Weibull distributions, the ERG provided Table 5.6. If the Gompertz distribution is adopted, this could substantially increase the estimated ICERs.

c) Additional information regarding the methods to calculate the transition probabilities between health states defined by KCCQ-TSS quartiles was provided in response to clarification question B4.[8] Moreover, the impact of the four months cut-off point assumption as well as using last observation carried forward for imputing missing values were explored. These analyses indicate that the cost effectiveness (for populations #2 and #3) is robust to the methods used to calculate the transition probabilities between health states defined by KCCQ-TSS quartiles, even when assuming these transition probabilities are treatment independent.

d) Transition probabilities between KCCQ-TSS quartile health states were derived based on the ITT population (rather than the relevant subset of patients for populations #1, #2 and #3). This was justified (clarification response B5) by indicating that the company preferred to use all available data.[8] In addition, it is reassuring that the probabilities between KCCQ-TSS quartile health states do not have a substantial impact on the cost-effectiveness (for populations #2 and #3), see also previous comment.

e) For extrapolating treatment effectiveness, the company assumed that the dapagliflozin treatment effect would be maintained while on treatment. In response to clarification question B7, the company explored the impact of treatment waning through restricted dapagliflozin treatment to three years (the maximum follow-up in the DAPA-HF trial was 28 months according to CSR Table 14.3.1.1) representing complete waning of the treatment effect after this time point.8, 15 These analyses resulted in ICERs of ~£6,200 per QALY gained (for populations #2 and #3) indicating the cost effectiveness (for population #2 and #3) is robust to treatment waning assumptions.

f) Treatment discontinuation was incorporated assuming an exponential distribution (resulting in time independent probabilities). The response to clarification question B8 clarified that this simplifying assumption was made as there was little evidence of time dependency in the data.[8] Moreover, it was shown (Table 24 of the response to request for clarification) that the cost effectiveness (for population #2 and #3) is robust to different (time dependent) treatment discontinuation approaches.[8]

g) Table 10 of the CS shows that there are slight differences between the European subgroup and the overall population of the DAPA-HF trial.[1] Furthermore, in Figure 11 of the CS the treatment effect of dapagliflozin [redacted] in the European subgroup compared to other geographic regions.[1] The ERG therefore considered the European subgroup to be more representative to the UK setting than the overall population (see also section 4.2.1 for more details) and adopted relative effectiveness based on the European subgroup in its base-case. Because the DAPA-HF was originally not powered to find a treatment effect in the European sub-population, the ERG acknowledges that these effect estimates might be accompanied with higher statistical uncertainty compared to the full DAPA-HF population.

Table 5.6: Estimated survival (all-cause mortality as applied in the CS base-case)

Time (months)	Weibull (CS base-case)		Gompertz (CS scenario)	
	Dapagliflozin	SC	Dapagliflozin	SC
Population #1				
0	100.0%	100.0%	100.0%	100.0%
12	92.8%	91.4%	92.8%	91.4%
24	84.5%	81.6%	84.4%	81.5%
36	76.2%	72.1%	74.9%	70.6%
60	60.9%	55.0%	53.0%	46.5%
120	32.6%	25.9%	6.6%	3.7%
180	16.4%	11.3%	0.0%	0.0%
240	7.9%	4.7%	0.0%	0.0%
Population #2				
0	100.0%	100.0%	100.0%	100.0%
12	92.7%	91.3%	92.6%	91.3%
24	84.4%	81.6%	84.3%	81.6%
36	76.2%	72.2%	74.9%	71.0%
60	61.1%	55.5%	54.0%	48.2%
120	33.2%	26.8%	8.9%	5.6%
180	17.1%	12.1%	0.0%	0.0%
240	8.5%	5.2%	0.0%	0.0%
Population #3				
0	100.0%	100.0%	100.0%	100.0%
12	94.9%	92.8%	94.8%	92.8%
24	86.2%	81.1%	85.9%	80.8%
36	76.1%	68.0%	71.5%	62.3%

Time (months)	Weibull (CS base-case)		Gompertz (CS scenario)	
	Dapagliflozin	SC	Dapagliflozin	SC
60	55.6%	43.7%	26.7%	15.6%
120	19.1%	9.6%	0.0%	0.0%
180	4.8%	1.4%	0.0%	0.0%
240	0.9%	0.1%	0.0%	0.0%
CS = company submission				

5.2.7 Adverse events

The company included the most common serious AEs reported in the DAPA-HF trial (CS Table 38) in the economic model. AE incidences of genital infection and urinary tract infection were not routinely collected in the DAPA-HF trial and were therefore based on dapagliflozin and placebo arms of the cardiovascular outcomes trial of dapagliflozin in T2DM patients (DECLARE) [32]. Patients who discontinued dapagliflozin were subject to the risk of AE associated with the placebo arm of DAPA-HF.

AE was assumed to impact costs and quality of life in the economic model (no impact on mortality was assumed).

ERG comment: The company clarified in response to clarification questions B10 and B11 how the adverse events were selected as well as why the association between AE and mortality was not incorporated. This was considered reasonable by the ERG.

5.2.8 Health-related quality of life

5.2.8.1 Health-related quality of life data identified in the review

An SLR was conducted to identify studies reporting on preference-based health state utility values (HSUVs) associated with HF. In total, there were ten studies that fully met the NICE requirements.[33-42] For the base-case analysis, the company has used utility and disutility values derived from the DAPA-HF study. These were considered, according the company, the most robust and applicable source of utility data for this population.

5.2.8.2 Health state utility values and disutilities

To estimate patient reported utility values derived from EQ-5D-5L questionnaires, linear mixed effects regression models were fitted using DAPA-HF clinical trial data collected at randomisation, day 120, day 240, day 360, and every 12 months thereafter (the maximum follow-up in the DAPA-HF trial was 28 months according to CSR Table 14.3.1.1).[15] The mixed-models adjusted for time from baseline, gender, KCCQ-TSS quartile, T2DM at baseline, body mass index, and age. EQ-5D-5L responses were mapped to EQ-5D-3L responses, according to a mapping function developed by van Hout et al.[43] These responses were converted to utility index scores using published UK utility values for EQ-5D health states, using the time trade-off method described in Dolan.[44] The utility model used to inform health state utilities and utility decrements associated with clinical events are presented in Table 5.7.

Table 5.7: Health state and adverse events utility values

State and adverse events	Utility value (SE)	Reference	Justification
KCCQ-TSS: 1 to <58	0.600 (0.016)	DAPA-HF	

State and adverse events	Utility value (SE)	Reference	Justification
KCCQ-TSS: 58 to <77	0.705 (0.016)	DAPA-HF	
KCCQ-TSS: 77 to <92	0.773 (0.016)	DAPA-HF	
KCCQ-TSS: 92 to 100	0.833 (0.016)	DAPA-HF	
T2DM (decrement)	0.017 (0.003)	DAPA-HF	
hHF (decrement)	0.321 (0.020)	DAPA-HF	
uHFv (decrement)	0.036 (0.011)	DAPA-HF	
Volume depletion (decrement)	0.051 (0.012)	DAPA-HF	
Renal events (decrement)	0.076 (0.014)	DAPA-HF	
Hypoglycaemic events (decrement)	0.014 (0.001)	Currie et al.[45] (symptomatic hypoglycaemic event), identified systematically by Beaudet et al.[46].	No other utility values identified.
Fractures (decrement)	0.149 (0.033)	DAPA-HF	
DKA (decrement)	0.000 (0.000)		Assumed; no evidence identified
Amputation (decrement)	0.280 (0.053)	UKPDS 62 [47]	Identified systematically by Beaudet et al.[46]. No other utility values identified.
UTI (decrement)	0.003 (0.001)	Barry et al. [48]	As per previous NICE appraisals of dapagliflozin in T2DM and T1DM
Genital infection (decrement)	0.003 (0.001)	Barry et al. [48]	As per previous NICE appraisals of dapagliflozin in T2DM and T1DM

Based on Table 40 of the CS[1]

DKA = diabetic ketoacidosis; hHF = hospitalisation for heart failure; KCCQ-TSS = Kansas City Cardiomyopathy Questionnaire – Total Symptom Score; NICE = National Institute for Health and Care Excellence; SE = standard error; T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus; uHFv = urgent heart failure visit; UTI = urinary tract infection

ERG comment: The main concern of the ERG relates to the relatively high utility values for patients with HFrEF. Specifically, the utility values associated with KCCQ TSS Q4: 92 to 100 and Q3 77 to <92 in the economic model (0.833 and 0.773, respectively) appear to be relatively high for patients with HFrEF when considering the general population utility (see for instance supplemental data provided by Sullivan et al. indicating a mean utility of 0.774 for people aged 60-69 years).[49] The company stated that the utility values are comparable to previous estimates of quality of life in patients with HFrEF for the cost effectiveness evaluation of sacubitril valsartan.[50] In additional sensitivity analyses, using a

lower utility value based on the population estimates from Sullivan et al., showed that the cost effectiveness conclusions were not substantially impacted by the lower health state utilities.[51]

5.2.9 Resources and costs

The cost categories included in the model were treatment costs, health state costs and costs related to adverse events.

All costs applied in the model were inflated to a 2018/19 cost-year, based on the Hospital and Community Health Services (HCHS) pay and price inflation index (up to and including 2016/17) and the NHS Cost Inflation Index (NHSCII, from 2015/2016 onwards), as reported in the relevant Personal Social Services Research Unit (PSSRU) publications (Unit Costs of Health and Social Care).[52]

5.2.9.1 Resource use and costs data identified in the review

According to the CS, the SLR identified 14 publications[31, 53-65] reporting on 13 unique studies (two abstracts reported on a single clinical-linkage database study[57, 60] that reported costs and/or resource use in the management of HF in the UK). One study identified in the SLR by McMurray et al. was used to inform the costs for HF management.[34]

5.2.9.2 Treatment costs

The annual treatment costs are shown in Table 5.8. Calculation of costs of beta blockers and diuretics prescription was based on recommended doses and included in the annual health state costs. Costs of treatment administration and titration were assumed to be captured in background health state costs. For dapagliflozin additional costs (£476.98 annually) related to dapagliflozin treatment are added (see also response to clarification question B13 for additional details).[8]

Table 5.8: Treatment acquisition costs

Drug class	Source	Weighted average annual cost	Proportion of patients on therapies in base-case analyses		
			#1	#2	#3
ACEi	eMIT for costs; assumption for market share	£6.89	56%	56%	56%
ARB	eMIT for costs; assumption for market share	£36.27	28%	28%	28%
MRA	eMIT for costs; assumption for market share	£39.56	71%	71%	71%
Sacubitril valsartan	MIMS for costs	£1,193.55	100%	0%	11%

Based on Tables 41 and 42, and Appendix N of the CS as well as the economic model.[1, 66]
ACEi = angiotensin-converting enzyme inhibitor, ARB = angiotensin II receptor blocker; CS = company submission; eMIT = Electronic Marketing Information Tool; MRA = mineralocorticoid receptor antagonists

5.2.9.3 Health state/events costs

Annual health state costs associated with HF were sourced from McMurray et al. to capture general practitioner (GP) visits, accident and emergency (A&E) referrals, cardiologist outpatient visits and other outpatient visits.[16] Background health state costs in the model were constant across the KCCQ-TSS quartile health states, and increased costs resulting from worsening disease severity were captured

by increasing hHF incidence. Inpatient (£459) and outpatient (£532) costs associated with T2DM were based on a study of Alva et al., and the sum of the average in and outpatient costs was used to calculate total direct cost of T2DM, see Table 5.9.[67]

Table 5.9: Health state related costs

Health state/event	Mean annual cost	Reference
Background HF management, including cost of beta-blockers and diuretics	£932.75	McMurray et al.; assume all patients to take recommended doses of bisoprolol (beta-blocker) and furosemide (diuretic), unit costs from eMIT 2019[16]
T2DM	£1,090.56	Alva et al.; uplifted to 2018/19[67]
hHF	£2,831.72	NHS Reference Costs 2017/18; weighted by finished consultant episode (EB03A-E, heart failure or shock, non-elective long stay)[68]
uHFv	£401.62	NHS Reference Costs 2017/18; weighted by finished consultant episode (EB03A-E, heart failure or shock, day case)[68]
CV death	£1,673.80	Alva et al., cost of fatal myocardial infarction (conservatively selected; MI was the lowest cost fatal CV event reported); uplifted to 2018/19[67]
Based on Table 43 of the CS[1] CS = company submission; CV = cardiovascular; eMIT = Electronic Marketing Information Tool; HF = heart failure; hHF = hospitalisation for heart failure; NHS = National Health Service; T2DM = type 2 diabetes mellitus; uHFv = urgent heart failure visit		

5.2.9.4 Adverse event related costs

Costs related to AEs captured in the economic model are summarised in Table 5.10.

Table 5.10: Adverse event related costs

Adverse event	Mean per event costs	Reference
Volume depletion	£39.00	PSSRU 2019, assume one GP visit[52]
Renal events	£1,865.01	NHS National Reference Costs 2017/18; total HRG, weighted average of LA07 unit costs[68]
Hypoglycaemic events	£453.70	Hammer et al. 2009; severe hypoglycaemic events, €537, conversion to Euros at rate of 1.473 (Hammer et al. 2009), uplifted from 2007 cost year to 2018/19[69]
Fractures	£2,428.76	NHS National Reference Costs 2017/18; total HRG, weighted average of HE11, HE21, HE41, HE31, HE51 and HE71
Diabetic ketoacidosis	£2,208.80	Dhatariya et al 2017; £2,064 in 2014, uplifted to 2018/19 cost year[70]

Adverse event	Mean per event costs	Reference
Amputation	£13,475.12	Alva et al. 2015; inpatient care cost and outpatient care cost, uplifted to 2018/19 cost year[67]
Genital infection	£39.00	PSSRU 2019, assume one GP visit[52]
Urinary tract infection	£39.00	PSSRU 2019, assume one GP visit[52]
Based on Table 44 of the CS[1] CS = company submission; GP = general practitioner; HRG = Healthcare Resource Group; NHS = National Health Service; PSSRU = Personal Social Services Research Unit		

ERG comment: The main concerns of the ERG relate to a) not incorporating costs related to death due to other (non-CV related) causes and b) the costs of standard care for population #3.

a) Costs related to CV deaths were incorporated while costs related to non-CV related deaths were not. In response to clarification question B16, the company provided an additional scenario analyses, assuming that the costs were assumed equivalent to that of CV death.[8] These analyses seemed to illustrate that the cost effectiveness (for populations #2 and #3) is robust to the inclusion of costs associated with non-CV death.

b) According to Figure 3 of the CS, it would have been expected that the proportion of patients receiving ACEi (or ARB) for population #3 would be lower than for populations #1 and #2 as it is stated in Figure 3 of the CS that ACEi (or ARB) is replaced by sacubitril valsartan if ejection fraction <35%.[1] The impact of this apparent inconsistency based on the incremental results is however likely negligible given the annual costs of ACEi and ARB are estimated to be £15 and are applied to both strategies (given dapagliflozin is an add-on treatment).

6. Cost effectiveness results

6.1 Company's cost effectiveness results

The company conducted analyses to evaluate the cost effectiveness of dapagliflozin in three populations as also described in sections 5.2.3 and 5.2.4. A cost minimisation analysis was performed to compare dapagliflozin as an add-on therapy to ACEi/ARB, BB ±MRA with sacubitril valsartan (added to ACEi/ARB, BB ±MRA) for patients not previously treated with sacubitril valsartan (population #1). In this analysis dapagliflozin had lower costs compared to sacubitril (-£3,131) over a lifetime time horizon, see Table 6.1.

Table 6.1: Population #1 deterministic results

	Dapagliflozin + SC (intervention)	Sacubitril valsartan + SC (comparator)	Incremental	ICER (£/QALY)
Life years	6.214	6.214	0.000	Dominant
QALYs	4.627	4.627	0.000	
Costs (£)	£14,514	£17,645	-£3,131	

Based on Table 46 of CS[1]
CS = company submission; ICER = incremental cost effectiveness ratio; LYG = life years gained; QALYs = quality-adjusted life years, SC = standard care

Dapagliflozin, as an add-on therapy to ACEi/ARB, BB ±MRA was compared to ACEi/ARB, BB ±MRA without sacubitril valsartan for patients not previously treated with sacubitril valsartan (population #2). In this cost effectiveness analysis, the ICER was £5,830 per QALY gained (Table 6.2), with estimated incremental QALY gains and incremental costs of 0.472 and £2,750, respectively.

Table 6.2: Population #2 deterministic results

	Dapagliflozin + SC (intervention)	Placebo + SC (comparator)	Incremental	ICER (£/QALY)
Life years	6.184	5.609	0.575	£5,830
QALYs	4.597	4.125	0.472	
Costs (£)	£14,976	£12,226	£2,750	

Based on Table 47 of CS[1]
CS = company submission; ICER = incremental cost effectiveness ratio; LYG = life years gained; QALYs = quality-adjusted life years, SC = standard care

Dapagliflozin, as an add-on therapy to sacubitril valsartan, BB ±MRA, was compared, to sacubitril valsartan, BB ±MRA for patients previously treated with sacubitril valsartan (population #3). In this cost effectiveness analysis, the ICER was £5,866 per QALY gained (Table 6.3), with estimated incremental QALY gains and incremental costs of 0.461 and £2,707, respectively.

Table 6.3: Population #3 deterministic results

	Dapagliflozin + SC (intervention)	Placebo + SC (comparator)	Incremental	ICER (£/QALY)
Life years	5.990	5.428	0.563	£5,866
QALYs	4.444	3.983	0.461	
Costs (£)	£15,620	£12,913	£2,707	

Based on Table 47 of CS[1]

	Dapagliflozin + SC (intervention)	Placebo + SC (comparator)	Incremental	ICER (£/QALY)
CS = company submission; ICER = incremental cost effectiveness ratio; LYG = life years gained; QALYs = quality-adjusted life years, SC = standard care				

6.1.1 Probabilistic sensitivity analysis

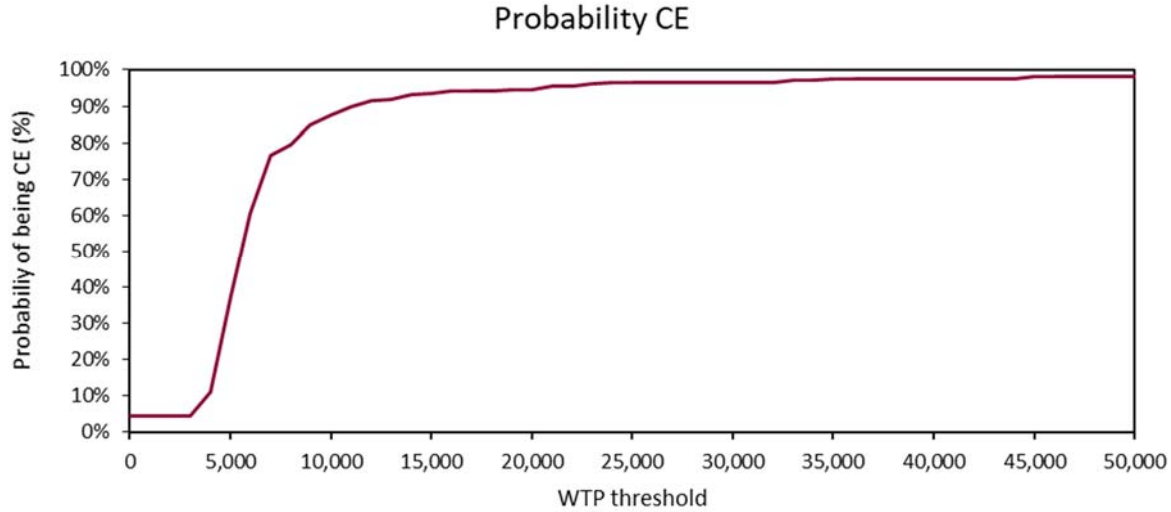
The company stated that no PSA was conducted for population #1, because this was a cost minimisation analysis. For populations #2 and #3 200 PSA iterations were run in order to obtain stable estimates of the mean model results (200 PSA iterations appears sufficient based on the ICER convergence plots, see Figures 30 and 33 of the CS).[1]

The probabilistic ICER per QALY gained for population #2 was £5,701 (Table 6.4). The probability of cost effectiveness was 94.5% and 96.5% assuming cost effectiveness thresholds of £20,000 and £30,000 per QALY, respectively (Figure 6.1). The incremental QALYs and costs of dapagliflozin versus SC were 0.484 QALYs and £2,760, compared with 0.472 QALYs and £2,750 in the deterministic analysis.

Table 6.4: Population #2 probabilistic results

	Dapagliflozin + SC (total)	Placebo + SC (total)	Incremental	ICER (£/QALY)
Life years	6.061	5.468	0.593	£5,701
QALYs	4.506	4.022	0.484	
Costs (£)	£14,671	£11,911	£2,760	
Based on Table 49 of CS[1] CS = company submission; ICER = incremental cost effectiveness ratio; LYG = life years gained; QALYs = quality-adjusted life years, SC = standard care				

Figure 6.1: Cost effectiveness acceptability curve – population #2



Based on Figure 29 of CS
CE = cost effective; CS = company submission; WTP = willingness to pay

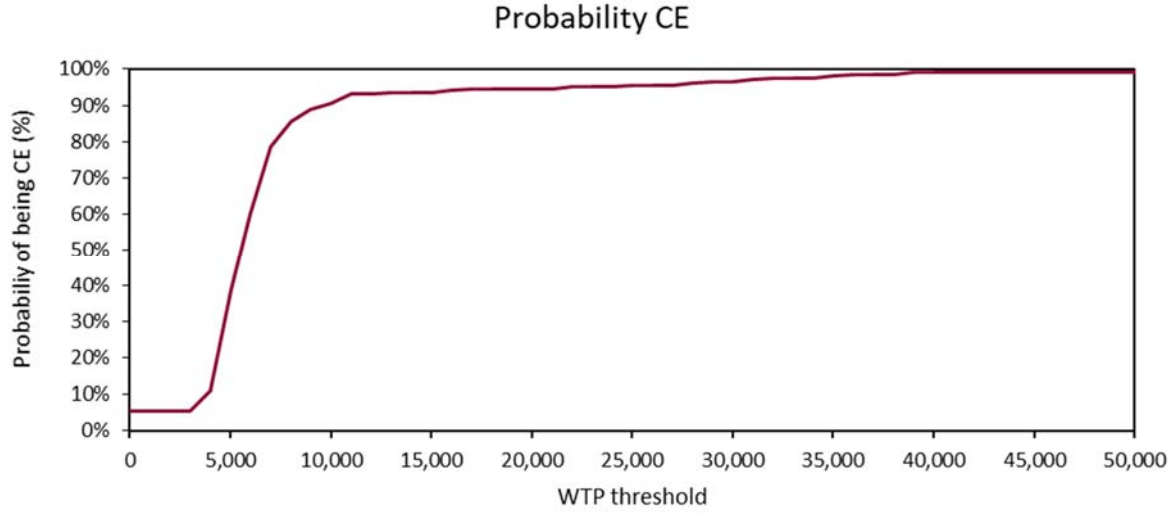
The ICER per QALY gained in population #3 was £5,757 (Table 6.5). The probability of cost effectiveness was 94.5% and 96.5% assuming cost effectiveness thresholds of £20,000 and £30,000 per QALY respectively (Figure 6.2). The incremental QALYs and costs of dapagliflozin versus SC were 0.472 QALYs and £2,718, compared with 0.461 QALYs and £2,707 in the deterministic base-case.

Table 6.5: Population #3 probabilistic results

	Dapagliflozin + SC (total)	Placebo + SC (total)	Incremental	ICER (£/QALY)
Life years	5.852	5.274	0.578	£5,757
QALYs	4.343	3.871	0.472	
Costs (£)	£15,235	£12,518	£2,718	

Based on Table 50 of CS[1]
CS = company submission; ICER = incremental cost effectiveness ratio; LYG = life years gained; QALYs = quality-adjusted life years, SC = standard care

Figure 6.2: Cost effectiveness acceptability curve – population #3



Based on Figure 32 of CS[1]
CE = cost effective; CS = company submission; WTP = willingness to pay

6.2 Company's sensitivity analyses

The company performed various sensitivity and scenario analyses. In the deterministic sensitivity analyses for population #1, a reduction in cost discounting to 0% (from 3.5% in the base-case), resulted in the largest reduction of incremental costs to -£3,574, whereas a reduction in time horizon to 10 years (from life-time in the base-case), and a cost discounting of 6.% resulted in the largest increase of the incremental costs (reducing the cost savings associated with dapagliflozin) to a maximum of -£2,878.

In the deterministic sensitivity analyses for population #2 and #3, a change of the discounting factor for benefits to 0%, and an increase of the health state utilities by 20% resulted in the largest reduction of the ICER to a minimum ICER per QALY gained of £4,379 (population #2) and £4,447 (population #3), whereas a decrease of health state utility values by 20%, and a change of the discounting factor for costs to 0% resulted in the largest increase of the ICER to a maximum ICER per QALY gained of £7,267 (population #2) and £7,311 (population #3).

The scenario analysis resulting in the largest increase in estimated ICER was using a Gompertz distribution (to estimate mortality) for population #2 and #3 (estimated ICERs £7,264 and £7,162 per QALY gained, respectively). No scenario analyses were listed in CS Table 56 for population #1.

ERG comment: The main concerns of the ERG relate to a) the lack of PSA analyses for population #1 and b) the lack of one-way sensitivity analyses for all parameters that are implemented stochastically in the PSA.

a) The sensitivity analyses performed by the company are not consistent with the NICE reference case, because no PSA analyses were performed for population #1. The company argued that the only determinant of differences in results for each treatment arm is the drug acquisition costs associated with each treatment strategy which is not sampled in PSA. Therefore, the company argued that a PSA would not be relevant. However, the ERG disagrees given that resource use as well as effectiveness and health state utility parameters (although identical for both treatments in the CS base-case for population #1) are stochastic parameters that would impact absolute outcomes and hereby potentially also impact incremental outcomes (despite the equal effectiveness assumption).

b) The company did not perform one-way sensitivity analyses (as requested in clarification question B20) for all parameters that are implemented probabilistically in the PSA, limiting the ability to identify impactful parameters

6.3 Model validation and face validity check

6.3.1 Face validity

Description of face validity was limited. The company stated that *"validation of the model was carried out through clinical expert input throughout the development and validation process of the model"*.[1]

6.3.2 Internal validity

Technical verification of the programmed model, i.e. whether the model is implemented correctly and accurately represents the conceptual model, was not explicitly discussed in the CS.[1]

6.3.3 Cross validity

Cross validity was not explicitly discussed in the CS. Although Table 30 of the CS provides an overview of features of the economic analyses compared with TA388 and TA267, this does not provide detailed information regarding model inputs, (intermediate) model outcomes or assumptions.[1, 7, 71]

6.3.4 External validity

The company provided an external validation comparing model predictions to data that were used to build the economic model. According to the company, the model produced results which closely aligned with trial outcomes, with treatment specific survival outcomes corresponding to trial outcomes.[1] Validation plots of all-cause mortality, CV mortality, and hHF event incidence are shown in Figures 37 to 39 of the CS.[1]

ERG comment: The ERG considered the a) internal validity, b) face validity, c) cross-validity as well as d) external validity of the economic model:

a) Internal validity: the ERG noted that in the economic model people are unable to discontinue dapagliflozin treatment during the first cycle in the company model, i.e. all people alive in the second model cycle are on dapagliflozin treatment. The company acknowledged this (response to clarification response B8) and stated that the impact of this is negligible.[8] Besides this, the ERG was able to reproduce the trace and QALY calculation and the company's assessment using the TECH-VER (TECHnical VERification) checklist (clarification response B22) also seems to support the internal validity of the economic model.[8, 72] There is however a small discrepancy

between the results produced by the model initial submitted by the company (v0.1) and the model submitted after the clarification phase (v0.3). The ERG was only able to replicate the CS base-case results with v0.1. The v0.3 version of the model, used in the ERG analyses (as it contained more options for scenario analyses), produced slightly different ICERs than reported in the CS (differences in ICER based on a selected number of comparisons were <£100, see Table 7.1).[1] In response to the request for clarification (question B8), the company explained that this is due to the assumption of a constant rate of drug discontinuation in the updated model compared to the assumption of a constant probability of drug discontinuation in the original model.[8]

b) Face validity: according to clarification response B22, the cost effectiveness model was developed in collaboration with clinical experts, who provided expert guidance on the appropriateness of the proposed model structure and subsequently in the development of multivariable risk equations describing the incidence of all-cause mortality, CV-specific mortality and hHF event incidence and final model results and intermediate outcomes.[8] No details are provided regarding exact methods used and results produced for the face validity assessment, making it challenging for the ERG to confirm the face validity.

c) Cross-validation: based on the company's response to clarification question B22, estimated LYs, QALYs and costs for population #2 control arm are in line with TA388 (which had slightly higher estimates) and TA267 (which had slightly lower estimates).[7, 8, 71] The company only reported TA388 outcomes and costs for ACEi (Table 34 of response to request for clarification) while sacubitril valsartan results from TA388 might have been informative for the cross-validation of the population #1 results.[7, 8] Here the differences are more pronounced with estimated costs for sacubitril valsartan of £20,734 (TA388) and £17,645 (current TA).[1, 7] The reason and thus the potential impact of this discrepancy are unclear to the ERG.

   Drug costs per month for BSC, excluding sacubitril valsartan, were slightly lower than in TA267 (£4 vs £10 per month) while the background HF management costs are higher compared with TA267 (£78 vs £27 per month).[71] It should be noticed that, consistent with clarification response B14, lower drug costs would favour dapagliflozin and the cost effectiveness results seemed robust to changes in background HF management costs.[8]

   KCCQ-TSS quartiles were used compared to NYHA classes in TA267 to incorporate the impact of disease severity on health state utility values. The utility value for the fittest patients were comparably high (0.833 versus 0.823 in TA267).[71] However, utility values of the other three KCCQ-TSS quartiles were generally higher than utility values in NYHA classes 2-4 in TA267.[71] Moreover, it should be noted that the estimated health state utilities are relatively high when compared with general population utilities (for similar age categories), see also section 5.2.8.

d) External validity: based on CS section B.3.10 and clarification response B22, the observed (DAPA-HF) and predicted outcomes seem to be consistent and the differences do not seem to be main drivers of cost effectiveness.[1, 8]

7. Evidence Review Group's additional analyses

7.1 Exploratory and sensitivity analyses undertaken by the ERG

Based on all considerations in section 5.2, the ERG defined a new base-case. This base-case included multiple adjustments to the original base-case presented in the previous sections. These adjustments made by the ERG form the ERG base-case and were subdivided into three categories (derived from Kaltenthaler 2016 [73]):

- Fixing errors (correcting the model where the company's submitted model was unequivocally wrong)
- Fixing violations (correcting the model where the ERG considered that the NICE reference case, scope, or best practice had not been adhered to)
- Matters of judgement (amending the model where the ERG considers that reasonable alternative assumptions are preferred)

7.1.1 Fixing errors

After reproducing the results for populations #2 and #3, the only error that was identified was the inability to discontinue treatment during the first cycle. However, given the complexity of the model (making it difficult/resource intensive to correct) and the likely negligible impact of this error on the results (see clarification response B8.b and B8.c) this was not adjusted by the ERG.[8]

7.1.2 Fixing violations

1. The health state utilities for KCCQ TSS Q4: 92 to 100 and Q3 77 to <92 (0.833 and 0.773 respectively) appear to be relatively high for patients with HFrEF, especially when considering the general population utility of people aged 65 years and above (section 5.2.8).

   The ERG adopted the scenario provided by the company, using general population health state utilities for KCCQ TSS Q4: 92-100 and applying relative differences to obtain health state utilities for the health states KCCQ TSS Q1-Q3 (Q4=0.774, Q3=0.714, Q2=0.646, Q1=0.541).

2. The cost minimisation analyses, assuming equal effectiveness for population #1, was not considered appropriate by the ERG (section 5.2.6).

   The ERG informed the relative treatment effectiveness for dapagliflozin versus sacubitril valsartan using an indirect treatment comparison (Bucher method, see section 4.4).

7.1.3 Matters of judgment

3. The DAPA-HF European subgroup (see Table 10 of the CS for baseline characteristics versus the overall population) was considered more representative to the UK setting than the overall population (section 5.2.3).[1]

   The ERG adopted the relative effectiveness as estimated based on the European subgroup (only implemented by the company for populations #2 and #3).

Table 7.1 shows how individual adjustments impact the results plus the combined effect of all abovementioned adjustments simultaneously (if applicable), resulting in the ERG base-case.

7.2 Impact on the ICER of additional clinical and economic analyses undertaken by the ERG

In section 7.1 the ERG preferred assumptions were presented, which was based on various changes compared to the company base-case. Table 7.1 shows how individual changes impact the results plus

the combined effect of all changes simultaneously while Table 7.2 provides the probabilistic ERG base-case results. The exploratory scenario analyses are presented in Tables 7.3 (deterministic) and 7.4 (probabilistic). These exploratory scenario analyses are all conditional on the ERG base-case. For the probabilistic ERG base-case analyses (Table 7.2) and the probabilistic ERG worst-case scenario analyses (Table 7.4), 200 PSA iterations were run. The ERG analyses were performed based on model version 0.3 (received after the clarification phase).

Table 7.1: Deterministic ERG base-cases

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
Population #1					
CS base-case					
Dapagliflozin + SC	£14,514	4.627			
Sacubitril valsartan + SC	£17,645	4.627	-£3,131	0.000	Dominant
CS base-case reproduced by the ERG using model v0.3					
Dapagliflozin + SC	£14,496	4.626			
Sacubitril valsartan + SC	£17,623	4.626	-£3,127	0.000	Dominant
CS base-case (model v0.3) + adjusted health state utility values					
Dapagliflozin + SC	£14,496	4.262			
Sacubitril valsartan + SC	£17,623	4.262	-£3,127	0.000	Dominant
CS base-case (model v0.3) + indirect treatment comparison (Bucher method)					
Dapagliflozin + SC	£14,496	4.626			
Sacubitril valsartan + SC	£17,167	4.496	-£2,671	0.130	Dominant
ERG base-case					
Dapagliflozin + SC	£14,496	4.262			
Sacubitril valsartan + SC	£17,167	4.142	-£2,671	0.120	Dominant
Population #2					
CS base-case					
Dapagliflozin + SC	£14,976	4.597			
SC	£12,226	4.125	£2,750	0.472	£5,830
CS base-case reproduced by the ERG using model v0.3					
Dapagliflozin + SC	£14,958	4.596			
SC	£12,209	4.125	£2,749	0.471	£5,835

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
CS base-case (model v0.3) + adjusted health state utility values					
Dapagliflozin + SC	£14,958	4.234			
SC	£12,209	3.797	£2,749	0.438	£6,284
CS base-case (model v0.3) + European subgroup effectiveness					
Dapagliflozin + SC	£15,179	4.582			
SC	£12,974	4.453	£2,205	0.129	£17,087
ERG base-case					
Dapagliflozin + SC	£15,179	4.217			
SC	£12,974	4.095	£2,205	0.122	£18,018
Population #3					
CS base-case					
Dapagliflozin + SC	£15,620	4.444			
SC	£12,913	3.983	£2,707	0.461	£5,866
CS base-case reproduced by the ERG using model v0.3					
Dapagliflozin + SC	£15,601	4.444			
SC	£12,895	3.983	£2,706	0.461	£5,872
CS base-case (model v0.3) + adjusted health state utility values					
Dapagliflozin + SC	£15,601	4.093			
SC	£12,895	3.665	£2,706	0.428	£6,324
CS base-case (model v0.3) + European subgroup effectiveness					
Dapagliflozin + SC	£15,998	4.582			
SC	£13,777	4.453	£2,220	0.129	£17,203
ERG base-case					
Dapagliflozin + SC	£15,998	4.217			

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
SC	£13,777	4.095	£2,220	0.122	£18,140
CS = company submission; ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio; QALY = quality-adjusted life year; SC = standard care					

Table 7.2: Probabilistic ERG base-cases

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
Population #1					
ERG base-case					
Dapagliflozin + SC	£13,928	4.086			
Sacubitril valsartan + SC	£16,470	3.961	-£2,543	0.125	Dominant
Population #2					
ERG base-case					
Dapagliflozin + SC	£14,639	4.051			
SC	£12,507	3.933	£2,132	0.118	£18,037
Population #3					
ERG base-case					
Dapagliflozin + SC	£15,425	4.051			
SC	£13,278	3.933	£2,147	0.118	£18,159
CS = company submission; ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio; QALY = quality-adjusted life year; SC = standard care					

7.3 ERG's preferred assumptions

The ERG has incorporated various adjustments to the company base-cases. This resulted in ERG base-cases in which dapagliflozin remained dominant for population #1 while for populations #2 and #3 the estimated (probabilistic) ICERs increased to £18,037 and £18,159 per QALY gained, respectively. The most influential ERG adjustment was the use of the European subgroup relative effectiveness. The ERG performed exploratory scenario analyses using treatment independent transition probabilities between KCCQ-TSS health states (given the uncertainty related to the estimation of these probabilities) as well as assuming complete waning of the dapagliflozin treatment effect after three years (the maximum follow-up in the DAPA-HF trial was 28 months according to CSR Table 14.3.1.1), both increasing the estimated ICERs for populations #2 and #3.[15] When combined, these exploratory scenario analyses resulted in a worst-case scenario with (probabilistic) ICERs of £34,858 and £35,048 per QALY gained for populations #2 and #3 respectively. For population #1, dapagliflozin remained dominant.

At a £20,000 per QALY threshold, the probability that dapagliflozin is cost effective in the ERG base-cases is 100%, 88%, and 88% for population #1, #2 and #3 respectively while this is 100%, 96%, and 96% for a £30,000 per QALY threshold. For the worst-case scenarios this is 97%, 13%, and 13% (£20,000 per QALY threshold) and 94%, 49%, and 48% (£30,000 per QALY threshold), respectively.

7.3.1 Additional exploratory analyses performed based on the ERG base-case

Additional sensitivity analyses were performed to examine the potential impact of alternative assumptions on the cost effectiveness estimates. These were all performed conditional on the ERG base-case. Results are presented in Tables 7.3 and 7.4.

Exploratory analyses conditional on the ERG base-case:

1. Assuming the transition probabilities between health states defined by KCCQ-TSS quartiles are treatment independent (given the uncertainty related to the estimation of these probabilities, see response to clarification question B4).[8]
2. Assuming complete waning of the dapagliflozin treatment effect after three years (the maximum follow-up in the DAPA-HF trial) through assuming all patients would stop dapagliflozin treatment after three years.
3. Combination of exploratory analyses 1 and 2, representing a 'worst-case' scenario.

Table 7.3: Deterministic scenario analyses conditional on ERG base-case

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
Population #1					
ERG base-case					
Dapagliflozin + SC	£14,496	4.262			
Sacubitril valsartan + SC	£17,167	4.142	-£2,671	0.120	Dominant
ERG base-case + assuming treatment independent transition probabilities between KCCQ-TSS health states					
Dapagliflozin + SC	£14,561	4.312			
Sacubitril valsartan + SC	£17,235	4.194	-£2,674	0.118	Dominant
ERG base-case + assuming complete waning of the dapagliflozin treatment effect after 3 years					
Dapagliflozin + SC	£13,190	4.033			
Sacubitril valsartan + SC	£14,709	3.983	-£1,519	0.049	Dominant
ERG worst-case scenario					
Dapagliflozin + SC	£13,342	4.147			
Sacubitril valsartan + SC	£14,859	4.096	-£1,517	0.051	Dominant
Population #2					
ERG base-case					
Dapagliflozin + SC	£15,179	4.217			
SC	£12,974	4.095	£2,205	0.122	£18,018
ERG base-case + assuming treatment independent transition probabilities between KCCQ-TSS health states					
Dapagliflozin + SC	£15,179	4.232			
SC	£12,974	4.153	£2,205	0.079	£27,834
ERG base-case + assuming complete waning of the dapagliflozin treatment effect after 3 years					
Dapagliflozin + SC	£14,141	4.159			
SC	£12,974	4.095	£1,167	0.064	£18,219

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
ERG worst-case scenario					
Dapagliflozin + SC	£14,141	4.193			
SC	£12,974	4.153	£1,167	0.040	£29,280
Population #3					
ERG base-case					
Dapagliflozin + SC	£15,998	4.217			
SC	£13,777	4.095	£2,220	0.122	£18,140
ERG base-case + assuming treatment independent transition probabilities between KCCQ-TSS health states					
Dapagliflozin + SC	£15,998	4.232			
SC	£13,777	4.153	£2,220	0.079	£28,023
ERG base-case + assuming complete waning of the dapagliflozin treatment effect after 3 years					
Dapagliflozin + SC	£14,952	4.159			
SC	£13,777	4.095	£1,174	0.064	£18,337
ERG worst-case scenario					
Dapagliflozin + SC	£14,952	4.193			
SC	£13,777	4.153	£1,174	0.040	£29,469

CS = company submission; ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio; KCCQ-TSS = Kansas City Cardiomyopathy Questionnaire – Total Symptom Score; QALY = quality-adjusted life year; SC = standard care

Table 7.4: Probabilistic ERG worst-case scenarios

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
Population #1					
ERG worst-case scenario					
Dapagliflozin + SC	£12,810	3.966			
Sacubitril valsartan + SC	£14,279	3.912	-£1,469	0.054	Dominant
Population #2					
ERG worst-case scenario					
Dapagliflozin + SC	£13,646	4.022			
SC	£12,507	3.989	£1,139	0.033	£34,858
Population #3					
ERG worst-case scenario					
Dapagliflozin + SC	£14,423	4.022			
SC	£13,278	3.989	£1,145	0.033	£35,048

CS = company submission; ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio; QALY = quality-adjusted life year; SC = standard care

7.4 Conclusions of the cost effectiveness section

The company submission provided enough details for the ERG to appraise the literature searches. A good range of resources was searched, and the searches were transparent and reproducible. One set of searches was conducted to identify cost effectiveness evidence, HSUVs, and healthcare cost and resource data. The searches included study design filters to identify cost effectiveness studies, HSUVs and healthcare resource use data. Searches were conducted in December 2019.

The ERG was concerned with some aspects of the searches conducted, including the search terms used in the HFrEF population facet. Overall, the searches were satisfactory, and given the comprehensive list of interventions included, the study design filters used, and the range of resources searched, it was unlikely that any relevant studies were missed.

The company developed a de novo economic model. Key uncertainties in this cost effectiveness assessment are, according to the ERG, deviations from the NICE reference case, the applicability of the full DAPA-HF trial population to the UK setting, the estimation and extrapolation of transition probabilities and the estimated health state utility values.

The ERG considers that the model structure is appropriate to reflect this condition and treatment pathway. The economic model described in the CS is considered by the ERG to partly meet the NICE reference case. The main deviation from the NICE reference case was the type of economic evaluation for population #1, where the company assumed equal effectiveness and thus effectively performed a cost minimisation analysis. Notably, during the clarification phase, the company provided cost effectiveness analyses for population #1 relaxing the equal effectiveness assumption through informing the relative effectiveness by indirect treatment comparisons (used in the ERG base-case). Also, the sensitivity analyses performed by the company are not fully consistent with the NICE reference case given probabilistic sensitivity analyses are not performed for population #1. Related to this, the company did not perform one-way sensitivity analyses for all parameters that are implemented probabilistically in the PSA, limiting the ability to identify impactful parameters. Moreover, it can be

debated whether the full DAPA-HF population or the European subgroup should be used to inform the cost effectiveness analyses. The ERG adopted relative effectiveness based on the European subgroup in its base-case given the DAPA-HF European subgroup was considered more representative to the UK setting than the overall population. Because the DAPA-HF trial was originally not powered to find a treatment effect in the European sub-population, the ERG acknowledges that these effect estimates might be accompanied with a higher statistical uncertainty compared to the full DAPA-HF population. Additionally, the estimation and extrapolation of transition probabilities was a concern to the ERG. However, the company's clarification responses seem to indicate that the cost effectiveness of dapagliflozin was fairly robust to changes in the (assumptions related to the) transition probabilities (further explored by the ERG in exploratory scenarios analyses). This is however only fully applicable to the CS base-case. For instance, selecting a Gompertz distribution to estimate survival did have a substantial impact on the estimated ICERs for the ERG base-cases (deterministic ICERs increased to above £20,000 per QALY gain for populations #2 and #3) and worst-case analyses (deterministic ICERs increased to above £40,000 per QALY gain for populations #2 and #3). According to the CS, clinical expert opinion suggested that predictions made using the Gompertz distribution were likely to underestimate patient survival. It is however unclear to the ERG how this expert opinion was exactly derived, what the exact results were and thus whether the Gompertz distributions is a plausible option or not. Finally, the utilities derived from the DAPA-HF trial appear to be relatively high for patients with HFrEF, especially when considering the general population utility of people aged 65 years and above. Therefore, these utilities were adjusted in the ERG base-case analyses.

In the company base-case, dapagliflozin was dominant compared with sacubitril valsartan for patients not previously treated with and eligible for sacubitril valsartan (population #1), dapagliflozin versus standard care resulted in a probabilistic ICER of £5,701 per QALY for patients not previously treated with and ineligible for sacubitril valsartan (population #2) while for patients that were previously treated with sacubitril valsartan the probabilistic ICER was £5,757 per QALY gained for dapagliflozin versus standard care. The ERG has incorporated various adjustments to the company base-cases. This resulted in ERG base-cases in which dapagliflozin remained dominant for population #1 while for populations #2 and #3 the probabilistic ICERs increased to £18,037 and £18,159 per QALY gained, respectively. The most influential ERG adjustment was the use of the European subgroup relative effectiveness. The ERG performed exploratory scenario analyses using treatment independent transition probabilities between KCCQ-TSS health states (given the uncertainty related to the estimation of these probabilities) as well as assuming complete waning of the dapagliflozin treatment effect after three years (the maximum follow-up in the DAPA-HF trial was 28 months according to CSR Table 14.3.1.1), both increasing the estimated ICERs for populations #2 and #3.[15] When combined, these exploratory scenario analyses resulted in a worst-case scenario with probabilistic ICERs of £34,858 and £35,048 per QALY gained for populations #2 and #3 respectively.

In conclusion, the ERG analyses indicate that dapagliflozin dominated sacubitril valsartan (population #1) while for population #2 and #3 the cost effectiveness was estimated to be £18,037 and £18,159 per QALY gained respectively (which increased to £34,858 and £35,048 per QALY gained for the worst-case scenarios).

8. End of life

According to section B.2.13.3 of the CS, *"the population of interest in this appraisal face a high 5-year mortality rate of 54.5% and there is evidence to show that dapagliflozin reduces CV mortality and all-cause mortality.[3] However, the median survival in the population of interest exceeds 3 years, and therefore end-of-life does not apply to this appraisal"*.[1]

ERG comment: According to the company, end of life criteria have not been satisfied.

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National Institute for Health and Care Excellence
Centre for Health Technology Evaluation

ERG report – factual accuracy check

Dapagliflozin for treating heart failure with reduced ejection fraction [ID1656]

You are asked to check the ERG report to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies, you must inform NICE by **5pm on Thursday 6 August** using the below comments table. All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the committee papers.

The factual accuracy check form should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Issue 1 Clarification

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Page 13: The outcomes reported in the CS mostly reflect this list with the exception of all-cause hospitalisation which has not been reported and adverse event (AE) incidences of genital infection and urinary tract infection which were not routinely collected in the DAPA-HF trial, the main source of evidence.	Addition of the following text: **The incidence of genital infection and urinary tract infection AEs used in the cost effectiveness analyses were based on dapagliflozin and placebo arms of the cardiovascular outcomes trial of dapagliflozin in T2DM patients (DECLARE).**	It should be clarified that urinary tract infection and genital infection were included in the cost-effectiveness model. The source of genital infection and urinary tract infection rates should be added for clarity.	Not a factual inaccuracy. Statement in section 1.1.4 is correct, reference to DECLARE can be found in section 1.3.

Issue 2 Methodology of the clinical effectiveness systematic review

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Page 14, Page 30, and Page 54: The searches included RCT study design filters to identify clinical efficacy but did not include search terms to identify safety evidence.	Amendment of the text to: The searches included RCT study design filters to identify **condition, treatment, and study design, but terms for outcomes were excluded to ensure the SR was broad. The PICOS was used to identify any studies which reported from a defined list of both safety and efficacy outcomes.**	The SR search terms included terms based on condition, treatment, and study design, but terms for outcomes were excluded to ensure the SR was broad. The PICOS was used to identify any studies which reported from a defined list of both safety and efficacy outcomes. As such, the SR would have identified RCT	Not a factual inaccuracy. As discussed in section 4.1.1, additional searches should be undertaken when searches have been limited by inclusion of a study design filter.

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
		studies reporting efficacy and safety outcomes.	
Page 14 and Page 55: Non-English language studies were excluded which means that potentially relevant studies might have been missed. The company did not provide the list of all references excluded using this criterion as requested by the ERG.	Amendment of the text to: Non-English language studies were excluded which means that potentially relevant studies might have been missed. **Table 60 of the company submission Appendix D lists the studies identified in the clinical efficacy and safety SR that were excluded due to being non-English language. Additionally, the company confirmed that all publications that had been excluded as non-English language studies would also have been excluded for other reasons. This confirms that the issue of language bias did not occur**.	Table 60 of CS Appendix D lists the studies identified in the clinical efficacy and safety SR that were excluded due to being non-English language and provides full citation details. In response to ERG clarification question A10, the company provided a justification for why non-English language studies were excluded and why the company felt that the issue of language bias did not arise.	Not a factual inaccuracy. The ERG asked for clarification which was not provided.
Page 32: However, it should be noted that the company argued that exclusion of full text manuscripts in non-English is common practice but provide no references in support of this statement. Furthermore, the company did not provide the list of all references excluded using this criterion as requested by the ERG. Overall, the ERG does not agree that this approach is correct as	Amendment of the text to: However, it should be noted that the company argued that exclusion of full text manuscripts in non-English is common practice **and recommended by the Cochrane Handbook on a 'case-by-case' basis**. **Table 60 of the company submission Appendix D lists the studies identified in the clinical efficacy and safety SR that were excluded due to being non-English language. Additionally, the company confirmed that all publications that had been excluded as non-English language studies would also have been excluded for other reasons. This**		Not a factual inaccuracy. No sufficient justification was provided in response to the ERG request for clarification.

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
potentially relevant studies might have been missed.	**confirms that the issue of language bias did not occur**. Overall, the ERG does not agree that this approach is correct as potentially relevant studies might have been missed.		

Issue 3 Data correction

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Page 41 Table 4.8: Composite of CV death or hHF for the dapagliflozin arm = 16.9%	Change the value of 16.9% to **16.1%.**	Typographical error, the value of 16.9% does not align with that reported in the company submission.	Corrected accordingly.
Page 42 : 'The CS concludes that dapagliflozin is well-tolerated in patients with HFrEF as SAEs were numerically less frequent with dapagliflozin (25.7%) than with placebo (40.2%)'	Change the value of 25.7% to **35.7%.**	Typographical error, the value of 25.7% does not align with that reported in the company submission.	Corrected accordingly.

Issue 4 MAIC methods

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Page 51: In addition, Table 69 in Appendix F of the company	Amendment of the text to: In addition, Table 69 in Appendix F of the company submission reported the "expected	As explained in response to ERG clarification questions A.21a, the expected bias reduction was only reported for those characteristics	Changed accordingly.

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
submission reported the "expected bias reduction" by adjustment on the log hazard ratio scale. However, this has not been performed for all characteristics.	bias reduction" by adjustment on the log hazard ratio scale. **The company explained in response to questions A21a that the "expected bias reduction" was reported for all characteristics that were found to be treatment effect modifying covariates for each individual endpoint in question.**	that were found to be treatment effect modifying covariates of each individual endpoint.	
Page 16: Overall, similar effect estimates were reported for both methods with narrower 95% CIs for the MAIC.	Amendment of the text to: Overall, similar effect estimates were reported for both methods with narrower 95% CIs for the **Bucher method.**	As shown in Figure 4.2–4.4 of the ERG report, the results from the Bucher method (labelled as "unadjusted" and also reported in Table 4.16) have narrower 95% CIs compared to the MAIC method (labelled as "Primary").	Changed accordingly.
Page 56: Overall, similar effect estimates were reported for both methods with narrower 95% CIs for the MAIC.	Amendment of the text to: Overall, similar effect estimates were reported for both methods with narrower 95% CIs for the **Bucher method.**	As shown in Figure 4.2–4.4 of the ERG report, the results from the Bucher method (labelled as "unadjusted" and also reported in Table 4.16) have narrower 95% CIs compared to the MAIC method (labelled as "Primary").	Changed accordingly.

Issue 5 European population

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Page 19, 70 and 90: Because the DAPA-HF was originally not	Amendment of the text to: Because the DAPA-HF was originally not powered to find a treatment effect in the European sub-population and **because the p-value for**	Additional text for clarity. As noted in the submission and ERG clarification questions response, while	Not a factual inaccuracy.

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
powered to find a treatment effect in the European sub-population, the ERG acknowledges that these effect estimates might be accompanied with higher statistical uncertainty compared to the full DAPA-HF population.	**interaction was not significant for the European sub-group for the primary endpoint,** the ERG acknowledges that these effect estimates might be accompanied with higher statistical uncertainty compared to the full DAPA-HF population.	the effect size in the European subgroup was slightly less than in the overall population, there was no indication of interaction [redacted], the subgroup analyses were not powered to detect statistically significant differences between treatment groups, and geographic location was not identified as a treatment effect modifier. The ITT data from DAPA-HF are therefore most relevant in the current assessment.	
Page 34: It should be noted that the proportion of European participants with any AE or any SAE was higher than in the overall study population.	Amendment of the text to: It should be noted that [redacted]	As shown in table 4.10 of the ERG report, the proportions of patients with AEs of any particular type is **not** consistently higher in the European subgroup compared to the overall trial population. The current sentence in the ERG report is therefore misleading.	Wording amended, see changes on pages 15, 45, and 56.
Page 81:	Amendment of the text to:	Additional text for clarity. As noted in the submission	Not a factual inaccuracy.

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
The DAPA-HF European subgroup (see Table 10 of the CS for baseline characteristics versus the overall population) was considered more representative to the UK setting than the overall population (section 5.2.3).	The DAPA-HF European subgroup (see Table 10 of the CS for baseline characteristics versus the overall population) was considered more representative to the UK setting than the overall population (section 5.2.3)**, even though p-value for interaction was not significant for the European sub-group for the primary endpoint.**	and ERG clarification questions response, while the effect size in the European subgroup was slightly less than in the overall population, there was no indication of interaction [redacted], the subgroup analyses were not powered to detect statistically significant differences between treatment groups, and geographic location was not identified as a treatment effect modifier. The ITT data from DAPA-HF are therefore most relevant in the current assessment.	

Issue 6 Model KCCQ-TSS health states

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Page 64: The company justified this choice (clarification response B1) by indicating that KCCQ-	Amendment of the text to: The company justified this choice (clarification response B1) by indicating that KCCQ-TSS encompasses HF symptoms only while the KCCQ quality of life score, clinical summary score or overall summary scores also encompass other aspects of HF disease. **The company**	Further justification for the use of KCCQ-TSS as a secondary endpoint in the trial, is also provided in	Changed accordingly.

TSS encompasses HF symptoms only while the KCCQ quality of life score, clinical summary score or overall summary scores also encompass other aspects of HF disease.	**also explained in clarification response A18c that** [redacted]	response to clarification question A18c.	

Issue 7 Model intervention and comparators

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Page 66: However, it should be noted that the professional organisation submission by the British Society for Heart Failure indicated that dapagliflozin treatment should be initiated by either heart failure (in case of heart failure with/without diabetes) or diabetes (in case of heart failure with diabetes) specialists. This could potentially increase the cost of dapagliflozin treatment for population #1.	Amendment of the text to: However, it should be noted that the professional organisation submission by the British Society for Heart Failure indicated that dapagliflozin treatment should be initiated by either heart failure (in case of heart failure with/without diabetes) or diabetes (in case of heart failure with diabetes) specialists. **This is unlikely to have an impact on incremental costs for population 1, because patients are currently reassessed by HF specialists before initiation of sacubitril valsartan.**	Population #1 concerns the comparison between dapagliflozin and sacubitril valsartan. In the base case of the model, costs for specialist reassessment have not been included in the dapagliflozin arm nor in the sacubitril valsartan arm. Any costs added to the model to capture the cost of specialist reassessment would need to be added to both treatment arms, and the net impact would be zero.	Wording amended, see changes on page 66.

Issue 8 Model discrepancies

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Page 79–80:	Amendment of the text to:	Results provided in response to ERG clarification questions were generated using the updated	Changed accordingly.

The v0.3 version of the model, used in the ERG analyses (as it contained more options for scenario analyses), produced slightly different ICERs than reported in the CS (differences in ICER based on a selected number of comparisons were <£100, see Table 7.1).	The v0.3 version of the model, used in the ERG analyses (as it contained more options for scenario analyses), produced slightly different ICERs than reported in the CS (differences in ICER based on a selected number of comparisons were <£100, see Table 7.1). **The company explained that this is due to the assumption of a constant rate of drug discontinuation in the updated model (in response to B8) compared to the assumption of a constant probability of drug discontinuation in the original model.**	version of the model which assume a constant rate of drug discontinuation (as requested in ERG clarification question B8). This is explained in the footnote of all relevant results tables in the response to ERG clarification questions.	

Issue 9 Model transition probabilities

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Page 69: These analyses indicate that the cost effectiveness (for populations #2 and #3) is robust to the methods used to calculate the transition probabilities between health states defined by KCCQ-TSS quartiles, even when assuming these transition probabilities are treatment independent.	Amendment of the text to: These analyses indicate that the cost effectiveness (for populations #2 and #3) is robust to the methods used to calculate the transition probabilities between health states defined by KCCQ-TSS quartiles, even when assuming these transition probabilities are treatment independent. **The company explained that the scenario analysis assuming transition probabilities between KCCQ-TSS health states to be independent systematically underestimates the treatment benefit associated with dapagliflozin. This is because the multivariable risk equations for all-cause mortality, CV mortality and hHF were derived in the context of the observed KCCQ-TSS benefit associate with**	As highlighted in response to question B3i, the assumption of treatment independent health state transition probabilities does not adequately capture the benefit of dapagliflozin as observed in the DAPA-HF trial. Because the multivariable risk equations for all-cause mortality, CV mortality and hHF were derived in the context of the observed KCCQ-TSS benefits which is in turn linked to patient outcomes in the risk equations. As such, a proportion of the observed reduction in hHF and death is mediated through improved KCCQ-TSS for patients treated with dapagliflozin. To correct for	Not a factual inaccuracy.

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
	dapagliflozin. To correctly implement the assumption of treatment independent transition probabilities, the multivariable risk equations would need to be re-derived.	this, it would be necessary to re-derive the multivariable risk equations, assuming the transition probabilities to be constant.	
Page 86 and 90: The ERG performed exploratory scenario analyses using treatment independent transition probabilities between KCCQ-TSS health states (given the uncertainty related to the estimation of these probabilities) as well as assuming complete waning of the dapagliflozin treatment effect after three years (the maximum follow-up in the DAPA-HF trial was 28 months according to CSR Table 14.3.1.1), both increasing the estimated ICERs for populations #2 and #3.	Amendment of the text to: The ERG performed exploratory scenario analyses using treatment independent transition probabilities between KCCQ-TSS health states (given the uncertainty related to the estimation of these probabilities) as well as assuming complete waning of the dapagliflozin treatment effect after three years (the maximum follow-up in the DAPA-HF trial was 28 months according to CSR Table 14.3.1.1), both increasing the estimated ICERs for populations #2 and #3. **The implementation of the assumption of treatment independent transition probabilities between KCCQ-TSS health states systematically underestimates the benefits associated with dapagliflozin, as some of the observed benefits of dapagliflozin on hHF and death are mediated through the transition probabilities in the cost-effectiveness model. To correctly implement the assumption of treatment independent transition probabilities, the multivariable risk equations for mortality and hHF would need to be re-derived (not implemented).**		Not a factual inaccuracy.
Page 86:	Amendment of the text to:		Not a factual inaccuracy.

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Assuming the transition probabilities between health states defined by KCCQ-TSS quartiles are treatment independent (given the uncertainty related to the estimation of these probabilities, see response to clarification question B4).	Assuming the transition probabilities between health states defined by KCCQ-TSS quartiles are treatment independent (given the uncertainty related to the estimation of these probabilities, see response to clarification question B4). **The implementation of the assumption of treatment independent transition probabilities between KCCQ-TSS health states systematically underestimates the benefits associated with dapagliflozin, as some of the observed benefits of dapagliflozin on hHF and death are mediated through the transition probabilities in the cost-effectiveness model. To correctly implement the assumption of treatment independent transition probabilities, the multivariable risk equations for mortality and hHF would need to be re-derived.**		

Issue 10 ERG probabilistic analyses

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Page 85 (Table 7.2) and page 89 (Table 7.4).	Please report the number of iterations that were used for the probabilistic analyses, so that the results can be reproduced and verified.	The ERG report does not state the number of iterations that were carried out for the probabilistic analyses.	Wording amended in main text, see changes on page 83.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Technical report

Dapagliflozin for treating heart failure with reduced ejection fraction [ID1656]

This document is the technical report for this appraisal. It has been prepared by the NICE technical team.

The technical report and stakeholder's responses to it are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the appraisal committee meeting.

This report is based on:

- the evidence and views submitted by the company, consultees and their nominated clinical experts and patient experts and
- the evidence review group (ERG) report.

The technical report should be read with the full supporting documents for this appraisal.

Commonly used abbreviations

ACEi	Angiotensin-converting-enzyme inhibitor
ARB	Angiotensin receptor blocker
BB	Beta-blocker
CS	Company Submission
GP	General practitioner
HF	Heart failure
HFrEF	Heart failure with reduced ejection fraction
ICER	Incremental cost-effectiveness ratio
KCCQ	Kansas City Cardiomyopathy Questionnaire
MAIC	Matching adjusted indirect comparison
MRA	Mineralocorticoid receptor antagonist
NYHA	New York Heart Association
RCT	Randomised controlled trial
SGLT2	Sodium/glucose cotransporter 2
SmPC	Summary of Product Characteristics
TA	Technology appraisal
T1DM	Type 1 diabetes mellitus

1 Key issues summary

Issue	Summary	Technical Team Preliminary Judgement
Issues related to the clinical evidence		
Positioning in the pathway	• The company proposed 3 potential positions for dapagliflozin in the treatment pathway: - #1: As an add on to standard care (angiotensin-converting-enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB), beta-blocker (BB), ± mineralocor-ticoid receptor antagonist (MRA)) when sacubitril valsartan is suitable (comparator = sacubitril valsartan) - #2: As an add on to standard care (ACEi or ARB, beta-blocker, ± MRA) when sacubitril valsartan is unsuitable (comparator = placebo) - #3: As an add on to standard care when people are already having specialist treatment with sacubitril valsartan, beta-blocker, ± MRA (comparator = placebo) (CS p27-28). • Populations #1 and #2 were initially presented as identical. At clarification, the company explained that they are different and population #1 includes people who can have sacubitril valsartan in line with its marketing authorisation (ejection fraction ≤35% without hyperkalaemia (serum potassium >5.4 mmol/l) / hypotension). Population #2 includes people who do not meet the above criteria, or do not have sacubitril valsartan for other reasons (such as the difficulties in dose adjustments) (clarification response p2-3) • The company's clinical experts note a preference for using dapagliflozin before sacubitril valsartan in the treatment pathway (population #1), as well as using dapagliflozin as an option after sacubitril valsartan (population not included in CS). • Clinical expert submissions to NICE state that dapagliflozin would ideally be used as an add on to sacubitril valsartan (population #3). Where relevant, treatment choice would be determined by presence of diabetes, ongoing congestion, degree of fluid overload, kidney function and blood pressure.	• The company's suggested positioning reflects relevant populations in the NHS. However, there are several uncertainties remaining for which clinical expert advice and clarification from the company is needed: o It is unclear from the company submission and discussion with clinical experts if additional populations should be included where dapagliflozin is used as an add on to standard care when people are responding to ACEi / ARBs ± MRAs (population a. in the figure in Appendix 1, page 17). o It is unclear how often dapagliflozin would be used instead of sacubitril valsartan when both are an option (population #1). o People who have sacubitril valsartan stop ACEi / ARBs as per NICE guideline 106. However, in this population, dapagliflozin is used as an add-on to ACEi / ARBs and is likely to be initiated earlier in the pathway

		(CS p29). The background therapies in population #1 are therefore different and sacubitril valsartan could potentially be considered a subsequent therapy. o It is uncertain how many people would fall under population #2 in the NHS and how this would be defined and implemented in clinical practice. o For company population #3, it is unclear: - why dapagliflozin would be added to the treatment pathway for people whose disease is already responding to standard care. - whether people currently taking sacubitril valsartan whose symptoms continue or disease stops responding were included in this population or would be treated with dapagliflozin in clinical practice. o It is unclear if dapagliflozin would be used after sacubitril valsartan and, if so, whether ACEi / ARBs would be reintroduced. • Further justification for the company's positioning is required.
Use in primary care	• The company anticipates that dapagliflozin will be initiated in primary care: o The company justification is the favourable safety profile, GPs familiarity with dapagliflozin from its use in diabetes and the fact	• The company's suggested positioning covers populations currently seen in specialist care. Clinical expert advice needed as to:

	that no adjustments to doses are required based on patient responses (CS p30-31, clarification response p5-6). o The company anticipates that initiation of dapagliflozin in primary care should not replace referral and disease management by a specialist heart failure multidisciplinary team. However, dapagliflozin could be initiated in primary care by GPs whilst people await specialist reassessment (CS p30). o Not all patients diagnosed with HF are seen by a specialist (clarification response p3-4) • A clinical expert submission to NICE suggested that dapagliflozin may require initiation and monitoring in specialist care due to risk of high urea and, when taken with diuretics, increased prevalence of dehydration and hypotension. • The ERG notes that HFrEF drugs used following progression on ACEi / ARBs ± MRAs require specialist guidance. Referral to secondary care to discuss treatment options should be standard practice: o TA288 recommends that sacubitril valsartan should be started by a heart failure (HF) specialist with access to a multidisciplinary team (ERG report p26). • Scenarios including the costs of secondary care for dapagliflozin were not provided at clarification as the company stated that no additional costs were expected due to the oral mode of administration. Specialist reassessment costs for sacubitril valsartan were not included in the company base cases #1 and #3 (clarification response p49).	o the plausibility of prescribing dapagliflozin in primary care in population #1 and #2, given that a specialist referral is suggested following progression on ACEi / ARBs ± MRAs. o whether administration in primary care is plausible for people responding to ACEi/ARBs ± MRA (technical team population a. in Appendix 1) o the need for extra monitoring for people who have dapagliflozin for heart failure with reduced ejection fraction (HFrEF). • Access to dapagliflozin in primary care may reduce access barriers. However, it could also lead to over-prescription of dapagliflozin. Especially as not every patient is referred to a specialist. • The technical team would like to see a scenario analysis including the costs of initiation and monitoring by a specialist team.
Generalisability of the DAPA-HF trial	• The direct clinical evidence comes from the DAPA-HF study, an international, blinded phase 3 RCT of dapagliflozin 10mg or 5mg daily (n=2,373) versus placebo (n=2,371) (CS p36-38). • People with type 1 diabetes mellitus (DM) were excluded from the DAPA-HF trial but are included in the dapagliflozin SmPC for diabetes. The trial also excluded people with current acute decompensated HF at baseline (ERG report p38). • Background therapy for people in the DAPA-HF trial may not reflect current clinical practice in the NHS (CS p27)	• Result of the full population from the DAPA-HF trial may not reflect the population seen in clinical practice in England as they are younger, have different dosage of background therapy and were recruited from various healthcare settings globally. • The European subgroup from the DAPA-HF trial is more generalisable to clinical practice in England.

	• The average age in the DAPA-HF trial was 66 years which is younger than the average age of people in whom the company expects dapagliflozin is likely to be used in clinical practice (≥76 years in men and ≥80 years in women) (CS p41). • 45% of people in the DAPA-HF trial were recruited from Europe (CS p41). • Subgroup analyses based on geographical region show a difference in efficacy as well as safety outcomes (CS p87). • The ERG noted that the DAPA-HF trial was not powered to detect differences in treatment effect by geographical location. However, it highlighted that results in the full population may not be generalisable to clinical practice in England and may overestimate treatment effect. This was because it used a younger population, with less severe disease classification and geographical variation in choice and dose of background therapy. The ERG preferred to use the European subgroup in all analyses (ERG report p38). • Technology appraisal (TA) 388 noted geographical differences in disease aetiology, clinical management, and baseline risk of HFrEF. The committee preferred the Western European subgroup for decision making. • Clinical experts to NICE suggest UK treatment is comparable to other European countries.	• There is no clinical effectiveness evidence in people with type 1 diabetes and current acute decompensated HF.
Indirect treatment comparison	• There is no direct evidence comparing dapagliflozin and sacubitril valsartan. • The relative effectiveness of dapagliflozin for population #1 is based on a matching-adjusted indirect comparison (MAIC). Evidence for sacubitril valsartan was taken from the PARADIGM-HF study, an RCT comparing sacubitril valsartan with enalapril (an ACEi) in combination with standard care (CS p57). • People who had ACEi in the placebo arm of the DAPA-HF trial and people in the control arm of the PARADIGM-HF study who had ACEi (enalapril) were used as the control (anchor) for the MAIC (CS p58). The population was then adjusted for the following characteristics at baseline: age, sex, race, region, blood pressure, heart rate, presence of ischemic heart failure, left ventricular ejection fraction (LVEF)	• The control arms in the MAIC are not identical. A class effect (assuming equal clinical effectiveness) has been accepted for ACEi's in NICE TA388 but is yet to be proven. • People who could not tolerate treatment with sacubitril valsartan would discontinue during the run-in period of PARADIGM-HF. However, people who could not tolerate dapagliflozin would discontinue during the trial period, so would be included in the primary

	classification, N-terminal pro B-type natriuretic peptide level, New York Heart Association (NYHA) score and cardiac history (CS p60-61). • The MAIC results suggested that dapagliflozin improves survival and time to hospitalisation for heart failure compared to sacubitril valsartan, however results were not statistically significant. So the company assumed equal effectiveness of dapagliflozin and sacubitril valsartan (CS p63-65) • The MAIC had several limitations: o Adjustment for covariates significantly reduced the DAPA-HF sample size (CS p60) o PARADIGM-HF included a 5-10 week period where people had ACEi and sacubitril valsartan prior to randomisation (CS p78) • The ERG noted there was no justification for choosing a MAIC to compare dapagliflozin and sacubitril valsartan over the Bucher method (ERG report p51). • Similar effect estimates were reported for both MAIC and Bucher methods with narrower 95% CIs for the Bucher method (ERG report p51).	analysis set. This may underestimate any treatment effect for dapagliflozin. • The results of the MAIC are uncertain: multiple adjustments and exclusion of [redacted] of people in the DAPA-HF trial had limited impact on treatment effect estimates. • The technical team agree that the MAIC has not been justified and prefer the ERG's approach to indirect treatment comparison.
Issues related to the cost effectiveness evidence		
Cost effectiveness versus sacubitril valsartan (base case #1)	• No probabilistic ICER or sensitivity analysis have been presented for the base case for population #1, so it is uncertain how sensitive the results are to changes in assumptions. • The ERG noted that although resource use, effectiveness and health state utility do not directly impact the difference between treatments, they could have an impact on the incremental outcomes (ERG report p79). This means that a PSA is necessary despite all the results being dominant.	• Dapagliflozin was dominant over sacubitril valsartan in all company and ERG scenarios. However, in line with the NICE reference case, a PSA should be provided for the base case for population #1.
Use of KCCQ-TSS quartiles in the model	• Kansas City Cardiomyopathy Questionnaire –Total Symptom Score (KCCQ-TSS) quartiles were used in the model to capture disease severity. • The ERG noted that the KCCQ-TSS only captures HF symptoms, but the KCCQ quality of life domain, the KCCQ clinical summary score or	• The technical team notes that other technology appraisals in HF used the NYHA classification instead of the KCCQ-TSS to measure disease severity. The subgroup analyses suggest cost effectiveness estimates

	the overall summary score capture other aspects of HF disease (ERG report p18). • The company stated that KCCQ-TSS was chosen based on best fit to the observed data and availability of data to produce stable estimates (clarification response p24). The ERG noted that the impact of other categorisations on transition probabilities, HRQoL, resource use or costs were not provided by the company (ERG report p64). • Clinical expert advice suggests that KCCQ-TSS scores are rarely used to measure disease severity in clinical practice, with NYHA Functional Classification used for decision making. • Subgroup analyses showed a [redacted] difference in treatment effect by NYHA class. The company stated this was a [redacted]: DAPA-HF was not designed to find differences between subgroups, average change in NYHA class in the trial did not reflect the chronic nature of HF, and results of other disease severity measures (e.g. LVEF, KCCQ-TSS) were not significant (CS p54-56, clarification response p53-54).	may differ if NYHA classes were used in the model. • Clinical advice needed on the importance of including the following domains in the health states: physical limitations, QoL and social inference.
Survival extrapolation	• The company selected the Weibull distribution to extrapolate survival in its base cases, assuming proportional hazards for all-cause and CV mortality. It stated that the Weibull produced long-term survival estimates consistent with clinical expert opinion, literature values and the PARADIGM-HF trial and fitted the DAPA-HF data well (CS p104-105). • The company stated alternative distributions did not reflect clinical practice as the Gompertz distribution produced underestimates for survival, whilst the log-logistic and lognormal distributions produced overestimates (CS p104). • The ERG was concerned that details of the expert opinion used to verify this statement have not been provided (ERG report p69). • The Gompertz distribution increased the ICERs for all populations. Company scenario analyses for populations #2 and #3 increased the ICERs to £7,264 and £7,162/QALY gained respectively compared to the company base case of £5,830 and £5,866/QALY gained. ERG scenarios (including its preferred assumptions around European population and use of adjusted health state utilities (see 'other	• The technical team agrees that the Weibull distribution is appropriate. The log-logistic and log-normal distributions likely overestimate survival, whilst the Gompertz distribution is likely an underestimate. • Clinical expert advice would be useful to confirm the appropriate long-term extrapolation given only 2 years of follow up data.

	issues')) were £20,838 and £20,953/QALY gained compared to £18,018 and £18,140/ QALY gained for ERG base cases #2 and #3 (CS p149, ERG report p90).	

2 Other issues for information

Issue	Explanation
DAPA-HF primary endpoint	The DAPA-HF trial used a composite outcome (time to the first occurrence of either CV death or hospitalization for HF or an urgent HF visit) for its primary endpoint, Though often difficult to use and interpret, composite outcomes are common in this disease area, with both TA388 and TA267 choosing a similar effectiveness measure. The company has presented hazard ratios for each component of the primary outcome, which were statistically significant (CS p53).
Adverse events	Data on genital infections and urinary tract infections were not collected in the DAPA-HF study. Incidence rates in the cost effectiveness analyses were based on dapagliflozin and placebo arms of the DECLARE study, which evaluated cardiovascular outcomes of dapagliflozin in type 2 DM patients. The ERG noted that genital infections are listed as a common adverse event in the dapagliflozin summary of product characteristics for type 1 and 2 DM (ERG report p45). It is likely that such infections would be less common in people without diabetes.
Transition probabilities	Transition probabilities between KCCQ-TSS quartiles were derived using monthly transition count data assuming last observation carried forward for imputing missing values. The ERG noted the following concerns (ERG report p69): • KCCQ-TSS was only measured every 4 months in the DAPA-HF trial (baseline, 4, 8, 12 and 24 months) • Different probabilities were used for the first four months of treatment based on a change in trajectory observed in the mean KCCQ-TSS scores from DAPA-HF. The ERG was concerned that the inflection point in the company submission showed this change at around 6-7 months, closer to the 8-month measurement. • Use of the last observation carried forward method may not account for the increased chance of missing data from people with worse health related quality of life. • Transition probabilities for the specific population used the full DAPA-HF data set as opposed to the relevant subgroup of patients. • Transition probabilities used in the model differed for treatment with and without dapagliflozin, based on the KCCQ-TSS data from each arm of the DAPA-HF trial. The company stated that this approach captured the observed reduction in death and hHF rates with dapagliflozin due to the improvement of KCCQ-TSS in the trial (clarification response p40).

	At clarification, the company provided alternative scenarios to explore each of the above points. Cost-effectiveness estimates were robust to the above changes (ICER remained under £8000/QALY gained at all times) (clarification response p38-40).
Utility values for KCCQ-TSS quartiles	Utilities were derived from the DAPA-HF trial. EQ-5D-5L questionnaires were collected at trial randomisation, day 120, 240, 360, and every 12 months thereafter. The ERG noted that the utility values for quartiles 3 and 4 (0.833 and 0.773 respectively) are high compared to the general population aged ≥65 (0 .774 for people aged 60-69) (ERG report p19). The ERG provided a scenario analysis using the general population health state utilities for KCCQ-TSS Q4: 92-10 and applied relative differences to obtain health state utilities for Q1-Q3 (Q4=0.774, Q3=0.714, Q2=0.646, Q1=0.541). A modest effect on the ICER was noted (ERG report p84). Although the company's probabilistic sensitivity analyses demonstrated that results were sensitive to a decrease of utility value by 20%, the ICER remained under £8000/QALY gained for both base cases #2 and #3 (CS p139-140).
Treatment waning effect	The maximum follow-up period in the DAPA-HF was [redacted] (clinical study report p514). The DAPA-HF trial did not include a stopping rule for dapagliflozin, so the company did not apply treatment waning in its base case. To demonstrate the effect on the ICER, at clarification the ERG requested a scenario analysis which assumed all treatment effect with dapagliflozin stopped at 3 years. Cost effectiveness estimates from both the company and ERG were robust to the incorporation of this assumption.

3 Questions for engagement

Questions for clinical experts/stakeholders

Positioning in the pathway

1. Are the company's populations #1, #2 and #3 as detailed in Appendix 1 (page 17) clearly distinguishable in clinical practice?
2. Is the company's positioning of dapagliflozin appropriate?
    a. Should the committee consider additional positions in the pathway?

i. Would dapagliflozin ever be used in people responding to existing treatments?

ii. Would dapagliflozin be used in people whose symptoms continue or disease is not responding to sacubitril valsartan?

1. If yes, would treatment with sacubitril valsartan stop or would dapagliflozin be added to current care?

2. If sacubitril valsartan is stopped, would ACEi / ARBs be restarted?

3. Would dapagliflozin be used instead of sacubitril valsartan where both are an option?

a. Would all people who have sacubitril valsartan be able to have dapagliflozin?

4. In what proportion of people not responding to ACEi/ARBs, beta-blockers ± MRA would you expect sacubitril valsartan to be unsuitable (population #2)?

5. Have all appropriate comparators been considered in the appraisal?

Use in primary care

6. Should dapagliflozin be initiated by a heart failure specialist?

a. If yes, what additional monitoring would be required?

b. Is it plausible that GPs could prescribe dapagliflozin in primary care prior to referral to a specialist?

c. If no, what additional training or resources would be necessary for primary care clinicians to prescribe dapagliflozin?

7. What percentage of people see a heart specialist after progressing on ARBs / ACEi's in clinical practice in the NHS:

i. For people starting MRAs?

ii. For people starting specialist treatment?

b. Does specialist referral reduce access to second line treatment options?

c. What additional costs and resources would be associated with dapagliflozin treatment in specialist care versus primary care? Would there be any costs/resources that would apply to dapagliflozin but not to sacubitril valsartan and vice versa?

Generalisability of the DAPA-HF trial

8. In NHS clinical practice, what percentage of patients would be expected to have HFrEF and type 1 diabetes mellitus? How would dapagliflozin be used in this population?

9. What percentage of people with HFrEF have acute decompensated HF?

10. How would disease aetiology, clinical management, and baseline risk for heart failure be expected to differ in Europe versus the rest of the world?

Indirect treatment comparison

11. Can a class effect be assumed for ACE inhibitors?

12. Can equivalence be assumed for ACEi and ARBs?

Use of KCCQ-TSS quartiles in the model

13. Should the following domains be included in the measurement of HFrEF disease severity?

    a. physical limitations

    b. quality of life

    c. social inference

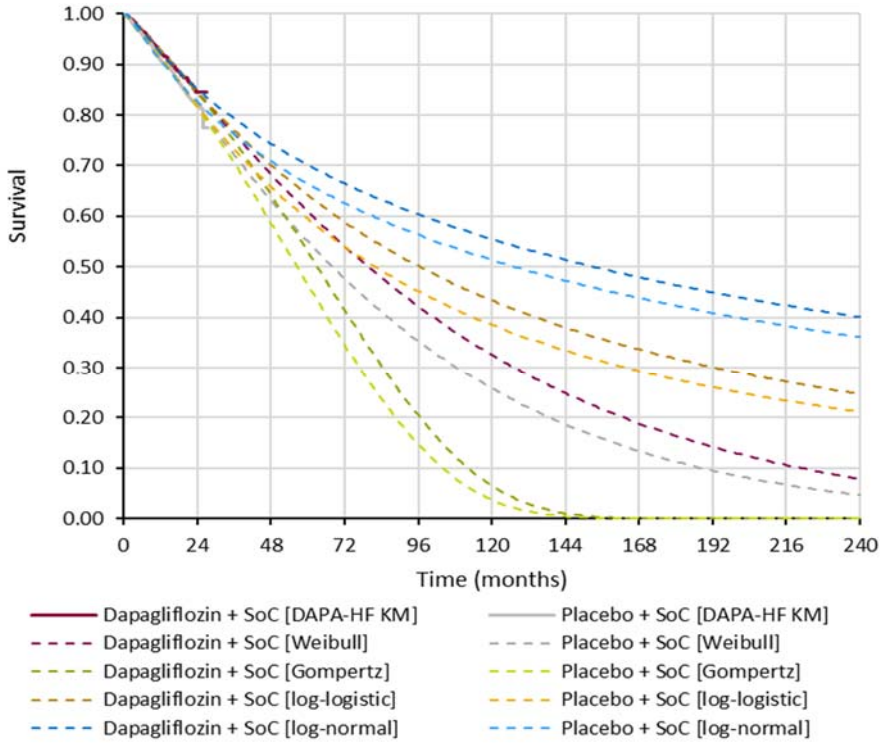
Survival extrapolation

14. Which long-term survival estimates would most accurately reflect what is expected in clinical practice in the NHS?

Months		0	12	24	36	60	120	180	240
Base case #1, people on ACEi or ARB, beta-blocker, ±MRA for whom sacubitril valsartan is suitable									
Weibull	**Dapagliflozin**	100.0%	92.8%	84.5%	76.2%	60.9%	32.60%	16.4%	7.9%
	Standard Care	100.0%	91.4%	81.6%	72.1%	55.0%	25.9%	11.3%	4.7%
Gompertz	**Dapagliflozin**	100.0%	92.8%	84.4%	74.9%	53.0%	6.6%	0.0%	0.0%
	Standard Care	100.0%	91.4%	81.5%	70.6%	46.5%	3.7%	0.0%	0.0%
Base case #2, people on ACEi or ARB, beta-blocker, ±MRA for whom sacubitril valsartan is unsuitable									
Weibull	**Dapagliflozin**	100.0%	92.7%	84.4%	76.2%	61.10%	33.20%	17.1%	8.5%
	Standard Care	100.0%	91.3%	81.6%	72.2%	55.5%	26.8%	12.1%	5.2%
Gompertz	**Dapagliflozin**	100.0%	92.6%	84.3%	74.9%	54.0%	8.9%	0.0%	0.0%
	Standard Care	100.0%	91.3%	81.6%	71.0%	48.2%	5.6%	0.0%	0.0%
Base case #3, people on sacubitril valsartan, beta-blocker, ±MRA									
Weibull	**Dapagliflozin**	100.0%	94.9%	86.2%	76.1%	55.6%	19.1%	4.8%	0.9%
	Standard Care	100.0%	92.8%	81.1%	68.0%	43.7%	9.6%	1.4%	0.1%
Gompertz	**Dapagliflozin**	100.0%	94.8%	85.9%	71.5%	26.7%	0.0%	0.0%	0.0%
	Standard Care	100.0%	92.8%	80.8%	62.3%	15.6%	0.0%	0.0%	0.0%

15. Based on the company's goodness of fit criteria estimates (AIC/BIC) the log-logistic and log-normal curves could be a suitable fit to the data but predict more optimistic extrapolations that the Weibull (as shown in the graph below). Would you expect improved survival in clinical practice compared to what is estimated using the Weibull extrapolation curve (see table from question 14)?

Company's alternative all-cause mortality survival curves (scenario analyses) (CS p109)



Treatment waning effect

16. **NHS England:** Would a stopping rule apply for dapagliflozin in the NHS?
17. Would treatment effect be expected to continue after stopping dapagliflozin?
    a. If yes, how long after stopping treatment would this effect last?
    b. Is this observed in patients having sacubitril valsartan?

Questions for company

1. Based on the technical team populations a. – e. in Appendix 1 (page 17), please complete the below table to detail each place dapagliflozin would be used in the HF pathway:

Technical team population	Population in company submission	Population size in NHS	Background therapy*	Comparator	Primary or specialist care initiation and monitoring	Justification
a.						
b.						
c.						
d.						
e.						
[other]						
*if failing treatment please clarify changes to previous treatment regime						

2. Given the [redacted] (shown in figure 11 of the company submission), what differences in the cost effectiveness estimates would be anticipated if NHYA classification score was used in place of KCCS-TSS in the model, (please provide justification)?

a. Please explain the different trends seen in NHYA class versus KCCQ-TSS change from baseline in the DAPA-HF trial. Given that they should both reflect disease severity and that KCCQ-TSS is used in the model but NHYA class is used in clinical practice, it is important that this difference is explored.

3. Will dapagliflozin be used in people with acute decompensated HF in the NHS? If yes, please clarify how this population is included in the evidence base.

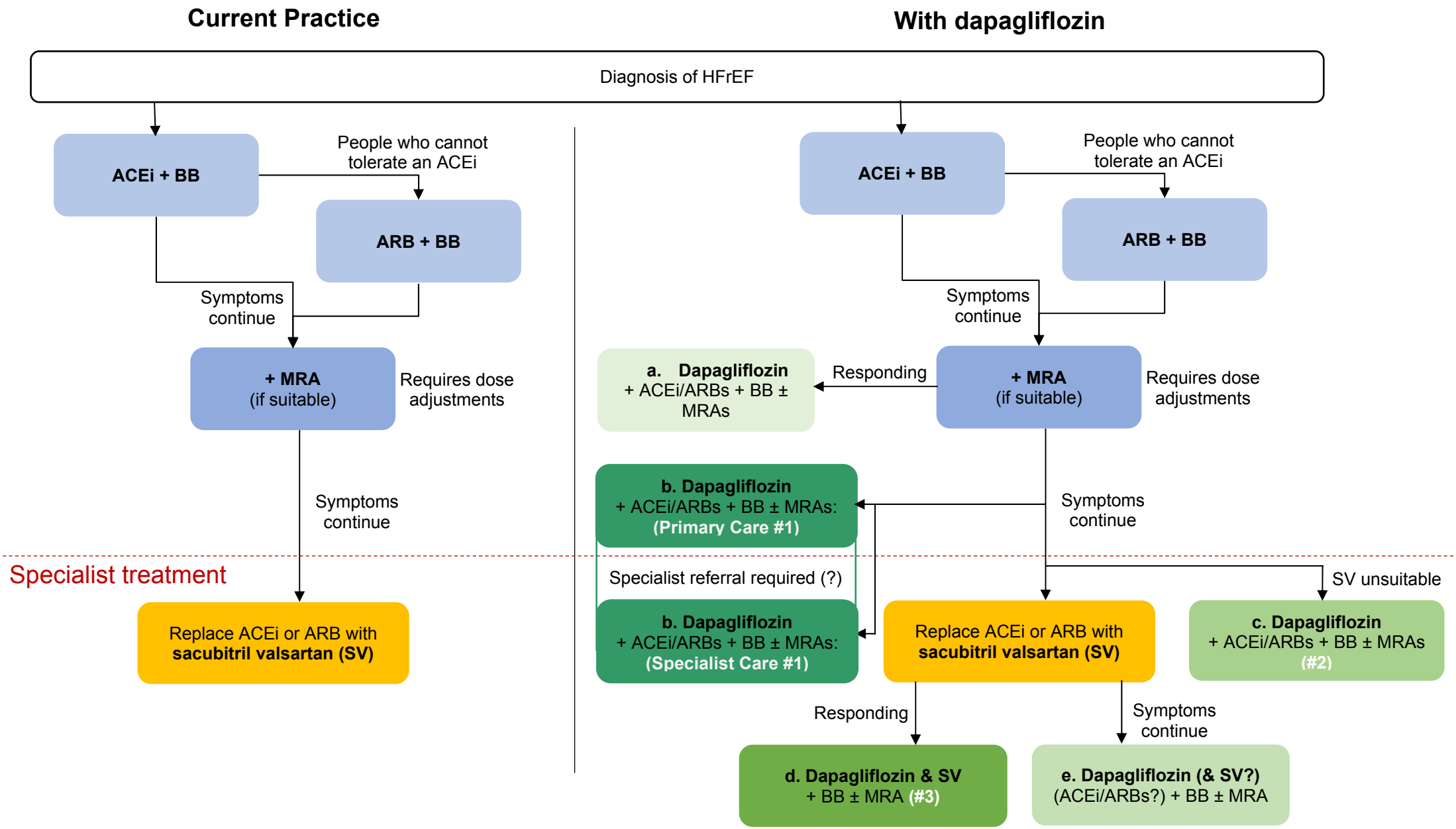
4. How many people discontinued dapagliflozin due to lack of efficacy in the DAPA-HF trial? Is this likely to be different in clinical practice.

5. Please complete the additional analyses below:

Issue	**Further information**
Positioning in pathway	Scenario analyses including use of dapagliflozin as an add on to standard therapy for each positioning described in response to question 1 [appendix 1] Please include subsequent therapies (such as sacubitril valsartan) if appropriate.
Use in primary care	Scenario analyses including costs of treatment and monitoring in specialist care
Generalisability of the DAPA-HF trial	1. MAIC results using baseline characteristics from the European population 2. Effectiveness results using the European population survival adjusted based on the same characteristics as in the full population 3. Scenario analyses using these efficacy estimates in the model.
Cost effectiveness versus sacubitril valsartan (base case #1)	Probabilistic sensitivity analysis for base case #1 (comparison with sacubitril valsartan).
Use of KCCQ-TSS quartiles in the model	Scenario analyses that use the KCCQ clinical summary score and overall summary score in the model
Treatment waning effect	Scenario analyses applying a three-year discontinuation rule and a range of different durations of treatment effect (e.g. between 5 and 10 years).

6. In review of the technical report please provide a revised base case if appropriate.

Appendix 1: Technical team interpretation of dapagliflozin placement in the HFrEF pathway



Technical team's positioning	Company's positioning	Population
a.		As an add on to standard treatment (ACEi / ARBs + BB ± MRAs) when responding to first line options
b.	#1	As an add on to standard treatment (ACEi / ARBs + BB ± MRAs) when symptoms continue and sacubitril valsartan would be suitable but not yet used
c.	#2	As an add on to standard treatment (ACEi / ARBs + BB ± MRAs) when symptoms continue and sacubitril valsartan would not be suitable
d.	#3	As an add on to second line treatment (sacubitril valsartan + BB ± MRA) when responding to second line treatment
e.		As an add on to second line treatment (BB ± MRA) when no longer responding to second line treatment. Unclear whether sacubitril valsartan or ACEi / ARBs would also be given.

ID1656 Dapagliflozin – Technical Engagement Response

Questions for company

1. Based on the technical team populations a. – e. in Appendix 1 (page 17), please complete the below table to detail each place dapagliflozin would be used in the HF pathway:

The expected licensed indication for dapagliflozin in heart failure with reduced ejection fraction (HFrEF) is for the treatment of [redacted]. Therefore, any patient who is NYHA class I will not be eligible for dapagliflozin for the treatment of HFrEF. However, these patients may be eligible for dapagliflozin for other licensed indications e.g. diabetes.

HFrEF symptoms, such as breathlessness, swelling and fatigue, rarely resolve entirely, even following a response to therapy, and patients classified as NYHA class I (asymptomatic) represent less than 10% (1) of all people living with HFrEF. The overall therapeutic goal with any medication is to control HF symptoms and reduce risk of hospitalisation and mortality. Approaches towards the medical management of HFrEF patients vary across the UK with regards to the timeframe by which patients are escalated to subsequent treatments, however, there is general consensus that if symptoms remain fully or partially unresolved, a patient should progress to the next treatment in the pathway. In the case of the proposed positioning of dapagliflozin, if symptoms persist following initial therapy (angiotensin-converting enzyme inhibitor/ angiotensin receptor blocker [ACEi/ARB], beta-blocker, ± mineralocorticoid receptor antagonist [MRA, in patients who can tolerate MRA]), the treating health care professional (see details on treatment setting below) should consider the addition of dapagliflozin.

With this approach, a patient taking ACEi/ARB, beta-blocker, dapagliflozin ±MRA who continues to show symptoms would be considered for subsequent treatment to manage the unresolved symptoms. If eligible, a likely next step following dapagliflozin initiation would be initiation of sacubitril valsartan and discontinuation of ACEi/ARB. In the DAPA-HF trial (2), a benefit in cardiovascular (CV) death and worsening HF was observed with dapagliflozin compared with placebo regardless of whether patients received sacubitril valsartan as part of their background HF therapy (10.5% of patients received sacubitril valsartan as part of their background therapy). The trial investigated dapagliflozin as an add-on therapy to background HF therapy, and as such, data from DAPA-HF provides evidence of the safety and efficacy of concomitant use of dapagliflozin and ongoing treatment with sacubitril valsartan. Based on the eligibility criteria for sacubitril valsartan as detailed in NICE TA388 (3) and the sacubitril valsartan SmPC, all patients who would be eligible for sacubitril valsartan would also be eligible for dapagliflozin.

It should be clarified that the statement “clinical expert submission to NICE state that dapagliflozin would ideally be used as an add on to sacubitril valsartan” on page 3 of the Technical Report is likely to be a misinterpretation. It is understood from the Technical Engagement call that this statement is based on the following statements from the clinical experts:

- *“Sac/Val is an alternative agent. Dapagliflozin is an add-on. If the patient is not responding to ACEi, one might change to Sac/Val or use Dapa. Ideally, one would use both.”* [page 267, Technical Engagement Papers]
- *“I would not see this as a ‘one or the other’ situation, patients may require both. I would envisage it [dapagliflozin] being an option alongside sacubitril/valsartan where clinical judgement would decide what the most appropriate option was.”* [page 282, Technical Engagement Papers]

AstraZeneca believe the clinical expert statements should be interpreted as follows based on our understanding of the HFrEF treatment pathway:

- Sacubitril valsartan is an alternative agent to ACEi/ARB, as sacubitril valsartan includes the ARB, valsartan, which should not be used together with any other ACEi/ARB. Dapagliflozin is an add-on therapy to current standard care. If patients still have symptoms after the use of ACEi, they should either initiate sacubitril valsartan (and discontinue the ACEi) or they should initiate dapagliflozin (without the need to discontinue the ACEi). Ideally patients should receive both sacubitril valsartan and dapagliflozin.
- It is not a situation of using either sacubitril valsartan or dapagliflozin, instead patients may require treatment with both sacubitril valsartan and dapagliflozin. Dapagliflozin is likely to be a treatment option for patients who would currently be considered for sacubitril valsartan and clinical judgement would decide whether dapagliflozin or sacubitril valsartan would be the most appropriate treatment option.

In summary, nearly all HF patients would continue to experience symptoms following initiation and use of ACEi/ARB, beta-blocker, ±MRA, and would therefore be captured as part of population ‘b’ illustrated in Appendix 1 of the Technical Report. The remainder of patients in whom symptoms fully resolve, would belong to population ‘a’ – there will be very few patients in this category, and these patients would not be eligible for treatment with dapagliflozin if they no longer have any HF symptoms (i.e. no fatigue, no breathlessness, no swelling). Similarly, nearly all HF patients would continue to still experience symptoms following initiation of sacubitril valsartan, and as such the majority of patients on sacubitril valsartan would belong to population ‘e’ as illustrated in Appendix A of the Technical Report.

With respect to the treatment initiation setting, AstraZeneca proposes that dapagliflozin can be initiated in all treatment settings listed below, so that patients with a confirmed diagnosis of HFrEF can benefit from treatment with dapagliflozin as soon as possible:

- Primary care setting, by general practitioner (GP), practice nurse, pharmacist, or GP with specialist interest (GPwSI)
- Community care setting by HF community nurse or community HF pharmacist
- HF specialist setting by HF consultant, HF nurse or HF pharmacist

A significant proportion of symptomatic HF patients are already managed in primary care. In NG106, NICE recommends that *'the primary care team should take over routine management of heart failure as soon as it has been stabilised and its management optimised'* (4). For symptomatic HFrEF patients being managed in primary care, dapagliflozin should be one of the available options for treatment escalation based on the strength of evidence from DAPA-HF and feedback from UK clinical experts. In many situations, primary care clinicians are positioned to initiate dapagliflozin treatment in a safe and timely manner. AstraZeneca recognises that primary care teams have extensive experience in prescribing dapagliflozin, which has been licenced for uncontrolled type 2 diabetes mellitus (T2DM) since 2012, including in patients with comorbid HF.

[redacted]

In response to the current COVID-19 pandemic, a key NHS priority is to keep patients away from the hospital setting when possible to minimise the risk of virus transmission (5, 6). In a letter issued by the CEO of the NHS, Simon Stevens, in August 2020 laying out the priorities for the third phase of the NHS COVID-19 response, it is stressed that physical outpatient appointments should be avoided and a collaborative approach between primary and secondary care should be adopted, including the use of advice and guidance where possible to treat patients without an onward referral. Some organisations have issued advice on this issue, including the British Cardiovascular Society (BCS) which recommends in its recently published 'Future of Cardiology' paper, that once a treatment plan has been initiated by a HF specialist, patients may be integrated into the community HF nurse service or primary care to minimise the need for future face-to-face consultations (7). The British Society for Heart Failure also state in their position statement on the COVID-19 planned recovery stage that only intermediate and high-risk HF patients should be prioritised for specialist care at this time (8).

Referral into specialist care solely for consideration of dapagliflozin will result in unnecessary delay to therapeutic escalation, increasing the risk of decompensation and hospitalisation, while introducing unnecessary COVID-19 infection risk associated with face-to-face outpatient appointments. As such, AstraZeneca propose that primary care managed HF patients do not require a specialist care referral for consideration and initiation of dapagliflozin; i.e. AstraZeneca proposes that dapagliflozin can be initiated in primary care without specialist recommendation. Furthermore, AstraZeneca propose that no specific training or resources will be required for primary care initiation of dapagliflozin in HF, above and beyond the training already required for initiation of existing HF treatments, such as ACEi, ARB, beta-blocker and MRA. NICE NG106 recommends that the primary care team should arrange access to specialist HF services if needed (4). Should this be required, AstraZeneca propose that primary care clinicians could consider initiation of dapagliflozin in conjunction with the referral to specialist HF services. This will ensure that patients with a confirmed diagnosis of HFrEF can benefit from treatment with dapagliflozin whilst awaiting specialist reassessment.

AstraZeneca are concerned that restriction of dapagliflozin initiation to the HF specialist team may unnecessarily limit access to patients who would benefit. As 34% of HF patients can already access dapagliflozin in primary care due to the presence of comorbid T2DM, there is a significant risk of inequality of care for HF patients without T2DM (9).

Technical team population	Population in company submission	Population size in NHS	Background therapy*	Comparator	Primary or specialist care initiation and monitoring	Justification
a.	Not in company submission	N/A	ACEi/ARB, beta-blocker, ±MRA	N/A	N/A	All patients whose symptoms remain fully or partially unresolved with ACEi/ARB, beta-blocker, ±MRA would be classified as "symptoms continue" and therefore be part of populations 'b' or 'c'. Therefore, it can be assumed that patients in population 'a' do not have any symptoms. Population 'a' is not relevant for dapagliflozin, as dapagliflozin will be indicated [redacted].
b.	Base case analysis #1	~13,000 patients†	ACEi/ARB, beta-blocker, ±MRA	Sacubitril valsartan	Either primary care or specialist care initiation. All patients with HF are expected to be referred to and monitored by specialist care, as part of current standard care in line with NG106.	This population reflects patients who would currently be eligible to receive sacubitril valsartan in UK clinical practice, that is, in accordance with the marketing authorisation of sacubitril valsartan, this population excludes patients with EF>35% and excludes patients with high potassium levels and/or hypotension. It is proposed that dapagliflozin could be initiated in both the primary care or specialist care settings. The benefits with primary care initiation is that patients would not need to wait for a specialist appointment and could therefore benefit from dapagliflozin without delay.

Technical team population	Population in company submission	Population size in NHS	Background therapy*	Comparator	Primary or specialist care initiation and monitoring	Justification
c.	Base case analysis #2	~118,000 patients‡	ACEi/ARB, beta-blocker, ±MRA	Placebo	Either primary care or specialist care initiation. All patients with HF are expected to be referred to and monitored by specialist care, as part of current standard care in line with NG106.	This population reflects patients who would currently receive ACEi/ARB, beta-blocker, ±MRA (according to tolerability), and who would not receive any further treatment intensification with sacubitril valsartan, because their EF>35%, they have high potassium and/or hypotension. This patient group also includes patients who are eligible for sacubitril valsartan but who do not receive sacubitril valsartan due to the complexity associated with sacubitril valsartan initiation and titration. It is proposed that dapagliflozin could be initiated in both the primary care or specialist care settings. The benefit of primary care initiation is that patients would not need to wait for a specialist appointment and could therefore benefit from dapagliflozin without delay.
d.	Not in company submission	N/A	Sacubitril valsartan, beta-blocker, ±MRA	N/A	N/A	Assuming patients who ”respond” show no symptoms of HF, then this positioning is not relevant for dapagliflozin, as dapagliflozin is expected to be indicated [redacted]. All other patients with a background therapy of sacubitril valsartan, beta-blocker, ±MRA would have symptoms, and therefore be captured as part of e (see below).

Technical team population	Population in company submission	Population size in NHS	Background therapy*	Comparator	Primary or specialist care initiation and monitoring	Justification
e.	Base case analysis #3	~35,000 patients§	Sacubitril valsartan, beta-blocker, ±MRA	Placebo	Sacubitril valsartan is initiated in the specialist care setting. Subsequent monitoring and disease management is carried out in either the primary care setting or by the HF specialist team, depending on clinical judgement. Further treatments, including dapagliflozin add-on therapy, can be initiated and monitored either by the primary care team or by the HF specialist team.	This population reflects patients who would currently receive sacubitril valsartan, beta-blocker, ±MRA (according to tolerability), but who still experience HF symptoms. Sacubitril valsartan is initiated in the specialist setting, but these patients may subsequently be managed in the primary care setting following and sacubitril valsartan titration. It is proposed that dapagliflozin could be initiated by the primary care team or by the HF specialist team, as an add-on therapy.

* If failing treatment please clarify changes to previous treatment regime

† As per budget impact analysis form, there are 258,328 HFrEF patients eligible for dapagliflozin in England. The CPRD data (see Table 5 of company submission) suggest 50.8% of HF patients receive ACEi/ARB, beta-blocker, ±MRA. Assuming 10% of these patients are currently offered sacubitril valsartan, based on clinical expert opinion from 1:1 interviews, the number of patients for population "b" is ~13, 000 patients (258,328×0.508×0.10)

‡ As per budget impact analysis form, there are 258,328 HFrEF patients eligible for dapagliflozin in England. The CPRD data (see Table 5 of company submission) suggest 50.8% of HF patients receive ACEi/ARB, beta-blocker, ±MRA. Assuming 90% of these patients are not currently offered sacubitril valsartan, based on clinical expert opinion from 1:1 interviews, the number of patients for population "c" is ~118, 000 patients (258,328×0.508×0.90)

§ Based on IQVIA sales data of sacubitril valsartan in England between Aug 2019 to Jul 2020.

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; EF, ejection fraction; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; MRA, mineralocorticoid receptor antagonist; N/A, not applicable; UK, United Kingdom.

2. Given the potential interaction between treatment and NYHA class (shown in figure 11 of the company submission), what differences in the cost effectiveness estimates would be anticipated if NYHA classification score was used in place of KCCS-TSS in the model, (please provide justification)?

As discussed and accepted by NICE and the ERG during the decision problem meeting, a Kansas City Cardiomyopathy Questionnaire total symptom score (KCCQ-TSS) modelling approach was used to address the current decision problem, as an improved modelling approach to the two-state models previously used in NICE technology appraisals TA388 and TA267. Both New York Heart Association (NYHA) class and KCCQ-TSS were considered during model conceptualisation for defining the health states within the model. The KCCQ-TSS modelling approach was chosen based on the ability of the KCCQ to provide patient-reported health status comprehensively and robustly, for its sensitivity and responsiveness to change, and additionally to avoid the use of NYHA transition probabilities derived from the DAPA-HF trial which lacked face validity (see below).

KCCQ is a more reliable measure of HF symptom severity than NYHA classification

The KCCQ provides scores between 0 to 100, derived from patients answering 23 questions covering 6 domains (physical limitations, symptoms, social limitations and quality of life) and provides a more comprehensive and robust assessment of a patient's health status that is more responsive to change (10), compared to the NYHA classification system. The KCCQ-TSS is calculated based on the symptom frequency and symptom burden domains of the KCCQ. The NYHA classification system only provides 4 score options, and is derived based on a clinician's interpretation of the patient's functional limitation. NYHA classification is associated with poor inter-rater concordance, poor reproducibility, and poor correlation between NYHA classification and more objective HF severity measures (11-14). The subjectivity of the NYHA classification system could also be observed from the DAPA-HF trial data and the fluctuation in NYHA class assignment.

KCCQ-TSS data are more complete compared to NYHA classification data

KCCQ responses were collected at baseline, 4 months, 8 months, 12 months, every 12 months thereafter and at the study closure visit. While NYHA classification was only collected at baseline, 4 months, 8 months and at the study closure visit. As such, more data are available for KCCQ from DAPA-HF.

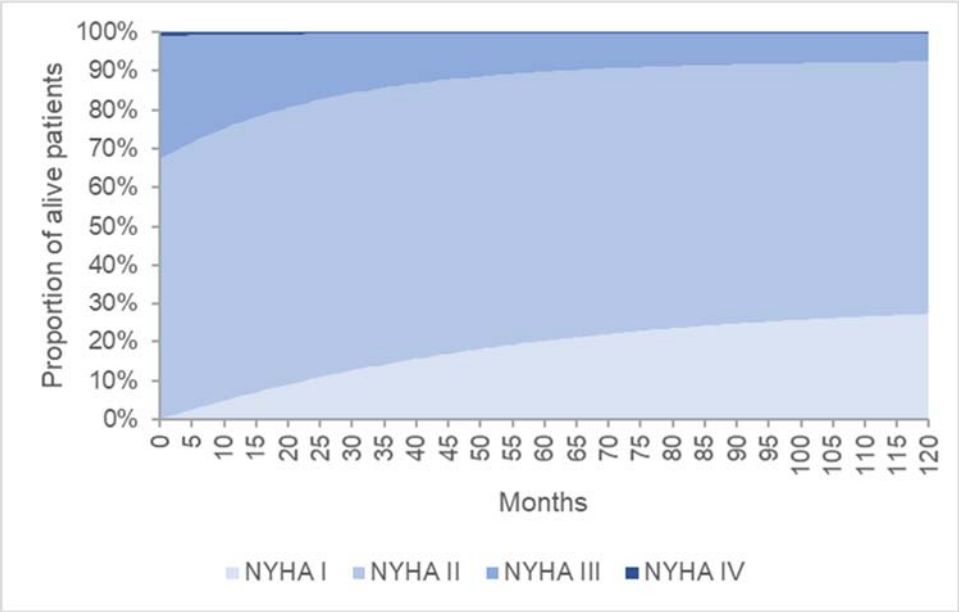
NYHA transition probabilities lack face validity; KCCQ-TSS transition probabilities are better aligned with expectations

As part of the model conceptualisation process, NYHA class transition probabilities were derived from the DAPA-HF trial. Overall, more patients improved in NYHA class than deteriorated in NYHA class, with the NYHA transition probabilities predicting an increasing proportion of alive patients with NYHA class I and II over time (see Figure 1), which is at odds with the chronic progressive nature of HF. Analysis of the individual patient data showed that the increase in the proportion of patient with NYHA I/II was due to patients transitioning into these health states from more severe health states, and **not** due to a survival effect (whereby patients in NYHA I/II survive longer than patients in NYHA III/IV, thus contributing to a larger proportion of the alive patients in later years). In contrast, the modelled health state occupancy by KCCQ-TSS quartiles showed an initial improvement in symptoms in the first 4–8 months of the trial, and remained generally constant thereafter without further improvement over time (see Figure 2). The health state occupancy by KCCQ-TSS quartiles over time were therefore better aligned with the expected changes in HF symptoms.

Additionally, there were no or very few patients with NYHA I and IV at baseline, respectively, which means that the transition probabilities from these health states were based on small patient numbers and therefore highly uncertain.

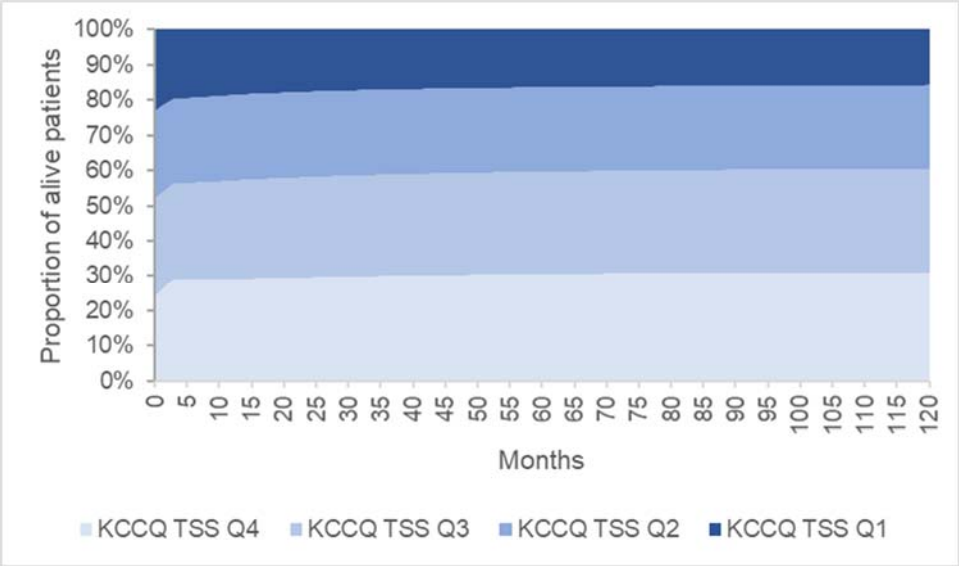
If the NYHA transition probabilities had been implemented in a NYHA class based cost-effectiveness model, the cost-effectiveness estimates for the overall population would be biased in favour of dapagliflozin. This is because the treatment effect of dapagliflozin was observed to be greater in patients with NYHA II (likely chance finding, see below), compared with NYHA III and IV, and as such, when the proportion of patients with NYHA II increase, the dapagliflozin treatment effect will be skewed towards the higher treatment effect observed in the NYHA II subgroup.

Figure 1. Modelled health state occupancy over time by NYHA class, estimated using transition probabilities derived from DAPA-HF



Patients with NYHA IV have the most severe symptoms
Health state occupancy estimated based on NYHA transition probabilities derived based on data from the pooled placebo and dapagliflozin arms of DAPA-HF; transitions were counted between NYHA class health states in monthly intervals, using last observation carried forward to reconcile differences in the model cycle length (monthly) and the frequency of NYHA measurements (see clarification Q B4 for details)
NYHA classification was collected at baseline, 4 months, 8 months and at the study closure visit

Figure 2. Modelled health state occupancy over time by KCCQ-TSS quartiles at baseline, estimated using transition probabilities derived from DAPA-HF



Patients with KCCQ-TSS Q1 have the worse symptoms
Health state occupancy estimated based on KCCQ-TSS transition probabilities derived based on data from the placebo arm of DAPA-HF; transitions were counted between KCCQ quartile health states in monthly intervals, using last observation carried forward to reconcile differences in the model cycle length (monthly) and the frequency of KCCQ measurements (see clarification Q B4 for details)
KCCQ responses were collected at baseline, 4 months, 8 months, 12 months, every 12 months thereafter and at the study closure visit.

Overall, the results from a NYHA class based cost-effectiveness model are not expected to substantially differ from the KCCQ-TSS based model used in the company submission, with the exception for the likely bias in favour of dapagliflozin due to the NYHA transition probabilities skewing the population towards the NYHA I/II class health state.

2a. Please explain the different trends seen in NYHA class versus KCCQ-TSS change from baseline in the DAPA-HF trial. Given that they should both reflect disease severity and that KCCQ-TSS is used in the model but NYHA class is used in clinical practice, it is important that this difference is explored.

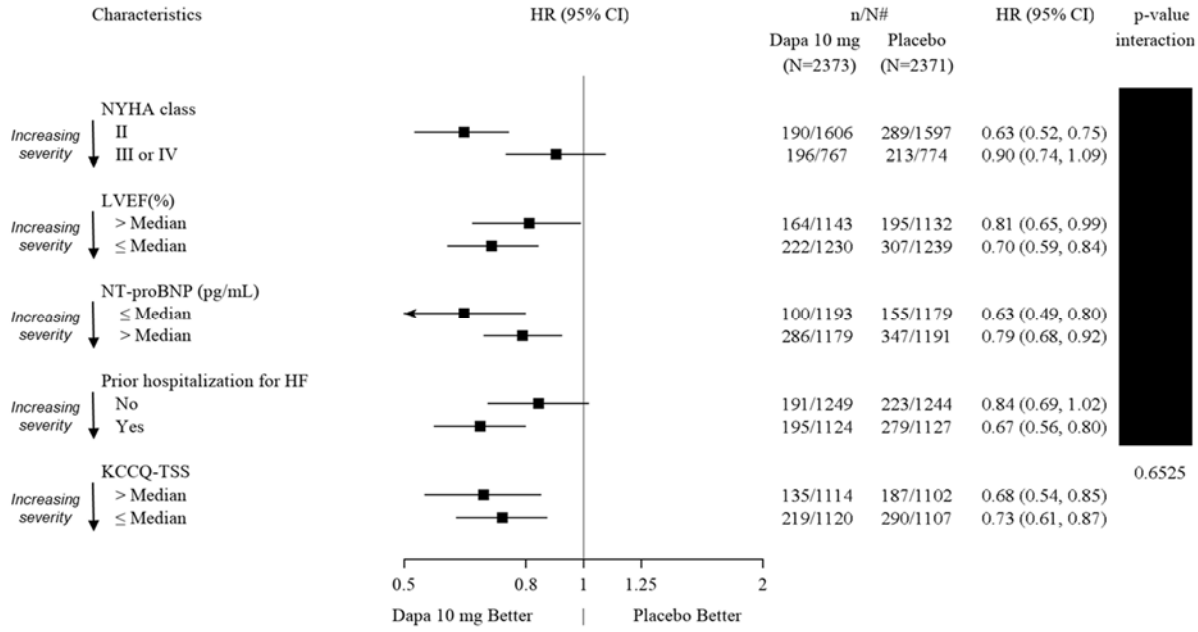
As clarified by the NICE Technical Team during the Technical Engagement call, this question concerns the results from the DAPA-HF subgroup analysis.

As discussed in response to clarification question B21c, the difference in treatment effect in patients with NYHA class III/IV versus NYHA class II at baseline is likely a chance finding, given the shortcomings of the NYHA classification and the consistency of treatment effect observed across subgroups by other measures of HF disease severity.

The consistency in treatment effect of dapagliflozin by HF disease severity is supported by subgroup analyses stratified by KCCQ-TSS, left ventricular ejection fraction (LVEF), NT-proBNP and prior hospitalisation for heart failure (hHF) at baseline (Figure 3) which do not support the presence of any interaction between treatment effect and HF disease severity. Additionally, the direction of trends in treatment effect with disease severity were not consistent across the different disease severity measures, lending further support that the results by NYHA II and III/IV represent a chance finding. For example, when disease severity is approximated by prior hHF or LVEF, patients with more severe HF (prior hHF – yes; LVEF ≤ median) appear to benefit from a numerically larger treatment effect, whereas the reverse is true when disease severity is approximated by KCCQ-TSS or NT-proBNP.

In summary, given the multiple testing and lack of type 1 error control associated with subgroup analyses, and the consistency in treatment effect across subgroups by disease severity as approximated by several measures, the difference in treatment effect between the two NYHA subgroups is thought to be a spurious finding, and the results from the adequately powered, pre-specified and multiplicity-controlled overall population represent the most robust and appropriate estimate of the treatment effect.

Figure 3. Subgroup analyses of the primary endpoint from DAPA-HF by different disease severity measures



3. Will dapagliflozin be used in people with acute decompensated HF in the NHS? If yes, please clarify how this population is included in the evidence base.

Acute HF refers to patients who have an acute HF decompensation, i.e. a sudden worsening of signs and symptoms of HF, often requiring hospitalisation to treat the acute fatigue, dyspnoea and oedema. The expected indication for dapagliflozin [redacted]

4. How many people discontinued dapagliflozin due to lack of efficacy in the DAPA-HF trial? Is this likely to be different in clinical practice.

Data on discontinuation due to “lack of efficacy” are not collected in cardiovascular outcome trials, such as HF trials, as the treatment goal in HF management is to reduce mortality and morbidity, and as such there is no objective way to measure efficacy other than through events avoided.

The reasons for discontinuation of study drug are summarised in the table below, with ‘subject decision’ and ‘adverse event’ being the most common reasons for discontinuation in both the dapagliflozin and placebo arms of the DAPA-HF trial. The number of patients discontinuing study drug was similar in both treatment groups and as such treatment discontinuation is not expected to influence the estimate of relative treatment effect compared to placebo.

Table 1. Reasons for discontinuation of study drug

	Number (%) of subjects	
	Dapagliflozin	Placebo
Subjects randomised	2,373	2,371
Subjects who did not receive IP	5 (0.2)	3 (0.1)
Subjects who discontinued IP	249 (10.5)	258 (10.9)
Subject decision	[redacted]	[redacted]
Adverse event	[redacted]	[redacted]
Severe non-compliance to protocol	[redacted]	[redacted]
Development of study specific discontinuation criteria	[redacted]	[redacted]
Confirmed DKA	[redacted]	[redacted]
Positive pregnancy test	[redacted]	[redacted]
Other	[redacted]	[redacted]

Abbreviations: DKA, diabetic ketoacidosis; IP, investigational product
Source: DAPA-HF CSR Table 14.1.1

5. Please complete the additional analyses below:

5a. Positioning in pathway: Scenario analyses including use of dapagliflozin as an add on to standard therapy for each positioning described in response to question 1 [appendix 1] Please include subsequent therapies (such as sacubitril valsartan) if appropriate.

As explained in response to question 1, there are three relevant positionings for dapagliflozin in the HF treatment pathway:

- In symptomatic HF patients, as an alternative to sacubitril valsartan in patients on ACEi/ARB, beta-blocker, ±MRA
- In symptomatic HF patients, as add-on therapy to ACEi/ARB, beta-blocker, ±MRA
- In symptomatic HF patients, as add-on therapy to sacubitril valsartan, beta-blocker, ±MRA

The cost-effectiveness associated with each of the 3 positionings in the HF treatment pathway are provided in response to question 6 (company revised base case analyses).

5b. Use in primary care: Scenario analyses including costs of treatment and monitoring in specialist care

HF patients are typically diagnosed by the HF specialist team, but are subsequently managed by either the multidisciplinary HF specialist team, or by the primary care team, depending on locality. As explained in response to question 1, AstraZeneca proposes that dapagliflozin can be initiated in all treatment settings listed below, so that patients with confirmed diagnosis of HFrEF can benefit from treatment with dapagliflozin as soon as possible:

- Primary care setting, by GP, practice nurse, pharmacist, or GPwSI
- Community care setting by HF community nurse or community HF pharmacist
- HF specialist setting by HF consultant, HF nurse or HF pharmacist

The annual health state costs in the model already capture the cost of GP visits, accident and emergency (A&E) referrals, cardiologist outpatient visits and other outpatient visits (based on McMurray et al. 2018 (15)). The initiation and use of dapagliflozin is unlikely to be associated with any additional monitoring or health care resource use beyond what would be expected as part of current HF management; [redacted] During the Technical Engagement call, the NICE Technical Team suggested it may be of interest to consider any costs associated with the monitoring of renal function in conjunction with the use of dapagliflozin. Renal function is already routinely monitored by the HF specialist team by measuring patients estimated glomerular filtration rate (eGFR) through a blood test.

In patients with T2DM, renal function is monitored by the primary care team on an annual basis in line with NG28 and CG182. As such, for HF patients with comorbid T2DM, eGFR is already monitored on an annual basis in the primary care setting. In HF patients who do not have comorbid T2DM, eGFR monitoring can take place in conjunction with routine GP appointments. The cost associated with a blood test for creatinine, including staff costs and equipment needed, is estimated to be £6.36 in 2018/2019 costs (NG45 Appendices: £6.00 in 2015 (16)). The impact of additional annual blood tests for eGFR monitoring in the dapagliflozin arm is minimal (+£62/QALY to +£63/QALY compared to the original company base cases) (Table 2, Table 3).

Table 2. Scenario analysis of analysis #2, with cost of annual blood-tests included

	Dapagliflozin + SC (intervention)	Placebo + SC (comparator)	Incremental	ICER (£/QALY)
Life years	6.183	5.609	0.574	£5,898
QALYs	4.596	4.125	0.471	
Costs (£)	£14,988	£12,209	£2,779	

Scenario analysis run by applying the relevant changes to the original company base case, using the v0.3 version of the model provided as part of the clarification question response.
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years, SC, standard care.

Table 3. Scenario analysis of analysis #3, with cost of annual blood-tests included

	Dapagliflozin + SC (intervention)	Placebo + SC (comparator)	Incremental	ICER (£/QALY)
Life years	5.990	5.428	0.562	£5,934
QALYs	4.444	3.983	0.461	
Costs (£)	£15,630	£12,895	£2,735	

Scenario analysis run by applying the relevant changes to the original company base case, using the v0.3 version of the model provided as part of the clarification question response.
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years, SC, standard care.

5c. Generalisability of the DAPA-HF trial:

5c1. MAIC results using baseline characteristics from the European population

The NICE Technical Team clarified during the Technical Engagement call that a matching-adjusted indirect comparison (MAIC) is not needed in response to this question, and that a indirect treatment comparison (ITC) using the Bucher method would be sufficient.

There are several reasons an ITC between the European subgroup from DAPA-HF and the Western European subgroup from PARADIGM-HF is **not** appropriate:

- The DAPA-HF trial was powered for the primary composite endpoint in the full study population and the PARADIGM-HF trial was powered for CV-mortality in the full study populations. As such, neither of the two trials were powered to evaluate the treatment effect in subgroups. The Europe subgroup only constituted 45% (or [redacted]% if restricting to subgroup with ACEi background therapy for better alignment with the comparator arm in PARADIGM-HF [ITC anchor]) of the full DAPA-HF trial population, whereas the Western Europe subgroup only constituted 20% of the full PARADIGM-HF trial population. The full study populations of the DAPA-HF trial and the PARADIGM-HF trial provide the best estimates of the treatment effects of dapagliflozin and sacubitril valsartan, respectively.
- As acknowledged by the NICE Technical Team in the Technical Report, there were differences in the study design of DAPA-HF and PARADIGM-HF including the presence of a run-in period in PARADIGM-HF which selected patient for tolerability of sacubitril valsartan (20% of patients discontinued study during the 6- to 8-week run-in period) (17). There was no run-in period in DAPA-HF. The NICE Technical Team concluded in the Technical Report that this would likely underestimate the treatment effect of dapagliflozin in the MAIC and ITC. The same bias would apply to an ITC of the Europe subgroup from DAPA-HF versus the Western Europe subgroup of PARADIGM-HF, due to differences in trial design and trial population characteristics.
- The European subgroup from DAPA-HF and the Western European subgroup from PARADIGM-HF are not comparable, as they do not capture the same countries.
- AstraZeneca understands that the NICE Technical Team's request for European data is in the context of generalisability of the trial data to UK clinical practice. However, it is likely that the overall DAPA-HF population is more relevant than the Europe subgroup to the multi-ethnic UK population, which consists of 86% white, 3% black, 8% Asian and 4% other/mixed (18). The baseline characteristics of the overall DAPA-HF population is more ethnically diverse with 70% white, 5.1% black, 23.3% Asian and 1.6% other, whereas the Europe subgroup was 99.9% white. Similarly, 98% of patients in the PARADIGM-HF Western European subgroup were caucasian (19). The focus on the use of data from Europe/Western Europe subgroups may therefore not provide an appropriate estimate of the treatment effect expected across the ethnically diverse UK HF population, and could further contribute to existing issues relating to ethnic inequalities in health, as highlighted by Public Health England (20). Additionally, given the harmonisation of HF guidelines, across Europe and North America, and the widespread use of these guidelines across all regions of the world (21), the overall DAPA-HF trial population is likely to provide the best estimate of the dapagliflozin treatment effect in UK clinical practice.

In order to comply with the request from the NICE Technical Team, despite the major limitations mentioned above, an ITC (Bucher method) of the Europe subgroup from DAPA-HF versus the Western Europe subgroup from PARADIGM-HF was conducted. As per the methods used in the original company submission, which were also selected by the ERG for the ERG base case, the subgroup of patients on ACEi background therapy from the Europe subgroup of DAPA-HF were used, to make the DAPA-HF control arm more similar to the PARADIGM-HF control arm (ITC anchor). The HRs for key endpoints for DAPA-HF overall population, Europe subgroup, and Europe + ACEi subgroup are presented in Table 4, alongside the HRs from the PARADIGM-HF overall population and Western Europe subgroup extracted from Kristensen et al. 2016 (19).

The results from the ITC show that there are no statistically significant differences between the DAPA-HF Europe subgroup and the PARADIGM-HF Western Europe subgroup (Table 4). The wide 95% confidence intervals (CIs) in the ITC results reflect the uncertainty associated with the use of underpowered subgroup data. Additionally, due to differences in DAPA-HF and PARADIGM-HF study designs, there is additional uncertainty associated with the ITC not captured by the wide 95% CIs. Given the limitations of this ITC as highlighted above, the results should be treated with major caution, and instead it would be more appropriate to refer to the ITC conducted in the overall populations of the DAPA-HF and PARADIGM-HF trials (see company submission, presented as “unadjusted comparisons” within the MAIC section).

For completeness, a scenario analysis of the cost-effectiveness analysis of dapagliflozin versus sacubitril valsartan was conducted using the results from the Europe/Western Europe subgroups ITC. The results are consistent with the revised company base case, with dapagliflozin remaining dominant over sacubitril valsartan (Table 5).

Table 4. ITC of dapagliflozin versus sacubitril valsartan based on the Europe subgroup from DAPA-HF and Western Europe subgroup from PARADIGM-HF

Endpoint	Dapagliflozin + SC vs placebo + SC, DAPA-HF overall (HR, 95% CI) N=4,744	Dapagliflozin + SC vs placebo + SC, DAPA-HF, Europe subgroup (HR, 95% CI) N=2,154 (45.4% of overall population)	Dapagliflozin + ACEi vs placebo + ACEi, DAPA-HF, Europe and ACEi background therapy subgroup (HR, 95% CI) [redacted] (% of overall population)	Sacubitril valsartan vs enalapril, PARADIGM-HF overall (HR, 95% CI) N=8,442	Sacubitril valsartan vs enalapril, PARADIGM-HF, Western Europe subgroup (HR, 95% CI) N=1,680 (19.9% of overall population)	ITC: dapagliflozin + ACEi vs sacubitril valsartan, Bucher method (HR, 95% CI)
CV death and hHF†	0.75 (0.65, 0.85)	[redacted]	[redacted]	0.80 (0.73, 0.87)	0.88 (0.71, 1.08)	[redacted]
hHF	0.70 (0.59, 0.83)	[redacted]	[redacted]	0.79 (0.71, 0.89)	0.89 (0.69, 1.15)	[redacted]
CV death	0.82 (0.69, 0.98)	[redacted]	[redacted]	0.80 (0.71, 0.89)	0.84 (0.63, 1.11)	[redacted]
All-cause mortality	0.83 (0.71, 0.97)	[redacted]	[redacted]	0.84 (0.76, 0.93)	0.99 (0.78, 1.26)	[redacted]

The ITC was carried out based on the HRs from the subgroup of patients from the Europe subgroup of DAPA-HF who received ACEi background therapy, to generate an anchor that is more aligned with the comparator arm of PARADIGM-HF. The ERG used the results from this ITC approach in their base case (but of the overall DAPA-HF population).
† Primary endpoint in PARADIGM-HF and secondary endpoint in DAPA-HF
Abbreviations: CI, confidence interval; CV, cardiovascular; HF, heart failure; hHF, hospitalisation for heart failure; HR, hazard ratio; ITC, indirect treatment comparison; vs, versus.
Sources: McMurray et al. 2019 (22), Kristensen et al. 2016 (19)

Table 5. Scenario analysis of base case analysis #1, using results from unadjusted ITC between European subgroup from DAPA-HF and Western European subgroup from PARADIGM-HF (Bucher method)

	Dapagliflozin + SC (intervention)	Sacubitril valsartan + SC (comparator)	Incremental	ICER (£/QALY)
Life years	6.213	6.157	0.056	Dominant
QALYs	4.262	4.221	0.040	
Costs (£)	£14,496	£17,448	-£2,952	

Scenario analysis run by applying the relevant changes to the original company base case, using the v0.3 version of the model provided as part of the clarification question response.
Abbreviations: ICER, incremental cost-effectiveness ratio; ITC, indirect treatment comparison; LYG, life years gained; QALYs, quality-adjusted life years, SC, standard care.

5c2. Effectiveness results using the European population survival adjusted based on the same characteristics as in the full population

As outlined above in response to question 5c1, there are several reasons the use of the data from the European subgroup does not provide a reliable estimate of the treatment effect that is generalisable to the UK population:

- The DAPA-HF trial was powered for the primary composite endpoint in the full study population. As such the trial is not powered to evaluate the treatment effect in subgroups. The full study population of the DAPA-HF trial provide the best estimates of the treatment effects of dapagliflozin. No interaction for the primary endpoint was observed by region from the subgroup analysis (p-value for interaction: [redacted]), and therefore there is no justification for using the results from the Europe subgroup (n=2,154; 45% of full study population), as subgroup data are associated with less power.
- There is no biological plausibility for treatment effect to differ by geographic region. The Technical Report states that TA388 previously noted that there may be geographical differences in disease aetiology, clinical management and baseline risk of HFrEF, that may contribute to the observed numerical differences in treatment effect between geographical regions. Subgroup analysis from DAPA-HF by disease aetiology (ischemic versus non-ischemic/unknown aetiology) shows the treatment effect of dapagliflozin to be consistent regardless of disease aetiology (HR for primary endpoint: 0.77 versus 0.71, p-value for interaction: [redacted], see Figure 11 of company submission). Similarly, extensive subgroup analyses by combinations of background therapy have been conducted and published in the peer-reviewed European Heart Journal (23), providing robust evidence that the treatment effect of dapagliflozin is consistent regardless of background therapy and dose of background therapy (see Figure 4 and Figure 5). As such, there is no evidence to support a biological plausibility for relative treatment effect to differ by geographic region.
- It is likely that the overall DAPA-HF population is more relevant than the Europe subgroup to the multi-ethnic UK population. For example, the baseline characteristics of the overall DAPA-HF population is more ethnically diverse with 70% white, 5.1% black, 23.3% Asian and 1.6% other, whereas the Europe subgroup was 99.9% white. The focus on the use of data from the Europe subgroup may therefore not provide an appropriate estimate of the treatment effect expected across the ethnically diverse UK HF population, and could further contribute to existing issues relating to ethnic inequalities in health, as highlighted by Public Health England (20).

Overall, guidelines and clinical management of chronic HF are similar across Europe and North America, with the guidelines consistently focusing on stabilisation of HF using evidence-based pharmacological or device therapies according to patient tolerability (21). The professional associations behind the guidelines in Europe (European Society of Cardiology), the US (American College of Cardiology, American Heart Association) and Canada (Canadian Cardiovascular Society) independently reached concordant recommendations (21, 24). Based on the concordant guidelines and HF management in North America and Europe, it may be relevant to also consider data from the North America subgroup, in a scenario analysis. The North America subgroup in DAPA-HF was generally comparable with the Europe subgroup, but was more racially diverse (Table 6). The baseline characteristics of the North America subgroup shows that the proportion of patients who were white, black, Asian and other were 76.8%, 17.9%, 2.8% and 2.5%, respectively. Results from DAPA-HF by geographic region are provided in Table 7.

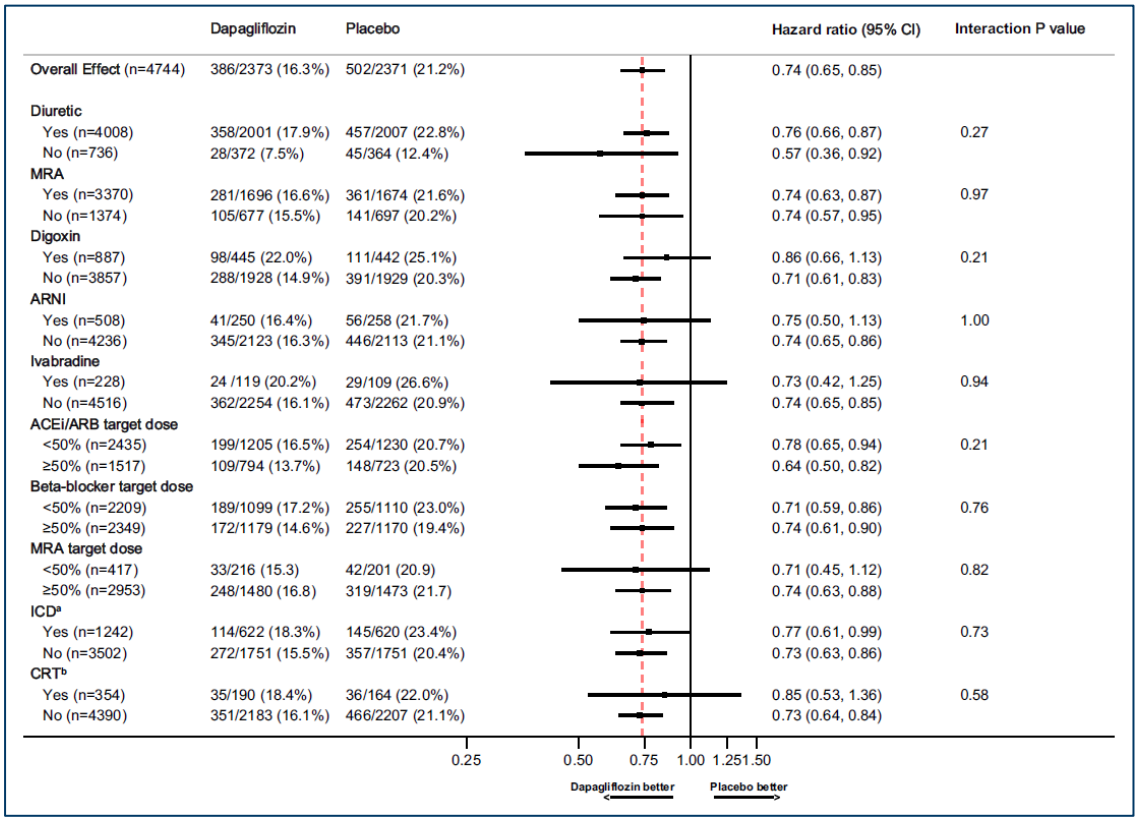
As outlined above, DAPA-HF was powered for the full study population, and therefore the results from the full population should be used in the first instance to provide the best estimates of the treatment effects of dapagliflozin. No interaction for the primary endpoint was observed by region from the subgroup analysis (p-value for interaction: [redacted]), and therefore there is no justification for using the results from a regional subgroup, as subgroup data are associated with loss of power.

Derivation of survival and risk equations

Due to the reasons provided above, the adjusted survival equations used in the model have not been re-derived using subgroup data. As with the cost-effectiveness results in the overall population based on the adjusted and unadjusted survival equations, the cost-effectiveness results based on adjusted survival equations derived from the Europe subgroup are also expected to be near-identical to the cost-effectiveness results based on the unadjusted survival equations from the Europe subgroup, as the source data are identical. The results using the adjusted and unadjusted survival equations for Europe are only expected to differ when the baseline characteristics inputs in the model differ to that of the Europe subgroup from the trial. Adjusted survival equations will 'adjust' the survival rate based on the baseline characteristics inputs used in the model, whereas the survival rate with unadjusted survival equations will not be adjusted ('unadjusted') and instead be based on the survival rate observed in the population/subgroup from which the equation was derived. Furthermore, due to the limited power associated with the use of subgroup data, it is likely that only a limited number of covariable would be statistically significant, limiting the number of coefficients in the resulting adjusted survival model.

As an alternative approach, the data from the North America subgroup have been pooled with data from the Europe subgroup (see rationale above) to generate unadjusted survival and risk equations for the pooled North America + Europe subgroup. These unadjusted survival and risk equations are used for scenario analyses in response to question 5c3 (Table 8–Table 9).

Figure 4. Subgroup analysis of primary endpoint in DAPA-HF by background therapy (from Docherty et al. 2020)



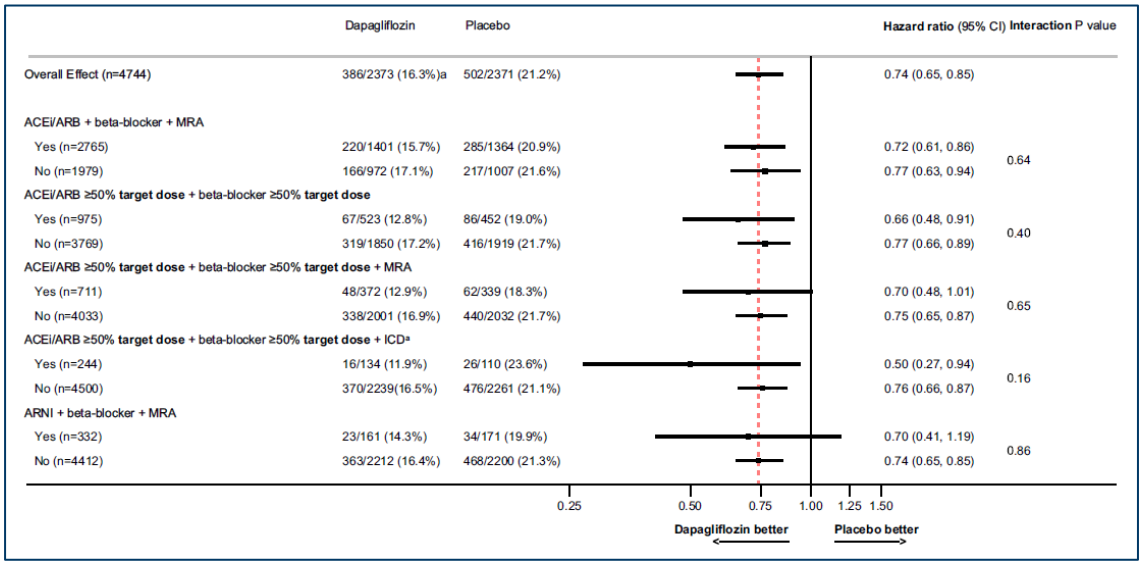
Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor neprilysin inhibitor; CI, confidence interval; CRT, cardiac resynchronization therapy; ICD, implantable cardioverter-defibrillator; MRA, mineralocorticoid receptor antagonist.

[a] ICD or cardiac resynchronization therapy with defibrillator.

[b] Cardiac resynchronization therapy with or without a defibrillator

Source: Docherty et al. 2020 (23)

Figure 5. Subgroup analysis of primary endpoint in DAPA-HF by background therapy (from Docherty et al. 2020)



Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor neprilysin inhibitor; CI, confidence interval; ICD, implantable cardioverter-defibrillator; MRA, mineralocorticoid receptor antagonist.

[a] ICD or cardiac resynchronization therapy with defibrillator.

Source: Docherty et al. 2020 (23)

Table 6. Baseline characteristics of Europe and North America subgroups of DAPA-HF

Demographic characteristic	Overall DAPA-HF population (N=4,744)	Europe (N=2,154)	North America (N=677)
Age, years, mean ± SD	66.3 ± 10.9	[redacted]	[redacted]
Female sex, n (%)	1,109 (23.4)	[redacted]	[redacted]
BMI, kg/m^2, mean ± SD	28.2 ± 6.0†	[redacted]	[redacted]
Race, n (%) White Black Asian Other	 3,333 (70.3) 226 (4.8) 1,116 (23.5) 69 (1.5)	[redacted]	[redacted]
NYHA functional classification, n (%) II III IV	 3,203 (67.5) 1,498 (31.6) 43 (0.9)	[redacted]	[redacted]
Heart rate, beats per min, mean ± SD	71.5 ± 11.7	[redacted]	[redacted]
Systolic blood pressure, mm Hg, mean ± SD	121.8 ± 16.3	[redacted]	[redacted]
LVEF, %, mean ± SD	31.1 ± 6.8	[redacted]	[redacted]
Median NT-proBNP, pg/mL (IQR)	1,437 (857, 2,650)	[redacted]	[redacted]
Principal cause of HF, n (%) Ischaemic Non-ischaemic Unknown	 2,674 (56.4) 1,687 (35.6) 383 (8.1)	[redacted]	[redacted]
Medical history, n (%) Hospitalisation for HF Atrial fibrillation Type 2 diabetes mellitus	 2,251 (47.4) 1,818 (38.3) 1,983 (41.8)†	[redacted]	[redacted]
eGFR Mean ± SD, mL/min/1.73 m^2 <60 mL/min/1.73 m^2, n (%)	 65.8 ± 19.4 1,926 (40.6)†	[redacted]	[redacted]
Heart failure medication, n (%) Diuretic ACEI ARB Sacubitril-valsartan Beta-blocker MRA Digitalis	 4,433 (93.4) 2,659 (56.0) 1,307 (27.6) 494 (10.4) 4,558 (96.1) 3,370 (71.0) 887 (18.7)	[redacted]	[redacted]

Abbreviations: ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BMI. Body mass index; eGFR, estimated glomerular filtration rate; HF, hear failure; IQR, interquartile range; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonists; NYHA, New York Heart Association; SD, standard deviation.
†N=4,742
‡N=675
Source: DAPA-HF CSR, data on file (IEMT5227) and data on file (IEMT5203).

Table 7: Efficacy outcomes in DAPA-HF by region subgroup

Outcome	Geographic subgroup region	Dapagliflozin		Placebo		HR (95% CI)	Interaction p-value
		N	Proportion with event	N	Proportion with event		
CV death, hHF or urgent HF visit (primary endpoint)	Asia	543	14.2%	553	20.6%	0.65 (0.49, 0.87)	[redacted]
	Europe	1,094	17.6%	1,060	20.6%	0.84 (0.69, 1.01)	
	N. America	335	16.1%	342	21.3%	0.73 (0.51, 1.03)	
	S. America	401	15.5%	416	23.3%	0.64 (0.47, 0.88)	
CV death (component of primary endpoint)	Asia	543	[redacted]	553	[redacted]	[redacted]	[redacted]
	Europe	1,094	[redacted]	1,060	[redacted]	[redacted]	
	N. America	335	[redacted]	342	[redacted]	[redacted]	
	S. America	401	[redacted]	416	[redacted]	[redacted]	
hHF or urgent HF visit (component of primary endpoint)	Asia	543	[redacted]	553	[redacted]	[redacted]	[redacted]
	Europe	1,094	[redacted]	1,060	[redacted]	[redacted]	
	N. America	335	[redacted]	342	[redacted]	[redacted]	
	S. America	401	[redacted]	416	[redacted]	[redacted]	
CV death or hHF (secondary endpoint)	Asia	543	[redacted]	553	[redacted]	[redacted]	[redacted]
	Europe	1,094	[redacted]	1,060	[redacted]	[redacted]	
	N. America	335	[redacted]	342	[redacted]	[redacted]	
	S. America	401	[redacted]	416	[redacted]	[redacted]	
All-cause death (secondary endpoint)	Asia	543	[redacted]	553	[redacted]	[redacted]	[redacted]
	Europe	1,094	[redacted]	1,060	[redacted]	[redacted]	
	N. America	335	[redacted]	342	[redacted]	[redacted]	
	S. America	401	[redacted]	416	[redacted]	[redacted]	

Source: DAPA-HF CSR Tables 14.2.2.3 (primary endpoint), 14.2.2.5 (CV death), 14.2.2.6 (hHF or urgent HF visit), 14.2.2.4 (CV death or hHF), 14.2.6.2 (all-cause death)
Abbreviations: CI, confidence interval; CV, cardiovascular; hHF, hospitalisation for heart failure; HR, hazard ratio.

5c3. Scenario analyses using these efficacy estimates in the model.

As outlined in response to question 5c2, it was not considered appropriate to derive adjusted survival equations based on data from subgroups. Instead, the following scenario analyses have been provided:

- Scenario analyses based on unadjusted survival and risk equations from the pooled North America + Europe subgroup.
- Scenario analyses using the treatment effect from the overall population (unadjusted survival equations) coupled with the baseline event rate from the Europe subgroup. This is implemented using the unadjusted survival and risk equations from the Europe subgroup by substituting the coefficient for dapagliflozin for the dapagliflozin coefficient derived from the unadjusted survival and risk equations of the overall DAPA-HF population.

Table 8. Scenario analysis of analysis #2, using unadjusted equations from the pooled Europe + North America subgroup

	Dapagliflozin + SC (intervention)	Placebo + SC (comparator)	Incremental	ICER (£/QALY)
Life years	6.095	5.787	0.308	£8,809
QALYs	4.483	4.211	0.272	
Costs (£)	£15,088	£12,691	£2,398	

Scenario analyses run by applying the relevant changes to the original company base case, using the v0.3 version of the model provided as part of the clarification question response.
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years, SC, standard care.

Table 9. Scenario analysis of analysis #3, using unadjusted equations from the pooled Europe + North America subgroup

	Dapagliflozin + SC (intervention)	Placebo + SC (comparator)	Incremental	ICER (£/QALY)
Life years	6.095	5.787	0.308	£8,958
QALYs	4.483	4.211	0.272	
Costs (£)	£15,888	£13,450	£2,438	

Scenario analyses run by applying the relevant changes to the original company base case, using the v0.3 version of the model provided as part of the clarification question response.
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years, SC, standard care.

Table 10. Scenario analysis of analysis #2, using dapagliflozin treatment effect from the overall DAPA-HF trial population and baseline event rate from the Europe subgroup

	Dapagliflozin + SC (intervention)	Placebo + SC (comparator)	Incremental	ICER (£/QALY)
Life years	6.645	6.119	0.526	£6,449
QALYs	4.889	4.453	0.436	
Costs (£)	£15,786	£12,974	£2,813	

Scenario analyses run by applying the relevant changes to the original company base case, using the v0.3 version of the model provided as part of the clarification question response.
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years, SC, standard care.

Table 11. Scenario analysis of analysis #3, using dapagliflozin treatment effect from the overall DAPA-HF trial population and baseline event rate from the Europe subgroup

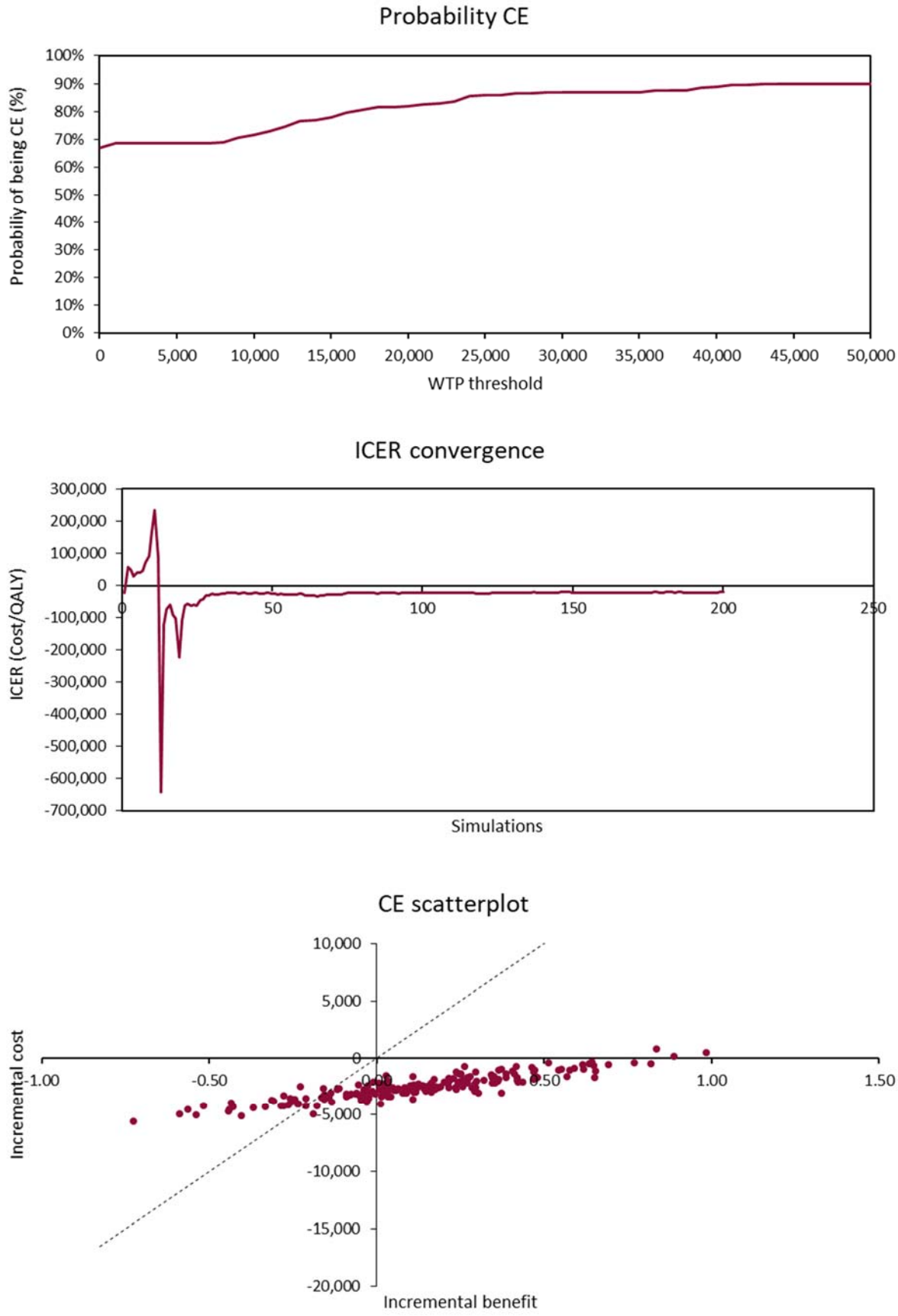
	Dapagliflozin + SC (intervention)	Placebo + SC (comparator)	Incremental	ICER (£/QALY)
Life years	6.645	6.119	0.526	£6,607
QALYs	4.889	4.453	0.436	
Costs (£)	£16,659	£13,777	£2,882	

Scenario analyses run by applying the relevant changes to the original company base case, using the v0.3 version of the model provided as part of the clarification question response.
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years, SC, standard care.

5d. Cost effectiveness versus sacubitril valsartan (base case #1): Probabilistic sensitivity analysis for base case #1 (comparison with sacubitril valsartan).

The results from the probabilistic sensitivity analyses of the revised base case analysis #1 (same as the ERG base case) are presented below (Figure 6). The probabilities of cost-effectiveness at a willingness-to-pay threshold of £20,000/QALY and £30,000/QALY are 82.0% and 87.0%, respectively.

Figure 6. Probabilistic sensitivity analysis results, revised company base case analysis #1 (same as ERG base case)



5e. Use of KCCQ-TSS quartiles in the model: Scenario analyses that use the KCCQ clinical summary score and overall summary score in the model

The model based on KCCQ-TSS health states was implemented as an alternative to a model with NYHA class health states. The questions contributing to the KCCQ-Total Symptom Score (TSS) include questions on the severity and impact of HF symptoms as characterised by the perceived burden and frequency of cardinal symptoms; shortness of breath, fatigue and ankle swelling. Therefore, the KCCQ-TSS was considered to be a good alternative to NYHA classification, which also measures the severity of HF symptoms.

Additionally, change in KCCQ-TSS at 8 months was a prespecified secondary endpoint in the hierarchical testing in the DAPA-HF trial, on [redacted], and therefore a further reason for implementing a KCCQ-TSS based model. In fact, during a pre-investigation new drug (IND) application meeting with the FDA for DAPA-HF, [redacted] TSS is a dedicated measure of HF-specific symptoms compared to Overall Summary Score (OSS) and CSS, which also include questions that are very broad and not specific to HF, such as the impact of HF on patients' social interactions.

The TSS is a component in both CSS and OSS (Figure 7), and it is therefore not a surprise that the point estimates and 95% CIs for the win ratios[1] are very similar regardless of which of these summary scores are used (Table 12). Similarly, the mean change from baseline at 4 months and 8 months, and responder analyses for clinically meaningful improvements/deterioration show the results to be highly consistent across KCCQ-TSS, -CSS and -OSS (25). These results are likely to be driven by the observed treatment effect on symptoms. Cost-effectiveness results from models based on the KCCQ-CSS or -OSS are thus not expected to substantially differ from the KCCQ-TSS model used. Models based on KCCQ-TSS will have a straightforward interpretation due to the consistency and relevance of included domains (HF symptom burden and frequency). The interpretation of modelled results would be less intuitive if entirely different domains were included (e.g. physical limitation due to HF, which is included in the KCCQ-CSS).

The use of KCCQ-CSS or -OSS in the cost-effectiveness model would require rederivation of health state transition probabilities, adjusted survival and risk equations, and re-derivation of the mixed-effect utility model to estimate health state utility values and adverse event disutility values. Due to time limitations, the cost-effectiveness model has not been re-derived using KCCQ-CSS and -OSS, but given the overlap in questions contributing to the three summary scores (Figure 7) and given the consistency in results across the three summary score, there is overwhelming evidence to suggest that the model outcomes of KCCQ-CSS and -OSS based models would be very similar to the existing KCCQ-TSS model.

[1] The win ratio is calculated as the total number of "wins" in the dapagliflozin group (instances where a patient in the dapagliflozin group was ranked higher, i.e. had a better change from baseline in TSS than in the placebo group, where patients who died were given the worst rank) divided by total number of "losses", with ties split evenly between "wins" and "losses". Thus, the win ratio is the odds of the dapagliflozin arm having better outcomes compared to the placebo arm.

Figure 7. Mapping of KCCQ items and scores to conceptual domains and summary scores

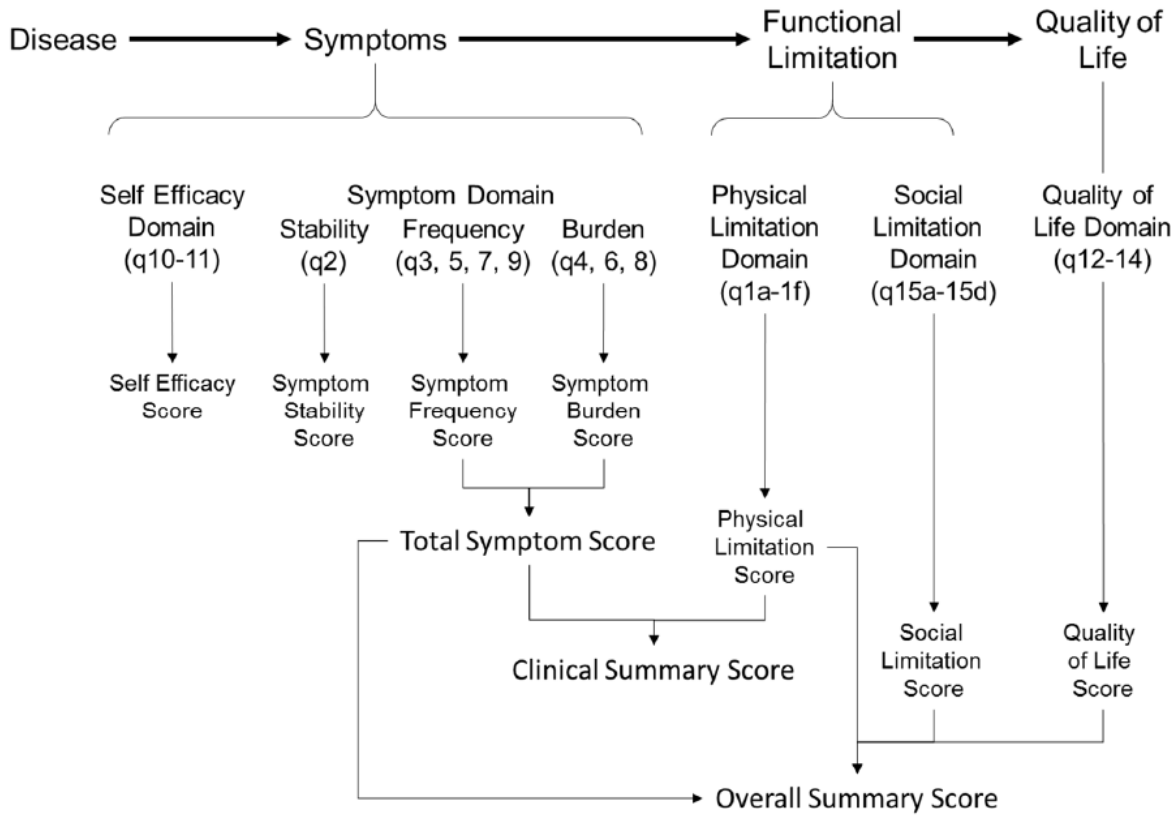


Table 12. Win ratio of KCCQ-TSS, -CSS and -OSS at 8 months

Time point	KCCQ score	Dapagliflozin 10 mg (N=2,373)	Placebo (N=2,371)	Difference between treatment groups		
		n	n	Win ratio	95% CI	p-value†
8 months	TSS	2,252	2,235	1.18	1.11, 1.26	<0.0001
	CSS	2,252	2,235	[redacted]	[redacted]	[redacted]
	OSS	2,252	2,235	[redacted]	[redacted]	[redacted]

† The p-value is obtained from a rank ANCOVA adjusted for baseline KCCQ and stratified by T2DM status at randomisation. Change from baseline to the respective assessment time point is converted to ranks. Patients who died prior to the assessment are assigned worst ranks. Among the deceased, the relative ranking is based on the last value of change from baseline while alive.
Win ratio >1 favours dapagliflozin. Win ratio estimates include baseline KCCQ score as a covariate and T2DM stratum.
Abbreviations: CI, confidence interval; CSS, clinical summary score; KCCQ, Kansas City Cardiomyopathy Questionnaire; OSS, overall summary score; T2DM, type 2 diabetes mellitus; TSS, total symptom score.
Abbreviations: CSS, Clinical Summary Score; KCCQ, Kansas City Cardiomyopathy Questionnaire; OSS, Overall Summary Score; TSS, Total Symptom Score.
Source: DAPA-HF CSR Table 14.2.4.1

5f. Scenario analyses applying a three-year discontinuation rule and a range of different durations of treatment effect (e.g. between 5 and 10 years).

There is no evidence to suggest that treatment with dapagliflozin is associated with any treatment waning and previous appraisals of treatments for HFrEF have assumed no treatment waning, including the NICE appraisal for sacubitril valsartan (TA388). The treatment effect of dapagliflozin is stable over the duration of the DAPA-HF trial as well as over the duration of previous trials in T2DM and type 1 diabetes mellitus (T1DM) patients, including the DECLARE TIMI58 trial with a median follow-up of 4.2 years.

[redacted]

For base case analysis #1 evaluating dapagliflozin versus sacubitril valsartan, inclusion of treatment waning would not have any impact on the cost-effectiveness estimate, as any treatment waning applied for dapagliflozin should also be applied sacubitril valsartan, thereby reducing the treatment effects and costs equally in the dapagliflozin arm and the sacubitril valsartan arm.

To address the request from the NICE Technical Report, scenario analyses assuming treatment waning (discontinuation of treatment effect and treatment costs, as per ERG request) after 5 year and 10 years were conducted (Table 13–Table 14).

Table 13. Scenario analysis of analysis #2, assuming treatment waning at 5 years and 10 years

	Dapagliflozin + SC (intervention)	Placebo + SC (comparator)	Incremental	ICER (£/QALY)
Assume treatment waning at 5 years				
Life years	6.000	5.609	0.392	£6,002
QALYs	4.448	4.125	0.323	
Costs (£)	£14,149	£12,209	£1,940	
Assume treatment waning at 10 years				
Life years	6.136	5.609	0.527	£5,867
QALYs	4.558	4.125	0.433	
Costs (£)	£14,750	£12,209	£2,540	

Scenario analyses run by applying the relevant changes to the original company base case, using the v0.3 version of the model provided as part of the clarification question response.
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years, SC, standard care.

Table 14. Scenario analysis of analysis #3, assuming treatment waning at 5 years and 10 years

	Dapagliflozin + SC (intervention)	Placebo + SC (comparator)	Incremental	ICER (£/QALY)
Assume treatment waning at 5 years				
Life years	5.817	5.428	0.390	£6,024
QALYs	4.304	3.983	0.321	
Costs (£)	£14,828	£12,895	£1,934	
Assume treatment waning at 10 years				
Life years	5.947	5.428	0.519	£5,901
QALYs	4.409	3.983	0.426	
Costs (£)	£15,409	£12,895	£2,514	

Scenario analyses run by applying the relevant changes to the original company base case, using the v0.3 version of the model provided as part of the clarification question response.
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years, SC, standard care.

6. In review of the technical report please provide a revised base case if appropriate.

The revised company base cases are outlined in Table 15. The base case for analysis #1 is the same as the ERG base case. The base cases for analyses #2 and #3 differ from the ERG base case in the use of the dapagliflozin treatment effect based on the DAPA-HF overall population, whilst the baseline event rates are based on the Europe subgroup (as in the ERG base cases). This is implemented in the model using the unadjusted survival and risk equations from the Europe subgroup, but substituting the dapagliflozin coefficient in the Europe unadjusted equations with the dapagliflozin coefficient from the unadjusted survival and risk equations of the overall DAPA-HF population.

Table 15. Revised company base case

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
Population #1					
Original base-case					
Dapagliflozin + SC	£14,514	4.627			
Sacubitril valsartan + SC	£17,645	4.627	-£3,131	0.000	Dominant
Company base-case using model v0.3					
Dapagliflozin + SC	£14,496	4.626			
Sacubitril valsartan + SC	£17,623	4.626	-£3,127	0.000	Dominant
Company base-case (model v0.3) + adjusted health state utility values					
Dapagliflozin + SC	£14,496	4.262			
Sacubitril valsartan + SC	£17,623	4.262	-£3,127	0.000	Dominant
Company base-case (model v0.3) + ITC (Bucher method)					
Dapagliflozin + SC	£14,496	4.626			
Sacubitril valsartan + SC	£17,167	4.496	-£2,671	0.130	Dominant
Revised base case (same as ERG base-case)					
Dapagliflozin + SC	£14,496	4.262			
Sacubitril valsartan + SC	£17,167	4.142	-£2,671	0.120	Dominant
Population #2					
Original base-case					
Dapagliflozin + SC	£14,976	4.597			

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
SC	£12,226	4.125	£2,750	0.472	£5,830
Company base case using model v0.3					
Dapagliflozin + SC	£14,958	4.596			
SC	£12,209	4.125	£2,749	0.471	£5,835
Company base-case (model v0.3) + adjusted health state utility values					
Dapagliflozin + SC	£14,958	4.234			
SC	£12,209	3.797	£2,749	0.438	£6,284
Company base-case (model v0.3) + European subgroup baseline event rate (relative treatment effect from overall trial population)					
Dapagliflozin + SC	£15,786	4.889			
SC	£12,974	4.453	£2,813	0.436	£6,449
Revised company base-case					
Dapagliflozin + SC	£15,786	4.500			
SC	£12,974	4.095	£2,813	0.405	£6,939
Population #3					
Original base-case					
Dapagliflozin + SC	£15,620	4.444			
SC	£12,913	3.983	£2,707	0.461	£5,866
Company base-case using model v0.3					
Dapagliflozin + SC	£15,601	4.444			
SC	£12,895	3.983	£2,706	0.461	£5,872
Company base-case (model v0.3) + adjusted health state utility values					
Dapagliflozin + SC	£15,601	4.093			
SC	£12,895	3.665	£2,706	0.428	£6,324
Company base-case (model v0.3) + European subgroup baseline event rate (relative treatment effect from overall trial population)					
Dapagliflozin + SC	£16,659	4.889			
SC	£13,777	4.453	£2,882	0.436	£6,607

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
Revised company base-case					
Dapagliflozin + SC	£16,659	4.500			
SC	£13,777	4.095	£2,882	0.405	£7,109

Abbreviations: ERG, Evidence Review Group; ICER, incremental cost effectiveness ratio; ITC, indirect treatment comparison; QALY, quality-adjusted life year; SC, standard care.

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NICE National Institute for Health and Care Excellence

Technical engagement response form

Dapagliflozin for treating heart failure with reduced ejection fraction [ID1656]

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We need your comments and feedback on the questions below. You do not have to answer every question. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be summarised and used by the technical team to amend or update the scientific judgement and rationale in the technical report.

Deadline for comments **5:00pm, Thursday 15 October 2020**

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

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- Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.
- If you provide journal articles to support your comments, you must have copyright clearance for these articles.
- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential

information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

About you

Your name	**Klaus Witte**
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**University of Leeds**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**

Questions for engagement

Issue 1: Positioning in the pathway	
1. Are the company's populations #1, #2 and #3 as detailed in Appendix 1 (page 17) clearly distinguishable in clinical practice?	Yes, although in practice, after ACEi+BB+MRA, people will choose either DAPA or Sac/Val based upon patient features, or personal preference. In this 'parallel' approach, I fully expect DAPA to end up being used more due to ease of use and familiarity
2. Is the company's positioning of dapagliflozin appropriate? a. Should the committee consider additional positions in the pathway? i. Would dapagliflozin ever be used in people responding to existing treatments? ii. Would dapagliflozin be used in people whose symptoms continue or disease is not responding to sacubitril valsartan? 1. If yes, would treatment with sacubitril valsartan stop or would dapagliflozin be added to current care? 2. If sacubitril valsartan is stopped, would ACEi / ARBs be restarted?	Bearing in mind my comments above, positioning is reasonable. The concept of response is incredibly difficult. What is response? Symptoms in HFrEF almost never go away, and the prognostic benefits are pretty much across the board. I worry that the requirement to be a 'non-responder' will lead to reduced access because patients often say they are a 'little better' to please their team such that they have 'responded' to what was done before but are still symptomatic. This could lead to inertia. 'Ongoing symptoms be they better or worse than following the previous treatment is all that is required. The drug is safe and well tolerated, so correctly, most people with HF will end up being on four pillars of treatment BB + ACEi/ARB/SacVal +MRA + DAPA. SacVal and DAPA are two different drugs. One should not be placed above another especially since changing to SacVal means several more uptitration visits, whereas DAPA is one dose and easy to use. There should be the option of choosing one or the other. Adding one or the other as I have suggested above will not lead to the first being stopped.

3. Would dapagliflozin be used instead of sacubitril valsartan where both are an option? a. Would all people who have sacubitril valsartan be able to have dapagliflozin?	In due course as I have said above, yes, and yes the contraindications to DAPA are far fewer than SacVal.
4. In what proportion of people not responding to ACEi/ARBs, beta-blockers ± MRA would you expect sacubitril valsartan to be unsuitable (population #2)?	Those with low blood pressure or markedly poor renal function.
5. Have all appropriate comparators been considered in the appraisal?	Yes
Issue 2: Use in primary care	
6. Should dapagliflozin be initiated by a heart failure specialist? a. If yes, what additional monitoring would be required? b. Is it plausible that GPs could prescribe dapagliflozin in primary care prior to referral to a specialist? c. If no, what additional training or resources would be necessary for primary care clinicians to prescribe dapagliflozin?	a) It should be initiated/prescribable by a GP on the advice of a specialist nurse, a GP with special interest, or a heart failure doctor. b) Yes after discussion or advice. No further referral/attendance needed. I would for example say 'if they remain symptomatic after drug X has been uptitrated, add DAPA at 10mg' c) None – they are more experienced at prescribing DAPA than HF teams.
7. What percentage of people see a heart specialist after progressing on ARBs / ACEi's in clinical practice in the NHS:	i) all people with proven HFrEF should see a HF specialist at least once. Many will be discharged to primary care with some degree of community based specialist nursing support.

i. For people starting MRAs? ii. For people starting specialist treatment? b. Does specialist referral reduce access to second line treatment options? c. What additional costs and resources would be associated with dapagliflozin treatment in specialist care versus primary care? Would there be any costs/resources that would apply to dapagliflozin but not to sacubitril valsartan and vice versa?	ii) if people are thinking about SacVal they will keep the patient under specialist care b) Yes it absolutely does limit access. c) Nothing different to SacVal (in fact less - less renal monitoring and no uptitration visits needed)
Issue 3: Generalisability of the DAPA-HF trial	
8. In NHS clinical practice, what percentage of patients would be expected to have HFrEF and type 1 diabetes mellitus? How would dapagliflozin be used in this population?	Very few – perhaps 1%. DAPA could be used under the advice of a diabetologist in these.
9. What percentage of people with HFrEF have acute decompensated HF?	Lots, if you wait long enough, but it's probably not relevant to DAPA
10. How would disease aetiology, clinical management, and baseline risk for heart failure be expected to differ in Europe versus the rest of the world?	I would use whole study as base-case. Effect of DAPA might be greater in UK population due to differing care and slightly greater baseline risk.
Issue 4: Indirect treatment comparison	

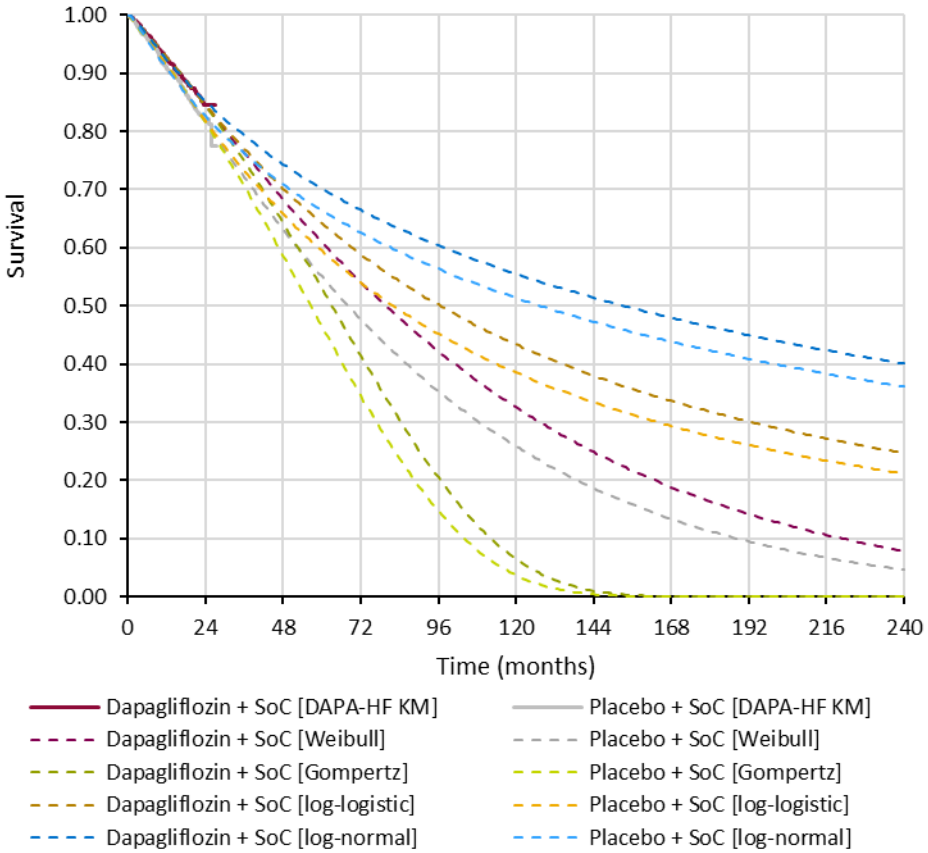
11. Can a class effect be assumed for ACE inhibitors?	Yes
12. Can equivalence be assumed for ACEi and ARBs?	Pretty much
Issue 5: Use of KCCQ-TSS quartiles in the model	
13. Should the following domains be included in the measurement of HFrEF disease severity? a. physical limitations b. quality of life c. social inference	From a patients' perspective, these are already included in the other questions of the KCCQ-TSS. Physical limitations is only one question for example.
Issue 6: Survival extrapolation	
14. Which long-term survival estimates would most accurately reflect what is expected in clinical practice in the NHS?	Weibull is most real option here based upon my experience and also data from Leeds.

Months		**0**	**12**	**24**	**36**	**60**	**120**	**180**	**240**
Base case #1, people on ACEi or ARB, beta-blocker, ±MRA for whom sacubitril valsartan is suitable									
Weibull	**Dapagliflozin**	100.0%	92.8%	84.5%	76.2%	60.9%	32.60%	16.4%	7.9%
	Standard Care	100.0%	91.4%	81.6%	72.1%	55.0%	25.9%	11.3%	4.7%
Gompertz	**Dapagliflozin**	100.0%	92.8%	84.4%	74.9%	53.0%	6.6%	0.0%	0.0%
	Standard Care	100.0%	91.4%	81.5%	70.6%	46.5%	3.7%	0.0%	0.0%
Base case #2, people on ACEi or ARB, beta-blocker, ±MRA for whom sacubitril valsartan is unsuitable									
Weibull	**Dapagliflozin**	100.0%	92.7%	84.4%	76.2%	61.10%	33.20%	17.1%	8.5%
	Standard Care	100.0%	91.3%	81.6%	72.2%	55.5%	26.8%	12.1%	5.2%
Gompertz	**Dapagliflozin**	100.0%	92.6%	84.3%	74.9%	54.0%	8.9%	0.0%	0.0%

	Standard Care	100.0%	91.3%	81.6%	71.0%	48.2%	5.6%	0.0%	0.0%
Base case #3, people on sacubitril valsartan, beta-blocker, ±MRA									
Weibull	**Dapagliflozin**	100.0%	94.9%	86.2%	76.1%	55.6%	19.1%	4.8%	0.9%
	Standard Care	100.0%	92.8%	81.1%	68.0%	43.7%	9.6%	1.4%	0.1%
Gompertz	**Dapagliflozin**	100.0%	94.8%	85.9%	71.5%	26.7%	0.0%	0.0%	0.0%
	Standard Care	100.0%	92.8%	80.8%	62.3%	15.6%	0.0%	0.0%	0.0%

15. Based on the company's goodness of fit criteria estimates (AIC/BIC) the log-logistic and log-normal curves could be a suitable fit to the data but predict more optimistic extrapolations that the Weibull (as shown in the graph below). Would you expect improved survival in clinical practice compared to what is estimated using the Weibull extrapolation curve (see table from question 14)?	I think again, the Weibull looks the least worst fit for real life.

Company's alternative all-cause mortality survival curves (scenario analyses) (CS p109)



Issue 7: Treatment waning effect	
16. **NHS England:** Would a stopping rule apply for dapagliflozin in the NHS?	No., it would be continued until death (or just before)

17. Would treatment effect be expected to continue after stopping dapagliflozin? a. If yes, how long after stopping treatment would this effect last? b. Is this observed in patients having sacubitril valsartan?	a) no, I suspect the effect after stopping would wane pretty quickly and it's not what we do in CHF b) we don't stop Sac Val either unless there's a major deterioration in renal function or until just before death – which often happen together.

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- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.
- If you provide journal articles to support your comments, you must have copyright clearance for these articles.
- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential

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About you

Your name	**Nick Hartshorne-Evans**
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**Pumping Marvellous Foundation**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**Already provided as the patient expert**

Questions for engagement

Issue 1: Positioning in the pathway	
1. Are the company's populations #1, #2 and #3 as detailed in Appendix 1 (page 17) clearly distinguishable in clinical practice?	**Yes**
2. Is the company's positioning of dapagliflozin appropriate? a. Should the committee consider additional positions in the pathway? i. Would dapagliflozin ever be used in people responding to existing treatments? ii. Would dapagliflozin be used in people whose symptoms continue or disease is not responding to sacubitril valsartan? 1. If yes, would treatment with sacubitril valsartan stop or would dapagliflozin be added to current care? 2. If sacubitril valsartan is stopped, would ACEi / ARBs be restarted?	**2 a. There is one extra option that hasn't been considered which I am guessing is quite common. ACE/ARB + BB + MRA (1st line optimised triple therapy) sometime the patient can't tolerate MRA due to kidney function therefore this gets dropped reverting to ACE/ARB + BB – there is no reason why Dapagliflozin couldn't be added here. Same if ARNI + BB + MRA where MRA is withdrawn, not being able tolerated, Dapagliflozin could be added.** **2 i. Patients may be responding to existing treatment, but it doesn't mean that we couldn't do better. The HF population is heterogenous therefore "responding to treatment" in HF is not linear therefore we need to think around additional treatments as we can't make a broad brush assessment.** **2 ii. Yes it is important for the patient to have other options. HF is lacking innovation and pharmacological treatments are limited, we should be thinking that HCP's should have as much in their armoury to tackle HF.** **2 ii. 1 Dapagliflozin introduction in the treatment should not stop Sacubitril Valsartan. If a patient is on SV it has taken time to optimise and up titrate ACE/ARB, down titrate ACE/ARB and then up titrate SV. To take the patient through this process again would be unacceptable** **2ii. 2 I am not sure why we are asking this question – are we suggesting taking patients off gold standard therapy unless it's a cost decision?**

3. Would dapagliflozin be used instead of sacubitril valsartan where both are an option? a. Would all people who have sacubitril valsartan be able to have dapagliflozin?	**3 I can't answer that question apart from they would be prescribed independently depending on what the problem is.** **3 a. Unless there is a contraindication then I see no reason why not – if the patient needs it, treat the patient**
4. In what proportion of people not responding to ACEi/ARBs, beta-blockers ± MRA would you expect sacubitril valsartan to be unsuitable (population #2)?	**I can't answer that**
5. Have all appropriate comparators been considered in the appraisal?	**As far as I am aware**
Issue 2: Use in primary care	
6. Should dapagliflozin be initiated by a heart failure specialist? a. If yes, what additional monitoring would be required? b. Is it plausible that GPs could prescribe dapagliflozin in primary care prior to referral to a specialist? c. If no, what additional training or resources would be necessary for primary care clinicians to prescribe dapagliflozin?	**1. No it shouldn't be initiated by a heart failure specialist and it doesn't have to be prescribed via an MDT. Many patients live under the care of primary care, having been discharged from the MDT, having been stabilised and optimised. This is a huge cohort of patients who are in the NYHAII/III bracket. Enabling Dapagliflozin prescribing by GP's would give a weapon to the GP's, who haven't got one at the moment. Their job currently, is keeping people optimised on their current set of meds unless they are a GPsi and referring to specialist services if the patient is decompensating. I don't think there would be any resource impact on GP training for the prescribing of Dapagliflozin as they have been doing this for diabetic patients without specialist intervention. To push the prescribing of Dapagliflozin would restrict access to the majority of heart failure patients. It could be argued G.P's are more skilled in prescribing Dapagliflozin than Cardiologists / HF specialists. I believe there is an equality and discrimination standpoint that can be justified. Why should heart failure patients not have access to the same prescriber type in primary care just like patients with diabetes. I see this as discriminatory, GP's having prescribing SGLT2i drug classes without specialist involvement, why is this any different for Chronic Heart Failure patients with or without diabetes? You**

	also need to calibrate the resource cost and time moving significant numbers of patients who are under the care of their GP back into specialist prescribing. The resource impact to do this is counterproductive to the cost effectiveness of the drug, it doesn't need a health economist to calculate this.
7. What percentage of people see a heart specialist after progressing on ARBs / ACEi's in clinical practice in the NHS: i. For people starting MRAs? ii. For people starting specialist treatment? b. Does specialist referral reduce access to second line treatment options? c. What additional costs and resources would be associated with dapagliflozin treatment in specialist care versus primary care? Would there be any costs/resources that would apply to dapagliflozin but not to sacubitril valsartan and vice versa?	**7 – Can't comment** **7 i. Can't comment** **7 ii Can't comment** **7 b. If a person has heart failure, they should be on guideline therapy and may never be discharged from an MDT. Those patients that are discharged from an MDT to primary care and then are referred back to a specialist MDT for further specialist input may mean reduced access or increased access to 2nd line treatment. Considering, as stated in NG106 there are only two, second line specialist treatments that need specialised prescribing, SV and Ivabradine this prescribing is down to the discretion of the MDT and clinical need of the individual patient. There is certainly more cost in the process of referring. Arming the GP with Dapagliflozin would increase access to the patient where they could be kept under primary care. Patients can always be referred. See above comments around resource impact in 6.**
Issue 3: Generalisability of the DAPA-HF trial	
8. In NHS clinical practice, what percentage of patients would be expected to have HFrEF and type 1 diabetes mellitus? How would dapagliflozin be used in this population?	**We have quite a large population of T1 diabetics with HFrEF.**

9. What percentage of people with HFrEF have acute decompensated HF?	**HFrEF disease trajectory is unpredictable and not linear. Acute decompensation generally occurs at the start leading to a diagnosis, leading to chronic heart failure with unpredictable acute decompensation events. HF is a roller coaster and not like cancer.**
10. How would disease aetiology, clinical management, and baseline risk for heart failure be expected to differ in Europe versus the rest of the world?	**Can't answer**
Issue 4: Indirect treatment comparison	
11. Can a class effect be assumed for ACE inhibitors?	**Can't answer**
12. Can equivalence be assumed for ACEi and ARBs?	**Can't answer**
Issue 5: Use of KCCQ-TSS quartiles in the model	
13. Should the following domains be included in the measurement of HFrEF disease severity? a. physical limitations b. quality of life c. social inference	**Yes absolutely – physical ability widely impacts quality of life, impacting individual's mental health and socio-economic position. Social inference is severely impacted by a heart failure diagnosis.**
Issue 6: Survival extrapolation	
14. Which long-term survival estimates would most accurately reflect what is expected in clinical practice in the NHS?	**For HF? Deep evidence suggests that the investment in gold standard therapies and innovative interventions in a structured system have a positive impact on mortality and morbidity in people living with HF. People with HF have long been impacted by lack of**

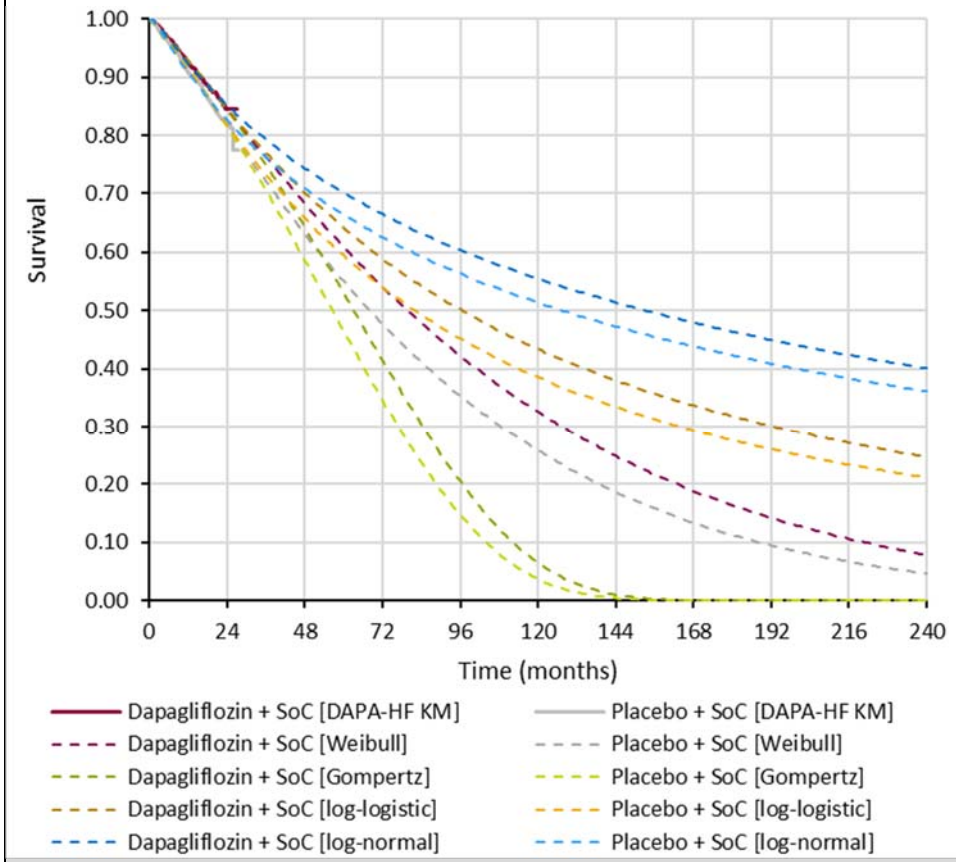
	choice and investment. Giving GP's the ability to prescribe Dapagliflozin, which they have good knowledge of gives them a prognostically significant weapon in the fight to beat HF.

Months		**0**	**12**	**24**	**36**	**60**	**120**	**180**	**240**
Base case #1, people on ACEi or ARB, beta-blocker, ±MRA for whom sacubitril valsartan is suitable									
Weibull	**Dapagliflozin**	100.0%	92.8%	84.5%	76.2%	60.9%	32.60%	16.4%	7.9%
	Standard Care	100.0%	91.4%	81.6%	72.1%	55.0%	25.9%	11.3%	4.7%
Gompertz	**Dapagliflozin**	100.0%	92.8%	84.4%	74.9%	53.0%	6.6%	0.0%	0.0%
	Standard Care	100.0%	91.4%	81.5%	70.6%	46.5%	3.7%	0.0%	0.0%
Base case #2, people on ACEi or ARB, beta-blocker, ±MRA for whom sacubitril valsartan is unsuitable									
Weibull	**Dapagliflozin**	100.0%	92.7%	84.4%	76.2%	61.10%	33.20%	17.1%	8.5%
	Standard Care	100.0%	91.3%	81.6%	72.2%	55.5%	26.8%	12.1%	5.2%
Gompertz	**Dapagliflozin**	100.0%	92.6%	84.3%	74.9%	54.0%	8.9%	0.0%	0.0%
	Standard Care	100.0%	91.3%	81.6%	71.0%	48.2%	5.6%	0.0%	0.0%
Base case #3, people on sacubitril valsartan, beta-blocker, ±MRA									
Weibull	**Dapagliflozin**	100.0%	94.9%	86.2%	76.1%	55.6%	19.1%	4.8%	0.9%
	Standard Care	100.0%	92.8%	81.1%	68.0%	43.7%	9.6%	1.4%	0.1%
Gompertz	**Dapagliflozin**	100.0%	94.8%	85.9%	71.5%	26.7%	0.0%	0.0%	0.0%
	Standard Care	100.0%	92.8%	80.8%	62.3%	15.6%	0.0%	0.0%	0.0%

15. Based on the company's goodness of fit criteria estimates (AIC/BIC) the log-logistic and log-normal curves could be a suitable fit to the data but predict more optimistic extrapolations that the Weibull (as shown in the graph below). Would you expect improved survival in clinical practice compared to what is estimated using	

the Weibull extrapolation curve (see table from question 14)?	

Company's alternative all-cause mortality survival curves (scenario analyses) (CS p109)



Issue 7: Treatment waning effect

16. **NHS England:** Would a stopping rule apply for dapagliflozin in the NHS?	**No as the HF disease trajectory is problematic and not known. I would not advocate a stopping rule as HF treatment is a continuum with system aims of reducing mortality and the cost of hospital admissions and readmissions ultimately impacting the patients QOL.**
17. Would treatment effect be expected to continue after stopping dapagliflozin? a. If yes, how long after stopping treatment would this effect last? b. Is this observed in patients having sacubitril valsartan?	**Can't answer.**

NICE National Institute for Health and Care Excellence

Technical engagement response form

Dapagliflozin for treating heart failure with reduced ejection fraction [ID1656]

As a stakeholder you have been invited to comment on the technical report for this appraisal. The technical report and stakeholders responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

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Deadline for comments **5:00pm, Thursday 15 October 2020**

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- Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.
- If you provide journal articles to support your comments, you must have copyright clearance for these articles.
- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential

information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

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Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

About you

Your name	[redacted] **on behalf of the British Cardiovascular Society**
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**British Cardiovascular Society (response a composite of feedback from colleagues including [redacted]. We also acknowledge the important input of colleagues at the British Society of Heart Failure**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**

Questions for engagement

Issue 1: Positioning in the pathway	
1. Are the company's populations #1, #2 and #3 as detailed in Appendix 1 (page 17) clearly distinguishable in clinical practice?	**Yes**
2. Is the company's positioning of dapagliflozin appropriate? a. Should the committee consider additional positions in the pathway? i. Would dapagliflozin ever be used in people responding to existing treatments? ii. Would dapagliflozin be used in people whose symptoms continue or disease is not responding to sacubitril valsartan? 1. If yes, would treatment with sacubitril valsartan stop or would dapagliflozin be added to current care? 2. If sacubitril valsartan is stopped, would ACEi / ARBs be restarted?	**The DAPA HF trial only included patients with class II-IV heart failure, in other words symptomatic patients, so it may be reasonable to apply the results only to to symptomatic patients. The mechanism of action of dapagliflozin would not however appear to be dependent on patient symptoms, and while further trials in asymptomatic patients would be informative, the expectation is that the benefit seen in symptomatic patients would also apply in the asymptomatic group with similar degrees of LV dyscfunction.** **However, in reality most patients with significant left ventricular systolic dysfunction will have NYHA II or more symptoms, so the asymptomatic group may not be large. Even if asymptomatic, NYHA class I patients who are also diabetic may benefit from dapa, given that it is well-established as a treatment for type 2 diabetes anyway. Other patients with NYHA class I HF may also benefit from dapa due to its beneficial effect on progression of renal disease (DAPA CKD trials)** **A) This guideline is being formulated at a time of great change in heart failure pathways. These developments do make it more difficult to know for sure where dapagliflozin should appear in treatment pathways. For example:**

	Vericiguat is being considered as a novel treatment in this population. This has not yet entered clinical practice, but may do so soon, as either an alternative to dapagliflozin or as an add-on. Currently this agent has far less data than dapagliflozin, which has been used widely as a diabetic agent for many years now. The VICTORIA trial did demonstrate reductions in HF hospitalisations as the main benefit of vericiguat, whilst there are harder endpoint benefits with dapagliflozin. Intravenous iron is indicated for some patients with heart failure in much the same areas as patients being considered for dapa/veriguat/sacubritil valsartan. However, intravenous iron has not been shown to have the mortality benefits of SV or dapagliflozin and so is unlikely to replace the need for these agents (ie iv iron likely to be used on top of dapa) Sacubritil valsartan could be used *instead* of an ACEi/ARB at the outset of a patient's treatment (instead of *replacing* ACEi/ARB. There is a major cost disbenefit to using SV, since ACEi/ARBs are substantially cheaper. A proportion of patients with LVSD may improve function enough on ACEi/ARB that they would no longer qualify for SV/dapa etc, so the place of primary initiation of SV (instead of ACEi/ARB) in newly diagnosed LVSD is not well-established. Empagliflozin has recently had trial data (EMPEROR-Reduced) suggesting it shares much of the same benefits as dapagliflozin. The trials do use slightly different endpoints, making direct comparison more difficult, but SGLT2is may have a class effect. We note that 20% of the patients in the empa trial were also taking SV, whereas the numbers taking the combination of dapa and SV was 10% in the earlier DAPA HF trial. So, dapa could fit in in a number of other permutations depending on where these other agents are to be used in the same patient populations. It seems most likely that the agents will be additive (ie BB+Aldosterone antagonist+SV+SGLT2i+/-vericuguat, assuming the patient has the relevant degree of LV dysfunction to suggest they will benefit from the additional medications. In diabetic patients, it seems likely that SGLT2is will be used much earlier if the patient has heart failure – why use an alternative diabetic agent when you could use one that is also a heart failure agent? This is recommended by international guidelines including the ESC.

	Or dapagliflozin could be used *never*, if empagliflozin (or another competitor) does the same job for less cost… i) Dapa would be used in patients who are responding to other heart failure treatment if they still have symptoms (eg have improved from NYHA III to II) and still have the degree of LV dysfunction seen at baseline in the DAPAHF trial. The additional benefit of DAPA in such "responders" may be greater than in patients with LVSD unresponsive to usual treatment. If by response to treatment, you are referring to response to dapagliflozin as opposed to other HF treatment, then we would consider the trial data to indicate that dapagliflozin should be continued in all patients initiated on the drug, irrespective of apparent response in terms of symptom or LV function, since the endpoints of the trial include mortality, above an beyond any symptomatic response. At this stage it is not possible to identify individual patients who are not going to benefit from dapagliflozin (or indeed any other HF treatment) as such individualized medicine is not currently available. We depend on large trials of similar populations to decide which drugs to give which patients. ii) Yes, dapa would be used on top of SV. SV would not be stopped. We do not think it likely that a patient established on SV would be changed back to ACEi/ARB on addition of dapa.
3. Would dapagliflozin be used instead of sacubitril valsartan where both are an option? a. Would all people who have sacubitril valsartan be able to have dapagliflozin?	3a) Almost all patients on SV could also have dapa (except Type I diabetes, hypotension/hypovolemia). This add-on use has been called a 5 pillar approach (Sacubritil+valsartan+SGLT2i+BB+Aldosterone antagonist). Dapagliflozin has not been shown to have benefit as an *alternative* to ACEi/ARB, but as an add-on. SV *has* been shown to have benefit as an alternative to ACEi/ARB, proving superiority over the older medications.
4. In what proportion of people not responding to ACEi/ARBs, beta-blockers ± MRA would you expect sacubitril valsartan to be unsuitable (population #2)?	Most common reason for not being able to take SV is hypotension. Symptomatic hypotension limited dose titration beyond step 1 in 14-15% in the both PARADIGM-HF and PIONEER –HF (acute HF), SBP was <90mmHg in 2.7%. I do not know the exact proportion of those in non-trial, unselected populations with HF who are unable to take SV for this reason, but estimate 10-20%, more in the older or more severely affected heart failure populations.

5. Have all appropriate comparators been considered in the appraisal?	No – see answer to Q1.
Issue 2: Use in primary care	
6. Should dapagliflozin be initiated by a heart failure specialist? a. If yes, what additional monitoring would be required? b. Is it plausible that GPs could prescribe dapagliflozin in primary care prior to referral to a specialist? c. If no, what additional training or resources would be necessary for primary care clinicians to prescribe dapagliflozin?	No, could easily be being initiated by a diabetic team, including community diabetic teams involving GPs. "heart failure specialist" is a broad term, that could easily include community heart failure nurses working with primary care, or a GP with a heart failure interest. So, whilst it does seem reasonable to require initiation to be done by a heart failure specialist, this may not involve hospital doctors. Initiation in this sense would likely also mean a written recommendation to primary care, not a hospital prescription or initiation in a hospital environment. Feedback from specialist heart failure nurses to this consultation highlighted the increasing burden on hospital-based heart failure teams to manage increasing numbers of HF patients with increasing numbers of medications. Existing HF specialist teams are not likely to be able to absorb increased workload of initiating and managing introduction of SGLT2is without increased staff levels. Therefore, wherever possible, initiation of this treatment should be community-based, again with increased staff levels to manage this. a) standard monitoring, which is already expected in patients with heart failure, should continue, such as monitoring BP, renal function and symptoms. Dapagliflozin may necessitate review and reduction of the dose of any diuretics the patient may previously have been taking. Patients who are diabetic may benefit from a wider review of their diabetic medications. b) Yes, if that GP was a GPSI in heart failure, or if the patient had previously been worked up by heart failure specialist teams – eg a patient with known severe LVSD presents to primary care on conventional heart failure medication with worsening breathlessness, in which case any experienced GP could start the dapa on top of existing medications. In time, it seems likely that dapa (or other SGLT2is) could be started by any GP in the community, once a diagnosis of heart failure had been confirmed.

	c) We suggest agreed network pathways be developed in each region. Not a lot of training would be needed to prescribe dapagliflozin. It's pretty straightforward. Unlike ACEi/ARB or other HF drugs, SGLT2i agents like dapagliflozin have a simple single dose to use, with no titration needed. As such, should be even easier to use in community setting than the existing drugs used in primary care for heart failure patients.
7. What percentage of people see a heart specialist after progressing on ARBs / ACEi's in clinical practice in the NHS: i. For people starting MRAs? ii. For people starting specialist treatment? b. Does specialist referral reduce access to second line treatment options? c. What additional costs and resources would be associated with dapagliflozin treatment in specialist care versus primary care? Would there be any costs/resources that would apply to dapagliflozin but not to sacubitril valsartan and vice versa?	BCS do not know the exact percentages. We suggest approaching heart failure audit team at NICOR. We support the BSH view that all patients with newly diagnosed, advanced or recently decompensated HF should be reviewed by a heart failure specialist, as per NICE NG106. b) Yes, inevitably. We believe this has already substantially slowed the growth in use of sacubritil valsartan, which now has trial data more than 6 years old. Access to specialist HF teams is not adequate across the whole country, leading to delays in accessing specialists who can advise about second line treatment options. c) SV more difficult to initiate than dapa as it often requires closer monitoring of BP. Additional costs of any hospital service would be the inconvenience and travel for the patient, the outpatient visit costs for the specialist team. This would be minimised by outreach services in the community/working from community hubs as envisaged in national documents (but not yet widely available). As noted above, current heart failure nurse teams are very stretched by increasing patient numbers and the wider range of treatments available for LVSD. Wherever the initiation of dapa was to happen, it would need to be accompanied by an expansion in the workforce of the nurses delivering this service. Otherwise patient waiting times will lengthen. Heart failure specialists used to the full range of HF treatments may introduce these drugs more quickly and efficiently than non-specialists less familiar with the medications, in other words, they may *reduce* costs and unnecessary additional visits for patients while their treatment is optimised. Dapagliflozin appears also to have benefits in delaying renal progression (DAPA CKD trial). This has the potential of greatly reducing the costs to the health economy of the consequences of such renal problems.

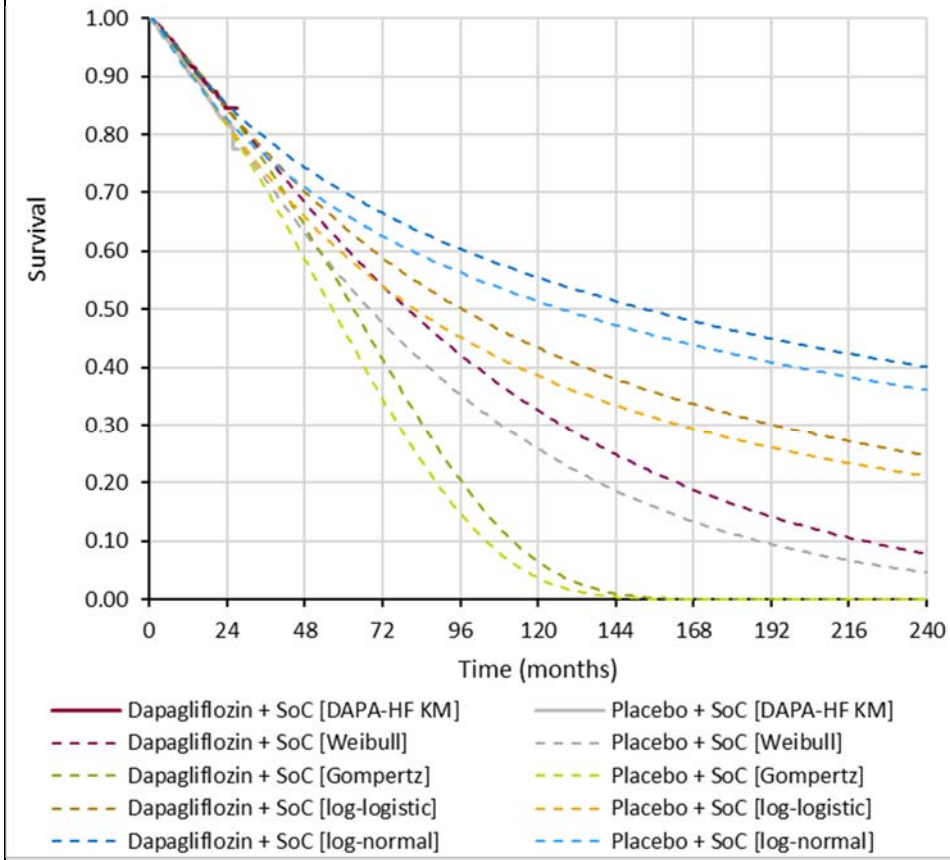
Issue 3: Generalisability of the DAPA-HF trial	
8. In NHS clinical practice, what percentage of patients would be expected to have HFrEF and type 1 diabetes mellitus? How would dapagliflozin be used in this population?	Approx 5%. Great majority of diabetes in this population will be Type II. Dapa would not be used in this population (pending further trial/safety data), although there may be exceptions on a case by case basis guided by specialist diabetic teams.
9. What percentage of people with HFrEF have acute decompensated HF?	This is an odd question. Acute decompensated HF is an event that may (or may not) happen at times in the longer term trajectory of any heart failure patient. Acute decompensated HF episodes will typically be more common as the condition worsens, especially in the final year of life. Episodes of acute decompensation are highly variable but estimated risk of acute compensation following HF-rEF diagnosis in studies is approx. 10-15% p.a. It is typically treated promptly and then the patient returns to their existing trajectory of chronic heart failure. We would not expect dapagliflozin to be initiated during such acute decompensations unless and until trials in this setting have been performed that provide data to support such a strategy.
10. How would disease aetiology, clinical management, and baseline risk for heart failure be expected to differ in Europe versus the rest of the world?	Assuming rest of world means South America/North America/China/Australasia, then the answer would be not much. We would not expect any differences in the approach to HF to differ based on ethnicity alone. If rest of world means sub-Saharan Africa/rural India, then the management of heart failure is likely to be wholly different, as would the etiology.
Issue 4: Indirect treatment comparison	
11. Can a class effect be assumed for ACE inhibitors?	Yes, this appears likely
12. Can equivalence be assumed for ACEi and ARBs?	Yes (more or less). Both classes of drug have shown similar efficacy in HF, although their mechanism of action is not the same, nor are their side effect profiles.

Issue 5: Use of KCCQ-TSS quartiles in the model	
13. Should the following domains be included in the measurement of HFrEF disease severity? a. physical limitations b. quality of life c. social inference	a) Yes b) Yes c) We are sorry we don't know what this term means in the context of HFrEF.
Issue 6: Survival extrapolation	
14. Which long-term survival estimates would most accurately reflect what is expected in clinical practice in the NHS?	Since most patients with HF are older (say in their 70's), it is inevitable that most of them will have died, no matter what treatment they have had, by 120 months follow up. 240 month follow up is likely to mean more or less 100^% mortality, with occasional exceptions for much younger patients. Weibull's 10 year survival seems very unrealistic, with or without dapa. So Gompertz feels more likely . The population in base case 2 are likely to have hypotension. That is a marker of more severe disease/older/frailer patients. As such, mortality in this group is likely to be much higher than in case 1. Case 3 is also likely to have more severe HF, if still symptomatic despite three agents. This appears to have been factored in to the modelling already.

Months		0	12	24	36	60	120	180	240
Base case #1, people on ACEi or ARB, beta-blocker, ±MRA for whom sacubitril valsartan is suitable									
Weibull	**Dapagliflozin**	100.0%	92.8%	84.5%	76.2%	60.9%	32.60%	16.4%	7.9%
	Standard Care	100.0%	91.4%	81.6%	72.1%	55.0%	25.9%	11.3%	4.7%
Gompertz	**Dapagliflozin**	100.0%	92.8%	84.4%	74.9%	53.0%	6.6%	0.0%	0.0%
	Standard Care	100.0%	91.4%	81.5%	70.6%	46.5%	3.7%	0.0%	0.0%
Base case #2, people on ACEi or ARB, beta-blocker, ±MRA for whom sacubitril valsartan is unsuitable									
Weibull	**Dapagliflozin**	100.0%	92.7%	84.4%	76.2%	61.10%	33.20%	17.1%	8.5%
	Standard Care	100.0%	91.3%	81.6%	72.2%	55.5%	26.8%	12.1%	5.2%
Gompertz	**Dapagliflozin**	100.0%	92.6%	84.3%	74.9%	54.0%	8.9%	0.0%	0.0%
	Standard Care	100.0%	91.3%	81.6%	71.0%	48.2%	5.6%	0.0%	0.0%
Base case #3, people on sacubitril valsartan, beta-blocker, ±MRA									
Weibull	**Dapagliflozin**	100.0%	94.9%	86.2%	76.1%	55.6%	19.1%	4.8%	0.9%
	Standard Care	100.0%	92.8%	81.1%	68.0%	43.7%	9.6%	1.4%	0.1%
Gompertz	**Dapagliflozin**	100.0%	94.8%	85.9%	71.5%	26.7%	0.0%	0.0%	0.0%
	Standard Care	100.0%	92.8%	80.8%	62.3%	15.6%	0.0%	0.0%	0.0%

15. Based on the company's goodness of fit criteria estimates (AIC/BIC) the log-logistic and log-normal curves could be a suitable fit to the data but predict more optimistic extrapolations that the Weibull (as shown in the graph below). Would you expect improved survival in clinical practice compared to what is estimated using the Weibull extrapolation curve (see table from question 14)?	No. I think the extrapolations of Weibull are themselves too optimistic. The projections in the company graph seem wholly unrealistic – for patients in their 70s with heart failure to have a 40% survival rate at 20 years seems nigh impossible. By 20years, I would expect all the curves to have reached 0-5% survival. Benefit is in extending median survival within this time frame, not exceeding a 20 year survival. Only the very youngest of heart failure patients can credibly expect to survive 20 years. They are a small minority.

Company's alternative all-cause mortality survival curves (scenario analyses) (CS p109)



Issue 7: Treatment waning effect	
16. **NHS England:** Would a stopping rule apply for dapagliflozin in the NHS?	This would seem highly appropriate, given that heart failure patients are often frail, often have multiple comorbidities and are facing a serious risk of polypharmacy, even just counting the heart

	failure medications they might take. As they get more frail or approach end of life, rationalisation of their medications away from those for prognostic reasons and towards those that improve quality of life is more logical. The benefit of the medications may be minimal in patients who are essentially terminally ill. Good palliative care is an integral part of heart failure management.
17. Would treatment effect be expected to continue after stopping dapagliflozin? a. If yes, how long after stopping treatment would this effect last? b. Is this observed in patients having sacubitril valsartan?	No b) Not that we are aware of, would expect benefit to wear off quickly.

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About you

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

Questions for engagement

Issue 1: Positioning in the pathway	
1. Are the company's populations #1, #2 and #3 as detailed in Appendix 1 (page 17) clearly distinguishable in clinical practice?	These three populations are clearly distinguishable in clinical practice, but all three populations would be expected to derive benefit from Dapagliflozin.
2. Is the company's positioning of dapagliflozin appropriate?	No. The concept of treatment response is unhelpful. The prognostic benefits that are seen with Dapagliflozin – improved survival and reduced hospitalisation – may occur irrespective of change in symptoms. Patients who report no symptomatic 'response' may have avoided death or hospitalisation.
a. Should the committee consider additional positions in the pathway?	Yes. Dapagliflozin should be considered as an option in the same position in the guideline as Sacubitril/Valsartan for initiation after ACEi/ARB + BB + MRA depending on clinical judgment of which is most appropriate.
i. Would dapagliflozin ever be used in people responding to existing treatments?	Yes, assuming that these patients meet the inclusion criteria in the DAPA HF trial. One would expect additional benefit from Dapagliflozin, irrespective of any benefit that has already been derived from existing treatments.
ii. Would dapagliflozin be used in people whose symptoms continue or disease is not responding to sacubitril valsartan?	Yes. Dapagliflozin would be added to existing therapy including sacubitril/valsartan for patients meeting the criteria.

1. If yes, would treatment with sacubitril valsartan stop or would dapagliflozin be added to current care?	Dapagliflozin would be added. Sacubitril-Valsartan would not be stopped.
2. If sacubitril valsartan is stopped, would ACEi / ARBs be restarted?	Not applicable – Sabubitril/Valsartan would not be stopped.
3. Would dapagliflozin be used instead of sacubitril valsartan where both are an option?	Not typically. Dapagliflozin and Sacubitril/Valsartan have different actions and each medication provides benefit when they are used together.
a. Would all people who have sacubitril valsartan be able to have dapagliflozin?	Yes, unless the patient had an isolated contra-indication to either medication.
4. In what proportion of people not responding to ACEi/ARBs, beta-blockers ± MRA would you expect sacubitril valsartan to be unsuitable (population #2)?	The concept of 'treatment response' in the question is unhelpful without defining what is meant by response or lack of response. All heart failure patients should receive best possible treatment according to their current LVEF, irrespective of whether there is objective or subjective evidence of 'response' to earlier treatments.
5. Have all appropriate comparators been considered in the appraisal?	Yes
Issue 2: Use in primary care	
6. Should dapagliflozin be initiated by a heart failure specialist?	Yes. Dapagliflozin should be initiated by a heart failure specialist (such as a cardiologist, physician with specialist interest in heart failure, general practitioner with specialist interest in heart failure, heart failure specialist nurse or heart failure specialist pharmacist).
a. If yes, what additional monitoring would be required?	Standard monitoring should take place i.e. BP and renal function. Other medications may need to be reviewed and adjusted, particularly loop diuretics and other medications used for control of diabetes mellitus
b. Is it plausible that GPs could prescribe	

dapagliflozin in primary care prior to referral to a specialist? c. If no, what additional training or resources would be necessary for primary care clinicians to prescribe dapagliflozin?	Yes. It is plausible that a GP could initiate Dapagliflozin prior to referral to a heart failure specialist. The patient may have a non-heart failure indication for the use of Dapagliflozin (diabetes mellitus).
7. What percentage of people see a heart specialist after progressing on ARBs / ACEi's in clinical practice in the NHS: i. For people starting MRAs? ii. For people starting specialist treatment? b. Does specialist referral reduce access to second line treatment options? c. What additional costs and resources would be associated with dapagliflozin treatment in specialist care versus primary care? Would there be any costs/resources that would apply to dapagliflozin but not to sacubitril valsartan and vice versa?	NICE guidance NG106 states very clearly that the specialist heart failure MDT should manage newly diagnosed, recently decompensated or advanced heart failure, optimise treatment, start new medicines that need specialist supervision, continue to manage heart failure after an interventional procedure and manage heart failure that is not responding to treatment. As such, one would expect ALL patients to see a heart failure specialist. Yes. There are areas of the country that do not have sufficient access to heart failure specialist care and this can reduce access to advanced treatment options. Uncertain but probably none. In order to safely initiate Dapagliflozin, any practitioner needs to ascertain the patient's type of heart failure (HFrEF, HFmrEF, HFpEF), review current treatment, check blood pressure and renal function and then counsel the patient about the risks and benefits of starting this new medication. A heart failure specialist is likely to be quicker and more confident in this process than a non-specialist. There are no costs/resources that would not apply to Sacubitril-Valsartan.
Issue 3: Generalisability of the DAPA-HF trial	
8. In NHS clinical practice, what percentage of patients would be expected to have HFrEF and	Less than 10% of UK patients with diabetes mellitus have type 1 diabetes. The vast majority have type 2 diabetes. The number of patients in the UK with both heart failure and type 1 diabetes is

type 1 diabetes mellitus? How would dapagliflozin be used in this population?	likely to be very small. Dapagliflozin should be not initiated in patients with Type 1 diabetes without specialist diabetic team involvement.
9. What percentage of people with HFrEF have acute decompensated HF?	At any given time point, the majority of patients with HFrEF have stable chronic heart failure. However, the majority of patient will have an acute decompensated episode at some point within their disease trajectory. Dapagliflozin should not be considered for initiation during an acute episode.
10. How would disease aetiology, clinical management, and baseline risk for heart failure be expected to differ in Europe versus the rest of the world?	The major risk factors for heart failure (age, smoking, hypertension, coronary artery disease, diabetes mellitus) are similar in Europe and the rest of the world. There is no good evidence to support different clinical management of heart failure in individuals of different ethnic background.
Issue 4: Indirect treatment comparison	
11. Can a class effect be assumed for ACE inhibitors?	No.
12. Can equivalence be assumed for ACEi and ARBs?	No.
Issue 5: Use of KCCQ-TSS quartiles in the model	
13. Should the following domains be included in the measurement of HFrEF disease severity? a. physical limitations b. quality of life c. social inference	Yes Yes Yes
Issue 6: Survival extrapolation	

14. Which long-term survival estimates would most accurately reflect what is expected in clinical practice in the NHS?	Unable to comment

Months		0	12	24	36	60	120	180	240
Base case #1, people on ACEi or ARB, beta-blocker, ±MRA for whom sacubitril valsartan is suitable									
Weibull	**Dapagliflozin**	100.0%	92.8%	84.5%	76.2%	60.9%	32.60%	16.4%	7.9%
	Standard Care	100.0%	91.4%	81.6%	72.1%	55.0%	25.9%	11.3%	4.7%
Gompertz	**Dapagliflozin**	100.0%	92.8%	84.4%	74.9%	53.0%	6.6%	0.0%	0.0%
	Standard Care	100.0%	91.4%	81.5%	70.6%	46.5%	3.7%	0.0%	0.0%
Base case #2, people on ACEi or ARB, beta-blocker, ±MRA for whom sacubitril valsartan is unsuitable									
Weibull	**Dapagliflozin**	100.0%	92.7%	84.4%	76.2%	61.10%	33.20%	17.1%	8.5%
	Standard Care	100.0%	91.3%	81.6%	72.2%	55.5%	26.8%	12.1%	5.2%
Gompertz	**Dapagliflozin**	100.0%	92.6%	84.3%	74.9%	54.0%	8.9%	0.0%	0.0%
	Standard Care	100.0%	91.3%	81.6%	71.0%	48.2%	5.6%	0.0%	0.0%
Base case #3, people on sacubitril valsartan, beta-blocker, ±MRA									
Weibull	**Dapagliflozin**	100.0%	94.9%	86.2%	76.1%	55.6%	19.1%	4.8%	0.9%
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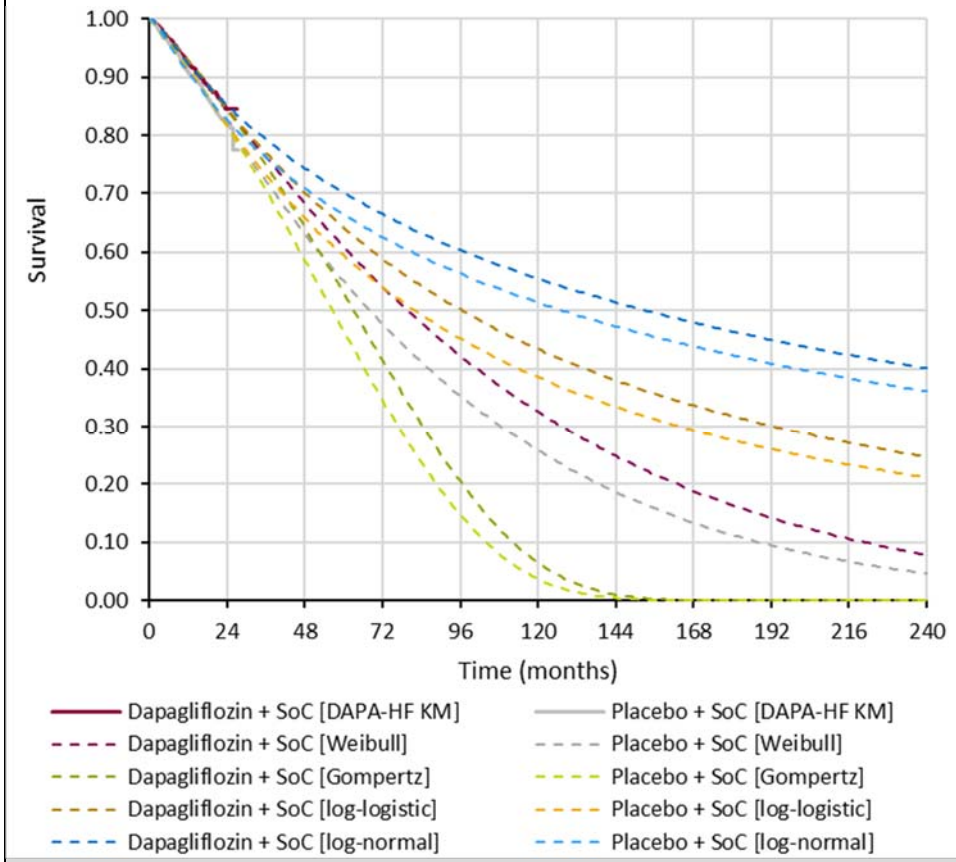
	Standard Care	100.0%	92.8%	80.8%	62.3%	15.6%	0.0%	0.0%	0.0%

15. Based on the company's goodness of fit criteria estimates (AIC/BIC) the log-logistic and log-normal curves could be a suitable fit to the data but predict more optimistic extrapolations that the Weibull (as shown in the graph below). Would you expect improved survival in clinical practice compared to what is estimated using	Unable to comment

the Weibull extrapolation curve (see table from question 14)?	

Company's alternative all-cause mortality survival curves (scenario analyses) (CS p109)



Issue 7: Treatment waning effect

16. **NHS England:** Would a stopping rule apply for dapagliflozin in the NHS?	No. Treatment would be lifelong.
17. Would treatment effect be expected to continue after stopping dapagliflozin? a. If yes, how long after stopping treatment would this effect last? b. Is this observed in patients having sacubitril valsartan?	No. No.

NICE National Institute for Health and Care Excellence

Technical engagement response form

Dapagliflozin for treating heart failure with reduced ejection fraction [ID1656]

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- Do not use abbreviations.
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- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential

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About you

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

Questions for engagement

Issue 1: Positioning in the pathway	
1. Are the company's populations #1, #2 and #3 as detailed in Appendix 1 (page 17) clearly distinguishable in clinical practice?	
2. Is the company's positioning of dapagliflozin appropriate? a. Should the committee consider additional positions in the pathway? i. Would dapagliflozin ever be used in people responding to existing treatments? ii. Would dapagliflozin be used in people whose symptoms continue or disease is not responding to sacubitril valsartan? 1. If yes, would treatment with sacubitril valsartan stop or would dapagliflozin be added to current care? 2. If sacubitril valsartan is stopped, would ACEi / ARBs be restarted?	
3. Would dapagliflozin be used instead of sacubitril valsartan where both are an option? a. Would all people who have sacubitril	

valsartan be able to have dapagliflozin?	
4. In what proportion of people not responding to ACEi/ARBs, beta-blockers ± MRA would you expect sacubitril valsartan to be unsuitable (population #2)?	
5. Have all appropriate comparators been considered in the appraisal?	
Issue 2: Use in primary care	
6. Should dapagliflozin be initiated by a heart failure specialist? a. If yes, what additional monitoring would be required? b. Is it plausible that GPs could prescribe dapagliflozin in primary care prior to referral to a specialist? c. If no, what additional training or resources would be necessary for primary care clinicians to prescribe dapagliflozin?	Dapagliflozin should not need to be initiated by a heart failure specialist. It is plausible that GPs prescribe dapagliflozin in primary care prior to referral to a specialist as the treatment is already well know and well used in primary care. Not enabling GPs to initiate dapagliflozin for heart failure would create unnecessary delay in treatment, especially during and in the aftermath of the current pandemic. This would also lead to an untenable situation where a person with heart failure and diabetes can access dapagliflozin without delay (c40% of HF population) via their GP but not if they have heart failure without diabetes.
7. What percentage of people see a heart specialist after progressing on ARBs / ACEi's in clinical practice in the NHS: i. For people starting MRAs? ii. For people starting specialist treatment? b. Does specialist referral reduce access to	

second line treatment options? c. What additional costs and resources would be associated with dapagliflozin treatment in specialist care versus primary care? Would there be any costs/resources that would apply to dapagliflozin but not to sacubitril valsartan and vice versa?	
Issue 3: Generalisability of the DAPA-HF trial	
8. In NHS clinical practice, what percentage of patients would be expected to have HFrEF and type 1 diabetes mellitus? How would dapagliflozin be used in this population?	
9. What percentage of people with HFrEF have acute decompensated HF?	
10. How would disease aetiology, clinical management, and baseline risk for heart failure be expected to differ in Europe versus the rest of the world?	
Issue 4: Indirect treatment comparison	
11. Can a class effect be assumed for ACE inhibitors?	

12. Can equivalence be assumed for ACEi and ARBs?	
Issue 5: Use of KCCQ-TSS quartiles in the model	
13. Should the following domains be included in the measurement of HFrEF disease severity? a. physical limitations b. quality of life c. social inference	
Issue 6: Survival extrapolation	
14. Which long-term survival estimates would most accurately reflect what is expected in clinical practice in the NHS?	

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Gompertz	**Dapagliflozin**	100.0%	92.6%	84.3%	74.9%	54.0%	8.9%	0.0%	0.0%
	Standard Care	100.0%	91.3%	81.6%	71.0%	48.2%	5.6%	0.0%	0.0%
Base case #3, people on sacubitril valsartan, beta-blocker, ±MRA									
Weibull	**Dapagliflozin**	100.0%	94.9%	86.2%	76.1%	55.6%	19.1%	4.8%	0.9%

	Standard Care	100.0%	92.8%	81.1%	68.0%	43.7%	9.6%	1.4%	0.1%
Gompertz	**Dapagliflozin**	100.0%	94.8%	85.9%	71.5%	26.7%	0.0%	0.0%	0.0%
	Standard Care	100.0%	92.8%	80.8%	62.3%	15.6%	0.0%	0.0%	0.0%

15. Based on the company's goodness of fit criteria estimates (AIC/BIC) the log-logistic and log-normal curves could be a suitable fit to the data but predict more optimistic extrapolations that the Weibull (as shown in the graph below). Would you expect improved survival in clinical practice compared to what is estimated using the Weibull extrapolation curve (see table from question 14)?	

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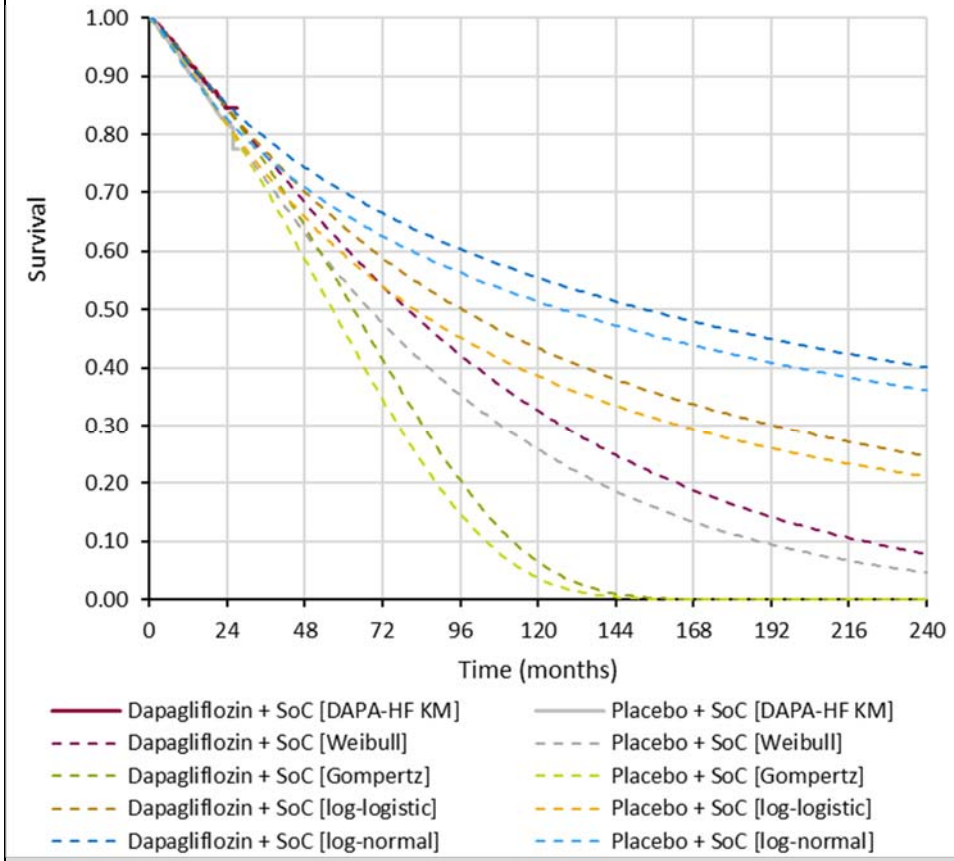

Issue 7: Treatment waning effect	
16. **NHS England:** Would a stopping rule apply for dapagliflozin in the NHS?	

17. Would treatment effect be expected to continue after stopping dapagliflozin? a. If yes, how long after stopping treatment would this effect last? b. Is this observed in patients having sacubitril valsartan?	

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About you

Your name	[redacted]
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**MSD**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**MSD does not have any links to the Tobacco industry**

Questions for engagement

Issue 1: Positioning in the pathway	
1. Are the company's populations #1, #2 and #3 as detailed in Appendix 1 (page 17) clearly distinguishable in clinical practice?	**MSD does not have any comments.**
2. Is the company's positioning of dapagliflozin appropriate? a. Should the committee consider additional positions in the pathway? i. Would dapagliflozin ever be used in people responding to existing treatments? ii. Would dapagliflozin be used in people whose symptoms continue or disease is not responding to sacubitril valsartan? 1. If yes, would treatment with sacubitril valsartan stop or would dapagliflozin be added to current care? 2. If sacubitril valsartan is stopped, would ACEi / ARBs be restarted?	**MSD does not have any comments.**
3. Would dapagliflozin be used instead of sacubitril valsartan where both are an option?	**MSD does not have any comments.**

a. Would all people who have sacubitril valsartan be able to have dapagliflozin?	
4. In what proportion of people not responding to ACEi/ARBs, beta-blockers ± MRA would you expect sacubitril valsartan to be unsuitable (population #2)?	**MSD does not have any comments.**
5. Have all appropriate comparators been considered in the appraisal?	**MSD does not have any comments.**
Issue 2: Use in primary care	
6. Should dapagliflozin be initiated by a heart failure specialist? a. If yes, what additional monitoring would be required? b. Is it plausible that GPs could prescribe dapagliflozin in primary care prior to referral to a specialist? c. If no, what additional training or resources would be necessary for primary care clinicians to prescribe dapagliflozin?	**MSD does not have any comments.**
7. What percentage of people see a heart specialist after progressing on ARBs / ACEi's in clinical practice in the NHS: i. For people starting MRAs? ii. For people starting specialist treatment?	**MSD does not have any comments.**

b. Does specialist referral reduce access to second line treatment options? c. What additional costs and resources would be associated with dapagliflozin treatment in specialist care versus primary care? Would there be any costs/resources that would apply to dapagliflozin but not to sacubitril valsartan and vice versa?	
Issue 3: Generalisability of the DAPA-HF trial	
8. In NHS clinical practice, what percentage of patients would be expected to have HFrEF and type 1 diabetes mellitus? How would dapagliflozin be used in this population?	**MSD does not have any comments.**
9. What percentage of people with HFrEF have acute decompensated HF?	**MSD does not have any comments.**
10. How would disease aetiology, clinical management, and baseline risk for heart failure be expected to differ in Europe versus the rest of the world?	**MSD does not have any comments.**
Issue 4: Indirect treatment comparison	
11. Can a class effect be assumed for ACE inhibitors?	MSD does not have any comments.

12. Can equivalence be assumed for ACEi and ARBs?	MSD does not have any comments.
Issue 5: Use of KCCQ-TSS quartiles in the model	
13. Should the following domains be included in the measurement of HFrEF disease severity? a. physical limitations b. quality of life c. social inference	MSD does not have any comments.
Issue 6: Survival extrapolation	
14. Which long-term survival estimates would most accurately reflect what is expected in clinical practice in the NHS?	MSD does not have any comments.

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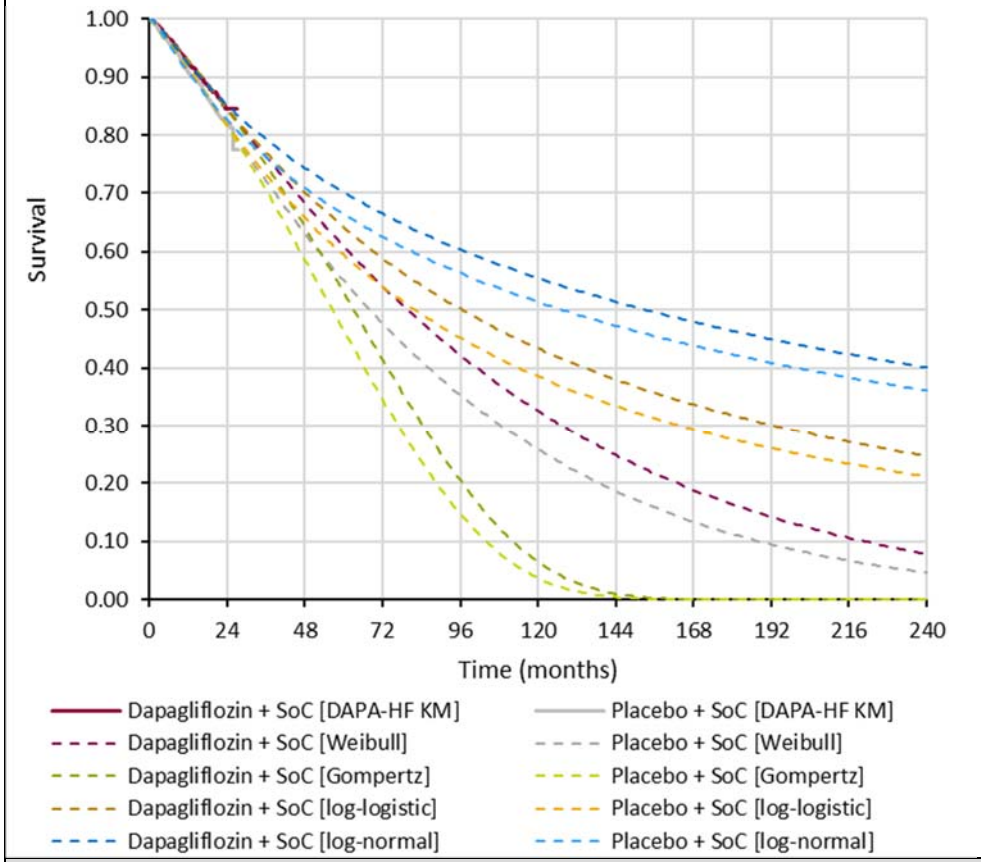

Issue 7: Treatment waning effect	
16. **NHS England:** Would a stopping rule apply for dapagliflozin in the NHS?	MSD does not have any comments.
17. Would treatment effect be expected to continue after stopping dapagliflozin?	MSD does not have any comments.

a. If yes, how long after stopping treatment would this effect last? b. Is this observed in patients having sacubitril valsartan?	

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About you

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Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**Primary Care Cardiovascular Society CIC**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**No disclosures related to the tobacco industry.**

Questions for engagement

Issue 1: Positioning in the pathway	
1. Are the company's populations #1, #2 and #3 as detailed in Appendix 1 (page 17) clearly distinguishable in clinical practice?	**They are clearly distinguishable, but we would also add that there is an additional group where sacubitril valsartan is used as the first line RAAS blocker along with beta blocker with/without MRA.** **We would anticipate that all three defined populations outlined by the company would derive benefit from dapaglifozin**
2. Is the company's positioning of dapagliflozin appropriate? a. Should the committee consider additional positions in the pathway? i. Would dapagliflozin ever be used in people responding to existing treatments? ii. Would dapagliflozin be used in people whose symptoms continue or disease is not responding to sacubitril valsartan? 1. If yes, would treatment with sacubitril valsartan stop or would dapagliflozin be added to current care? 2. If sacubitril valsartan is stopped, would ACEi / ARBs be restarted?	**Yes. The committee should consider additional pathway as above: dapagliflozin should be considered as an additional therapy when sacubitril valsartan is used as first line RAAS blocking agent along with beta blocker and with/without MRA.** **Yes, in keeping with the trial population in the DAPA-HF trial, one would anticipate additional benefit from dapagliflozin** **Yes, again in keeping with the trial population in the DAPA-HF trial** **Sacubitril valsartan would not be stopped but dapagliflozin would be added.** **Sacubitril valsartan would not be discontinued and dapaglifozin would be added.**

3. Would dapagliflozin be used instead of sacubitril valsartan where both are an option? a. Would all people who have sacubitril valsartan be able to have dapagliflozin?	**No. Dapagliflozin and sacubitril valsartan work differently in patient with HFrEF and therefore their benefits are complimentary when used in combination.** **Yes, unless either medication is contraindicated.**
4. In what proportion of people not responding to ACEi/ARBs, beta-blockers ± MRA would you expect sacubitril valsartan to be unsuitable (population #2)?	**We do not feel this is a well thought out question, since you have not defined what you mean by response.** **All patients should be considered for evidence-based treatment according to current guidance.**
5. Have all appropriate comparators been considered in the appraisal?	**Yes, but please see answer to question 1.**
Issue 2: Use in primary care	
6. Should dapagliflozin be initiated by a heart failure specialist? a. If yes, what additional monitoring would be required? b. Is it plausible that GPs could prescribe dapagliflozin in primary care prior to referral to a specialist? c. If no, what additional training or resources would be necessary for primary care clinicians to prescribe dapagliflozin?	**No, it should not be 'exclusively' initiated by a heart failure specialist.** **The HCP initiating dapagliflozin should arrange for appropriate monitoring of renal function, blood pressure and fluid status plus other relevant clinical areas. In patients with T2 Diabetes review of medication would also be required.** **Primary care teams have been initiating SGLT2 inhibitors including dapagliflozin for type 2 diabetic patients (a significant proportion of whom have co-existing heart failure) for the last 8 years. Dapagliflozin has a good safety profile and does not require any additional monitoring once initiated. No specialist knowledge is needed to initiate these well-established agents including dapagliflozin for diabetes and/or heart failure. The Primary Care Cardiovascular Society (PCCS) recommends that dapagliflozin should be initiated for eligible heart failure with reduced ejection fraction (HFrEF) patients in all treatment settings, including by primary health care teams (GPs, GPSI and clinical pharmacists), as well as hospital based and community based heart failure teams and cardiologists. These include those with an ejection fraction of <40% who remain symptomatic (NHYA Class II-III) despite**

	triple therapy of an ACEi or ARB, beta-blocker and a mineralocorticoid antagonist being used as tolerated by the patient. Consideration should be given to concomitant glycaemic status should be taken into consideration when initiating dapagliflozin in T2 diabetes patients. **Primary care teams have been initiating SGLT2 inhibitors including dapagliflozin for type 2 diabetic patients (a significant proportion of whom have co-existing heart failure) for the last 8 years. Dapagliflozin has a good safety profile and does not require any additional monitoring once initiated. No specialist knowledge is needed to initiate these well-established agents including dapagliflozin for diabetes and/or heart failure.** **NICE guidelines recommend that 'the primary care team should take over routine management of heart failure as soon as it has been stabilised and its management optimised' (NG106). Therefore a significant number of patients with HFREF are managed solely by GP teams.** **NICE also recommend that the primary care team should arrange access to specialist heart failure services if needed (NG106). If this is deemed necessary, the PCCS would support the position that primary care clinicians could consider initiation of dapagliflozin on top of triple therapy, ensuring that patients with a confirmed diagnosis of HFREF in the absence of glycaemic issues, benefit from treatment with dapagliflozin whilst awaiting specialist review.** **The PCCS are concerned that restriction of dapagliflozin initiation to heart failure specialists may lead to existing heart failure specialist services being overwhelmed by a rise in referrals, may unnecessarily limit access to patients who would benefit and lead to significant delays in initiation of evidence based therapy with dapagliflozin. The PCCS is concerned that this may in turn lead to potential decompensation of heart failure with increased morbidity, hospital admissions and mortality.** **New QOF heart failure indicators require primary health care teams to undertake at least annual functional capacity assessment, medication review and holistic heart failure review.**

	The PCCS will be involved in education of primary health care teams including Primary Care Network (PCN) CVD leads in comprehensive heart failure assessment which will include when to initiate dapagliflozin. The PCCS are concerned that whilst primary care teams can initiate dapaglifozin for type II diabetes patients with heart failure, to limit prescribing of dapaglifozin to those with heart failure without type II diabetes will create confusion and inequity of access to this life saving therapy. **All HCPs prescribing SGLT2 inhibitors may require additional appropriate education and training.**
7. What percentage of people see a heart specialist after progressing on ARBs / ACEi's in clinical practice in the NHS: i. For people starting MRAs? ii. For people starting specialist treatment? b. Does specialist referral reduce access to second line treatment options? c. What additional costs and resources would be associated with dapagliflozin treatment in specialist care versus primary care? Would there be any costs/resources that would apply to dapagliflozin but not to sacubitril valsartan and vice versa?	**In keeping with NICE Chronic heart failure guidance 2018(NG106) all patients with a new diagnosis of heart failure or those who have decompensated should be seen and assessed by the heart failure MDT.** **Yes. This will be particularly relevant when considering the initiation of dapagliflozin** **There may be additional expense to refer to a secondary care services for dapagliflozin intiation. Heart Failure specialist team support is not universally available and in some areas referral to the specialist team would involve extended waiting times. This would apply equally to dapaflozin and sacubitril valsartan**

Issue 3: Generalisability of the DAPA-HF trial	
8. In NHS clinical practice, what percentage of patients would be expected to have HFrEF and type 1 diabetes mellitus? How would dapagliflozin be used in this population?	**The number of patients with T1 Diabetes and HFrEF would be extremely small in our experience and we would not use dapagliflozin in these patients.**
9. What percentage of people with HFrEF have acute decompensated HF?	**We are not able to give accurate answer but the majority of patients with HFrEF would have an acute episode at some point.**
10. How would disease aetiology, clinical management, and baseline risk for heart failure be expected to differ in Europe versus the rest of the world?	**There are a large number of variables to this question and I do not therefore believe one can give an accurate answer. Overall the management of patients with HFrEF across the world is similar and reflects international guidelines.**
Issue 4: Indirect treatment comparison	
11. Can a class effect be assumed for ACE inhibitors?	**No.**
12. Can equivalence be assumed for ACEi and ARBs?	**No.**
Issue 5: Use of KCCQ-TSS quartiles in the model	
13. Should the following domains be included in the measurement of HFrEF disease severity? a. physical limitations b. quality of life	**Physical limitations: yes, Quality of life: yes, Social inference: yes**

c. social inference	

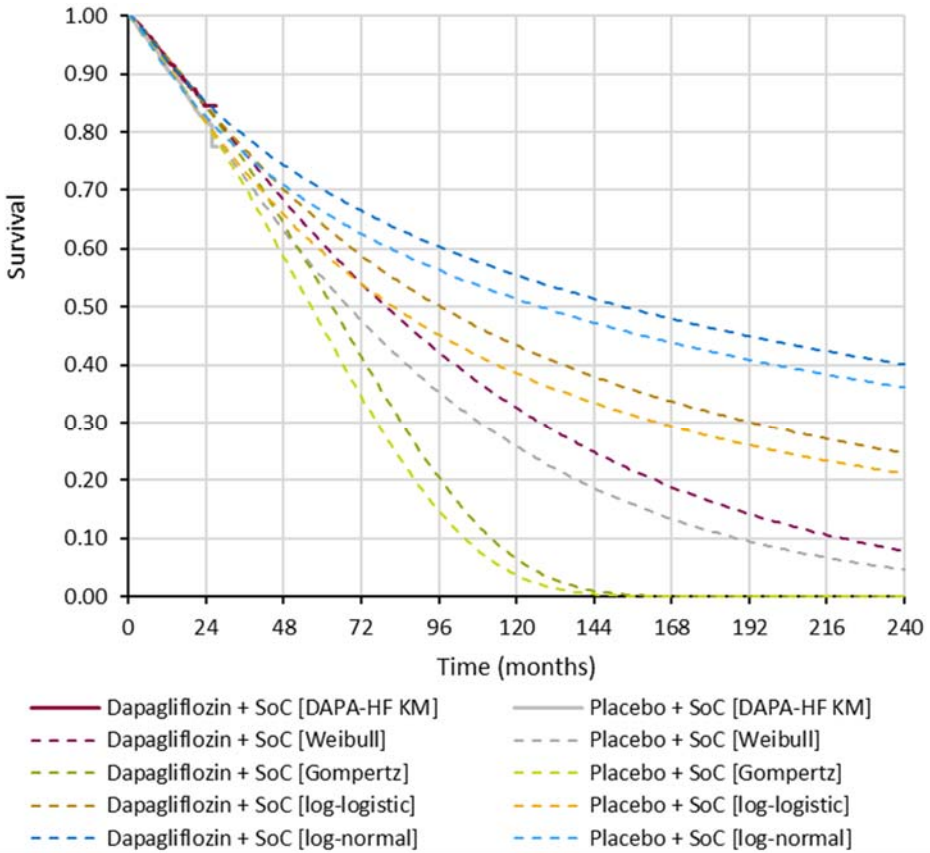
Issue 6: Survival extrapolation

14. Which long-term survival estimates would most accurately reflect what is expected in clinical practice in the NHS?	**We are not able to provide an accurate response**

Months		**0**	**12**	**24**	**36**	**60**	**120**	**180**	**240**
Base case #1, people on ACEi or ARB, beta-blocker, ±MRA for whom sacubitril valsartan is suitable									
Weibull	**Dapagliflozin**	100.0%	92.8%	84.5%	76.2%	60.9%	32.60%	16.4%	7.9%
	Standard Care	100.0%	91.4%	81.6%	72.1%	55.0%	25.9%	11.3%	4.7%
Gompertz	**Dapagliflozin**	100.0%	92.8%	84.4%	74.9%	53.0%	6.6%	0.0%	0.0%
	Standard Care	100.0%	91.4%	81.5%	70.6%	46.5%	3.7%	0.0%	0.0%
Base case #2, people on ACEi or ARB, beta-blocker, ±MRA for whom sacubitril valsartan is unsuitable									
Weibull	**Dapagliflozin**	100.0%	92.7%	84.4%	76.2%	61.10%	33.20%	17.1%	8.5%
	Standard Care	100.0%	91.3%	81.6%	72.2%	55.5%	26.8%	12.1%	5.2%
Gompertz	**Dapagliflozin**	100.0%	92.6%	84.3%	74.9%	54.0%	8.9%	0.0%	0.0%
	Standard Care	100.0%	91.3%	81.6%	71.0%	48.2%	5.6%	0.0%	0.0%
Base case #3, people on sacubitril valsartan, beta-blocker, ±MRA									
Weibull	**Dapagliflozin**	100.0%	94.9%	86.2%	76.1%	55.6%	19.1%	4.8%	0.9%
	Standard Care	100.0%	92.8%	81.1%	68.0%	43.7%	9.6%	1.4%	0.1%
Gompertz	**Dapagliflozin**	100.0%	94.8%	85.9%	71.5%	26.7%	0.0%	0.0%	0.0%
	Standard Care	100.0%	92.8%	80.8%	62.3%	15.6%	0.0%	0.0%	0.0%

15. Based on the company's goodness of fit criteria estimates (AIC/BIC) the log-logistic and log-normal curves could be a suitable	**Not able to provide an accurate response**

fit to the data but predict more optimistic extrapolations that the Weibull (as shown in the graph below). Would you expect improved survival in clinical practice compared to what is estimated using the Weibull extrapolation curve (see table from question 14)?	
Company's alternative all-cause mortality survival curves (scenario analyses) (CS p109)	



Issue 7: Treatment waning effect	
16. **NHS England:** Would a stopping rule apply for dapagliflozin in the NHS?	**Once initiated treatment would be for the foreseeable future**

17. Would treatment effect be expected to continue after stopping dapagliflozin? a. If yes, how long after stopping treatment would this effect last? b. Is this observed in patients having sacubitril valsartan?	**We would not anticipate stopping routinely the use of dapagliflozin – see answer to question 16** **Not aware of any ongoing treatment affect stopping sacubitril valsartan**

NICE National Institute for Health and Care Excellence

Technical engagement response form

Dapagliflozin for treating heart failure with reduced ejection fraction [ID1656]

As a stakeholder you have been invited to comment on the technical report for this appraisal. The technical report and stakeholders responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the questions below. You do not have to answer every question. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be summarised and used by the technical team to amend or update the scientific judgement and rationale in the technical report.

Deadline for comments **5:00pm, Thursday 15 October 2020**

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the technical report which summarises the background and submitted evidence. This will provide context and describe the questions below in greater detail.
- Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.
- If you provide journal articles to support your comments, you must have copyright clearance for these articles.
- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential

information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

About you

Your name	[redacted]
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**South Asian Health Foundation**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**Nil**

Questions for engagement

Issue 1: Positioning in the pathway	
1. Are the company's populations #1, #2 and #3 as detailed in Appendix 1 (page 17) clearly distinguishable in clinical practice?	**Yes**
2. Is the company's positioning of dapagliflozin appropriate? a. Should the committee consider additional positions in the pathway? i. Would dapagliflozin ever be used in people responding to existing treatments? ii. Would dapagliflozin be used in people whose symptoms continue or disease is not responding to sacubitril valsartan? 1. If yes, would treatment with sacubitril valsartan stop or would dapagliflozin be added to current care? 2. If sacubitril valsartan is stopped, would ACEi / ARBs be restarted?	**i: I think the algorithm is unnecessarily confusing. The data in Dapa-HF was iun patient with and without diabetes that were on current SoC- Standard of Care. Most were on ACE-I or ARB, Most on beta-blocker and many were on Saculbiltril/valsartan. The benefiial effects of Dapagliflozin were seen in all sub-groups including those on or not on sacubuil/valsartan. So dapagliflozin would be used in anyone with the exact inclusion criteria in the study- summary below.** **DAPA-HF** **1. Inclusion criteria included:** • **T2 DM or No DM** • **≥18 years of age** • **Chronic Heart Failure NYHA Class II, III, or IV.** • **Heart Failure reduced Ejection Fraction (HFrEF) (LVEF ≤ 40%)** • **Elevated NT-proBNP adjusted to HHF, AF** **2. Exclusion criteria included:** • **Side effects with SGLT-2 inhibitors** • **T1 DM** • **Symptoms of hypotension or SBP < 95mmHg** • **eGFR <30 ml/min/1.73 m^2 or rapidly declining renal function** Essential people need to on current standard of care and then dapagliflozin added once patient

	stable on treatment (ie stable renal function, treatments well tolerated). The simple stepwise treatment would be Level 1: existing standard of care in the Heart Failure Service- if stable add-on Level 2: Dapagliflozin This reflects the setting in the study from which all the beneficial effects were seen.
3. Would dapagliflozin be used instead of sacubitril valsartan where both are an option? a. Would all people who have sacubitril valsartan be able to have dapagliflozin?	**Ideally both should be used. Dapagliflozin was found to be of significant benefit in patients on or not on sacubutril/valsartan. So theoretically is only is affordable dapagliflozin could be added onto the generic standard of care alone for cost efficiencies.** **a: yes, if they fit the inclusion criteria of the study.**
4. In what proportion of people not responding to ACEi/ARBs, beta-blockers ± MRA would you expect sacubitril valsartan to be unsuitable (population #2)?	**Not sure at all. Clinically I suspect around 10- 20% of cases due to high potassium states.**
5. Have all appropriate comparators been considered in the appraisal?	**Yes**
Issue 2: Use in primary care	
6. Should dapagliflozin be initiated by a heart failure specialist? a. If yes, what additional monitoring would be required?	**No – this should be initiated by GPs if the criteria detail above apply- especially the need for the Ejection Fraction to be less than or equal to 40%** a: monitoring especially in patient with diabetes for infection (mainly thrush), DKA and deteriorating renal function as the dose may need to be changed.

b. Is it plausible that GPs could prescribe dapagliflozin in primary care prior to referral to a specialist? c. If no, what additional training or resources would be necessary for primary care clinicians to prescribe dapagliflozin?	b: GP should prescribe c: general update and educational webinars
7. What percentage of people see a heart specialist after progressing on ARBs / ACEi's in clinical practice in the NHS: i. For people starting MRAs? ii. For people starting specialist treatment? b. Does specialist referral reduce access to second line treatment options? c. What additional costs and resources would be associated with dapagliflozin treatment in specialist care versus primary care? Would there be any costs/resources that would apply to dapagliflozin but not to sacubitril valsartan and vice versa?	**1 and 2: Not sure but ? 25% are referred to a heart failure service. Access will not be limited** **B: Can do if waiting lists and poor access to services** **C: Cost of hospital care are always higher than in primary care- repeated visited and investigations. Only the most severely affected should have access to secondary care where there is a limited service.**
Issue 3: Generalisability of the DAPA-HF trial	
8. In NHS clinical practice, what percentage of patients would be expected to have HFrEF and type 1 diabetes mellitus? How would dapagliflozin be used in this population?	**Approximately 10-15% in those over 60 years of age. I personally would use dapagliflozin in these patients**

9. What percentage of people with HFrEF have acute decompensated HF?	**? 1-3% per year.**
10. How would disease aetiology, clinical management, and baseline risk for heart failure be expected to differ in Europe versus the rest of the world?	**This is a very important consideration for our UK population. We need a further analysis of the Dapa-HF data to ascertain what the results of the study are in these specific sub-groups:** South-Asians African Caribbean Chinese East European The data will exist from the Dapa-HF study.
Issue 4: Indirect treatment comparison	
11. Can a class effect be assumed for ACE inhibitors?	Not all were studied and only those with clear beneficial outcomes should be advocated.
12. Can equivalence be assumed for ACEi and ARBs?	No. I think meta-analysis shows that ACE-I are more efficacious thatn ARBs. ARBs often have to used due to side-effects with ACE-i
Issue 5: Use of KCCQ-TSS quartiles in the model	
13. Should the following domains be included in the measurement of HFrEF disease severity? a. physical limitations b. quality of life c. social inference	Yes to all.

	I guess you mean social interference? Or limitations on social life and activities of daily living.
Issue 6: Survival extrapolation	
14. Which long-term survival estimates would most accurately reflect what is expected in clinical practice in the NHS?	#3- as dapagliflozin was added into SoC (standard of care).

Months		**0**	**12**	**24**	**36**	**60**	**120**	**180**	**240**
Base case #1, people on ACEi or ARB, beta-blocker, ±MRA for whom sacubitril valsartan is suitable									
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	Standard Care	100.0%	91.4%	81.6%	72.1%	55.0%	25.9%	11.3%	4.7%
Gompertz	**Dapagliflozin**	100.0%	92.8%	84.4%	74.9%	53.0%	6.6%	0.0%	0.0%
	Standard Care	100.0%	91.4%	81.5%	70.6%	46.5%	3.7%	0.0%	0.0%
Base case #2, people on ACEi or ARB, beta-blocker, ±MRA for whom sacubitril valsartan is unsuitable									
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	Standard Care	100.0%	91.3%	81.6%	71.0%	48.2%	5.6%	0.0%	0.0%
Base case #3, people on sacubitril valsartan, beta-blocker, ±MRA									
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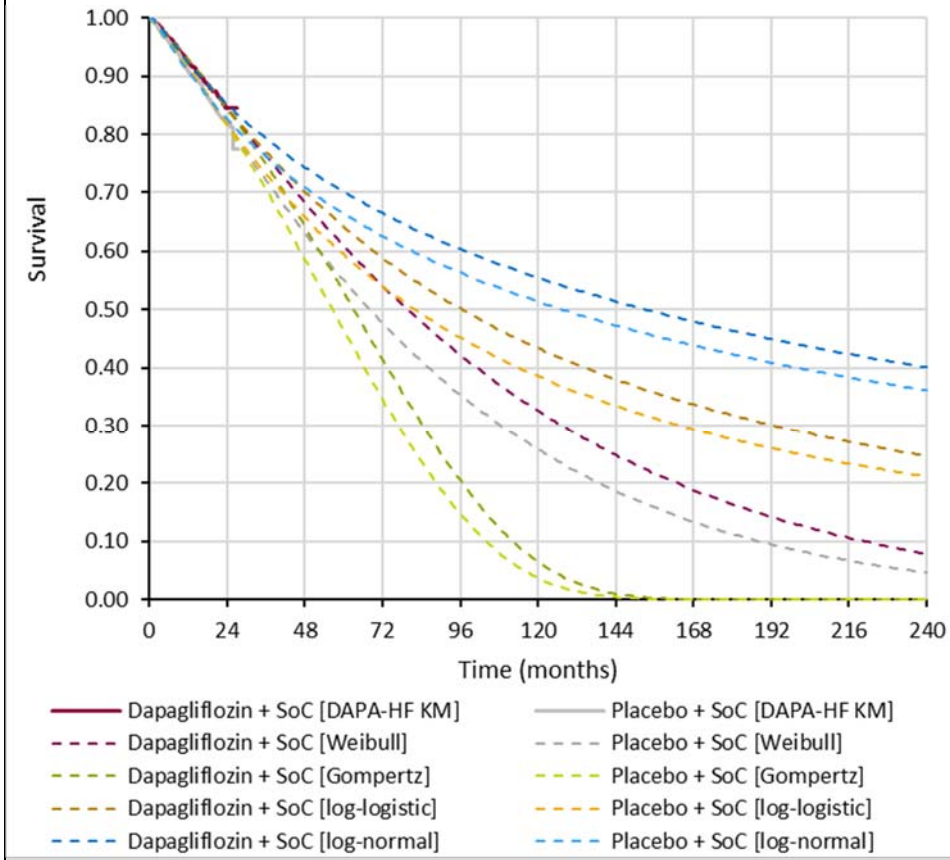
	Standard Care	100.0%	92.8%	81.1%	68.0%	43.7%	9.6%	1.4%	0.1%
Gompertz	**Dapagliflozin**	100.0%	94.8%	85.9%	71.5%	26.7%	0.0%	0.0%	0.0%
	Standard Care	100.0%	92.8%	80.8%	62.3%	15.6%	0.0%	0.0%	0.0%

15. Based on the company's goodness of fit criteria estimates (AIC/BIC) the log-logistic and log-normal curves could be a suitable fit to the data	I would predict log-normal graph for dapagliflozin. The phenomenon of diminishing returns will apply over time. We really only have a clear idea of benefits accrued after 1.5 years (median

but predict more optimistic extrapolations that the Weibull (as shown in the graph below). Would you expect improved survival in clinical practice compared to what is estimated using the Weibull extrapolation curve (see table from question 14)?	follow-up) in the Dapa-HF study. The rest is modelled data and speculative. I would expect a significant improvement in survival (legacy effect shown in other studies).

Company's alternative all-cause mortality survival curves (scenario analyses) (CS p109)



Issue 7: Treatment waning effect	
16. **NHS England:** Would a stopping rule apply for dapagliflozin in the NHS?	No. Unless there are significant side-effects, patient wishes or use falls outside of licensed use. Worsening renal failure would be an example of this. Currently, dapagliflozin can only be started

	above an eGFR of 60 and stopped when the eGFR is persistently below 45.
17. Would treatment effect be expected to continue after stopping dapagliflozin? a. If yes, how long after stopping treatment would this effect last? b. Is this observed in patients having sacubitril valsartan?	A: Unlikely in any great measure. The patient would be further advanced in their natural history and aging alone will result in poorer outcomes and less accrued benefits over time. B: Not sure.

NICE National Institute for Health and Care Excellence

Technical engagement response form

Dapagliflozin for treating heart failure with reduced ejection fraction [ID1656]

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Deadline for comments **5:00pm, Thursday 15 October 2020**

Thank you for your time.

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Notes on completing this form

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- Do not include medical information about yourself or another person that could identify you or the other person.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.
- If you provide journal articles to support your comments, you must have copyright clearance for these articles.
- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential

information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

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Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

About you

Your name	[redacted]
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**Novartis Pharmaceuticals UK Limited**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**

Questions for engagement

Issue 1: Positioning in the pathway	
1. Are the company's populations #1, #2 and #3 as detailed in Appendix 1 (page 17) clearly distinguishable in clinical practice?	Only heart failure specialists are expected to clearly distinguish between populations #1 and #2 in clinical practice. Both populations #1 and #2 represent patients who are currently being treated with angiotensin-converting-enzyme inhibitor (ACEi) / angiotensin receptor blocker (ARB) (+ beta-blocker [BB], ± mineralocorticoid receptor antagonist [MRA]) and only differ in terms of sacubitril/valsartan being a suitable (population #1) or unsuitable (population #2) treatment option for patients who continue to be symptomatic (New York Heart Association [NHYA] class II to IV). As per NICE TA388, the decision to start treatment with sacubitril/valsartan is made by a heart failure specialist with access to a multidisciplinary heart failure team. Therefore, only a heart failure specialist may be in a position to fully assess a patient's suitability for treatment with sacubitril/valsartan and distinguish between these two populations in clinical practice. Population #3 can be easily distinguished from populations #1 and #2 as it encompasses patients currently being treated with sacubitril/valsartan (+ BB ± MRA).
2. Is the company's positioning of dapagliflozin appropriate? a. Should the committee consider additional positions in the pathway?	The company's positioning of dapagliflozin, particularly as a replacement therapy for sacubitril/valsartan in population #1, is not aligned to the pivotal trial evidence from DAPA-HF. The

i. Would dapagliflozin ever be used in people responding to existing treatments? ii. Would dapagliflozin be used in people whose symptoms continue or disease is not responding to sacubitril valsartan? 1. If yes, would treatment with sacubitril valsartan stop or would dapagliflozin be added to current care? 2. If sacubitril valsartan is stopped, would ACEi / ARBs be restarted?	clinical evidence supports dapagliflozin as an add-on therapy to standard of care (SOC), as reflected in the NICE scope. i. In chronic heart failure, a decision for further pharmacological treatment is usually made based on the continued presence of heart failure symptoms. Typically, patients with a NYHA class of II to IV are considered symptomatic. According to the DAPA-HF study inclusion criteria, patients in the trial had to be symptomatic (NYHA II-IV) despite being optimally treated with pharmacological and/or device therapy, thus no data exist to support using dapagliflozin in non-symptomatic patients (NYHA class I). We would not expect dapagliflozin to be considered in patients responding to existing treatment. ii. Yes, dapagliflozin could be used in patients whose symptoms continue or disease is not responding to sacubitril/valsartan. The DAPA-HF study suggests a benefit of adding dapagliflozin for patients who remain symptomatic on sacubitril/valsartan (+BB ±MRA) (McMurray et al. 2019a). The DAPA-HF study only evaluated dapagliflozin as an add-on therapy, with the protocol strongly encouraging investigators not to reduce the dose of or discontinue treatments such as ACEi / ARBs or sacubitril/valsartan unless essential due to an adverse event. In the Western Europe subgroup, 24.5% of patients had a background therapy of sacubitril/valsartan (McMurray et al. 2019b). A post-hoc analysis of the DAPA-HF study showed that dapagliflozin and sacubitril/valsartan can be used together without compromising safety (Solomon et al. 2020). The DAPA-HF study provides no evidence for stopping background therapy with sacubitril/valsartan while initiating dapagliflozin. In conclusion, sacubitril/valsartan should not be stopped and dapagliflozin should be considered in addition to current care.

3. Would dapagliflozin be used instead of sacubitril valsartan where both are an option? a. Would all people who have sacubitril valsartan be able to have dapagliflozin?	The positioning of dapagliflozin as an alternative to sacubitril/valsartan does not reflect the evidence base nor clinical opinion. The DAPA-HF study assessed the efficacy and safety of dapagliflozin versus placebo as an add-on therapy to individually optimised standard of care. As per the study protocol, standard of care included sacubitril/valsartan. Dapagliflozin and sacubitril/valsartan are thus not mutually exclusive in clinical practice. Sacubitril/valsartan has been recommended (TA388) as a cost-effective treatment option for symptomatic patients with a left ventricular ejection fraction (LVEF) of 35% or less despite treatment with an ACEi or ARB (+BB ±MRA). To date no randomised, head-to-head comparison of dapagliflozin and sacubitril/valsartan has been undertaken and the presented indirect treatment comparisons had several limitations (see response to question 11). As stated above, the DAPA-HF study only provides evidence for the efficacy of dapagliflozin as an add-on treatment versus placebo. Furthermore, no evidence exists for the initiation of sacubitril/valsartan in patients who are already being treated with dapagliflozin. The data do not permit a conclusion on an optimal treatment sequence of sacubitril/valsartan and dapagliflozin. Clinical opinion and several publications, including a recent publication by Vaduganathan et al. (2020), support the combined use of sacubitril/valsartan, BB, MRA and a sodium/glucose cotransporter 2 (SGLT2) inhibitor. Vaduganathan et al. (2020) calls the combined treatments 'a new therapeutic standard', given the expected aggregated benefit in reducing both cardiovascular and all-cause mortality as well as hospitalisations due to heart failure. Clinical expert opinion given for the dapagliflozin appraisal specifically defines sacubitril/valsartan as an 'alternative agent', whilst dapagliflozin was labelled an 'add-on'. The evidence suggests that dapagliflozin should not

	be used instead of sacubitril/valsartan but rather in addition to, if patients are still symptomatic despite optimal standard of care treatment, as investigated in the DAPA-HF trial. a. Although most patients who have sacubitril/valsartan would be able to have dapagliflozin, patients with acute decompensated HF or hospitalisation due to decompensated HF <4 weeks prior to enrolment were excluded from the DAPA-HF trial. There are no data showing if these patients would benefit from dapagliflozin initiation in this setting without an associated increased risk of adverse events. The PIONEER-HF and TRANSITION trials provide evidence for the initiation of sacubitril/valsartan in haemodynamically stable hospitalised or recently hospitalised patients, and these patients currently receive sacubitril/valsartan in clinical practice (Velazquez et al. 2019, Wachter et al. 2019). A position statement published in 2019 by the European Society of Cardiology (ESC) also supports the use of sacubitril/valsartan for haemodynamically stabilised patients hospitalized with new-onset HF or decompensated chronic HF (Seferovic et al. 2019). In comparison, patients who suffer from both HF and type 2 diabetes mellitus may need to discontinue dapagliflozin if admitted to hospital. The dapagliflozin SmPC states that treatment should be interrupted in patients who are hospitalised for major surgical procedures or acute serious medical illnesses, due to the risk of diabetic ketoacidosis.
4. In what proportion of people not responding to ACEi/ARBs, beta-blockers ± MRA would you expect sacubitril valsartan to be unsuitable (population #2)?	The exact proportion of patients who remain symptomatic on an ACEi / ARB but are unsuitable for treatment with sacubitril/valsartan is not known. It is important to note however, that the safety profile of sacubitril/valsartan is similar to an ACEi based on data obtained from the PARADIGM-HF study (McMurray et al. 2014). In the study, patients taking sacubitril/valsartan did not discontinue the study drug significantly more often than those taking enalapril despite an

	increased incidence of hypotension-related events. This suggests that if patients can tolerate an ACEi then it is likely that they will also be able to tolerate sacubitril/valsartan.
5. Have all appropriate comparators been considered in the appraisal?	All comparators defined in the final scope have been considered.
Issue 2: Use in primary care	
6. Should dapagliflozin be initiated by a heart failure specialist? a. If yes, what additional monitoring would be required? b. Is it plausible that GPs could prescribe dapagliflozin in primary care prior to referral to a specialist? c. If no, what additional training or resources would be necessary for primary care clinicians to prescribe dapagliflozin?	Both clinical evidence and expert feedback suggest that dapagliflozin should be initiated by a heart failure specialist. In their professional organisation submission for ID1656, the British Society for Heart Failure (BSH) state that 'Dapagliflozin in heart failure patients without diabetes should be initiated by heart failure specialists. For patient with concomitant diabetes, treatment should be initiated by either a diabetes or heart failure specialist with collaborative working where appropriate to ensure patient safety with complex polypharmacy.' BSH also recommend the education of primary care physicians in the monitoring of such patients. The NICE guidelines (NG106) state that 'if symptoms persist despite first line treatment, seek specialist advice.' In order to achieve the best treatment outcomes for an individual patient, clinicians initiating further therapy in a patient still symptomatic on an ACEi or ARB + BB ± MRA should be able to consider all available treatment options (including other pharmacological treatments and device therapy). Only heart failure specialists with access to a multidisciplinary heart failure team have the full knowledge to do this. a. Heart failure patients can present as highly complex cases. Many have comorbidities and the number of concomitant treatments can be significant. BSH describe the need for collaborative working in the context of polypharmacy. For example, dapagliflozin may add to the diuretic effect

	of thiazide and loop diuretics and may increase the risk of dehydration and hypotension, requiring an adjustment of the diuretic dose in order to reduce the risk of adverse events related to volume depletion, which occurred more frequently with dapagliflozin compared to placebo in the DAPA-HF trial (Docherty et al. 2020). b. While the company submission states that even if dapagliflozin is initiated in primary care, patients could subsequently be referred to a specialist, this may not always happen in clinical practice. Patients initiating dapagliflozin in primary care may then be treated with dapagliflozin on a long-term basis when in fact a heart failure specialist may have provided access to other treatments that the primary care physician had no knowledge of or was not able to prescribe. These alternative treatments may be more suitable for a particular patient. Additionally, where subsequent specialist referral takes place, dapagliflozin may be discontinued by the heart failure specialist after consideration of other therapies. This may add confusion for patients and their carers and predispose to medication errors. For further consideration: Confirmed HFrEF diagnosis occurs in secondary care and many patients remain under the care of HF services. It would not be appropriate for primary care to routinely amend HF treatment while patient is under care of HF services. c. In the consultee comments for NICE TA388, BSH stated that sacubitril/valsartan should be initiated by a heart failure specialist due to the required education relating to the introduction of a new mode of action in the population of interest. This may have contributed to the NICE recommendation that sacubitril/valsartan should be initiated by a heart failure specialist. SGLT2 inhibitors were developed for the treatment of diabetes and, as stated in the NICE final scope of

	ID1656, their mechanism of action in heart failure is not yet fully understood. Applying consistency across the pathway, initiation of dapagliflozin may require a heart failure specialist in order to fully understand the implications of the new mode of action.
7. What percentage of people see a heart specialist after progressing on ARBs / ACEi's in clinical practice in the NHS: i. For people starting MRAs? ii. For people starting specialist treatment? b. Does specialist referral reduce access to second line treatment options? c. What additional costs and resources would be associated with dapagliflozin treatment in specialist care versus primary care? Would there be any costs/resources that would apply to dapagliflozin but not to sacubitril valsartan and vice versa?	Although we are unable to comment on the percentage of people who see a heart specialist after progressing on ARBs / ACEi's in clinical practice, we can provide insight to 7b and 7c. b. As stated in the response to question 6 above, the NICE guidelines recommend that specialist advice be sought for patients with persisting symptoms after first line treatment. Referral to a heart failure specialist with access to a multidisciplinary heart failure team ensures that patients with heart failure receive optimal care. Specialist referral allows for a wider number of treatment options, including device therapy, to be considered. While initiation of dapagliflozin in primary care may accelerate treatment of patients, it may not always be followed by a subsequent specialist referral. Individual patients may then remain on a therapy which a heart failure specialist, in full knowledge of all available options, would not have chosen for them long term. c. No additional costs and resources would be associated with dapagliflozin treatment in specialist care versus primary care. Both points of care would include at least one visit with a heart failure specialist whether that be at point of initiation, or a subsequent referral if dapagliflozin were initiated in primary care.
Issue 3: Generalisability of the DAPA-HF trial	
8. In NHS clinical practice, what percentage of patients would be expected to have HFrEF and	The exact number of patients in NHS clinical practice who have type 1 diabetes mellitus and HFrEF is not known, but type 1 diabetes represents approximately 10% of all diabetes patients

type 1 diabetes mellitus? How would dapagliflozin be used in this population?	(Diabetes UK 2020). A recently published study by Conrad et al. (2018) states that 22% of patients with incident heart failure also have diabetes. If an assumption is made that 10% of those are type 1, then approximately 2.2% of incident heart failure patients would have type 1 diabetes mellitus. Type 1 diabetes patients were excluded from the DAPA-HF study, whilst they were included in the PARADIGM-HF study (McMurray et al. 2014b). These patients can currently receive sacubitril/valsartan if otherwise indicated.
9. What percentage of people with HFrEF have acute decompensated HF?	In response to this question, we would like to clarify the acute decompensated HF patient population: HFrEF is a chronic condition whereby patients will sometimes experience a significant worsening of their symptoms which is defined as acute decompensated HF and often results in a hospital admission (Atherton et al. 2016). As such, chronic HFrEF and acute decompensated HF refer to patient stability and the severity of symptoms in a patient rather than being two distinct populations. Therefore, estimating the exact percentage of HFrEF patients with acute decompensated HF is not possible. The main consideration for use of disease modifying HF therapies is the time of initiation relative to a current or recent hospitalisation for HF due to acute decompensated HF, thus hospitalisations can provide insight to patient stability and the severity of symptoms. A significant proportion of HFrEF patients experience at least one HF hospitalisation during the course of the disease. In the DAPA-HF trial, 47% of patients had a history of HF hospitalisation at baseline. In PARADIGM-HF, the proportion was 63% (McMurray et al. 2019b). Furthermore, it is known that the short-term rates of rehospitalisation and death in patients recently hospitalised for acute decompensated HF are high (Velasquez et al. 2019). This warrants the use of disease modifying therapies in such patients as recommended by clinical guidelines

	(Atherton et al. 2016). As already mentioned in our response to question 3, patients who had acute decompensated HF or had been hospitalised due to decompensated HF <4 weeks prior to enrolment were excluded from the DAPA-HF trial. The results obtained from this study can therefore not be generalised to those patients.
10. How would disease aetiology, clinical management, and baseline risk for heart failure be expected to differ in Europe versus the rest of the world?	Overall, we question the use of a European subgroup data particularly when the interaction effect is not statistically significant in the European subgroup for the primary endpoint, but this was also the case in the sacubitril/valsartan NICE appraisal (TA388), where the appraisal committee concluded that the Western Europe subgroup of the clinical trial population was the most representative of clinical practice in England upon consideration of race, age, cardiac device use, aetiology of chronic heart failure, baseline risk of mortality and clinical management of heart failure. The decision-relevant ERG base case in TA388 thus used population characteristics, effectiveness estimates, utilities and hospitalisation costs of the Western European subgroup analysis. Similar considerations may apply in ID1656, where the ERG prefers the use of data from the European subgroup analysis due to concerns regarding the generalisability of results from the full trial population to clinical practice in England, in terms of age, disease severity and background therapy. Availability of subgroup data by geographic region from the DAPA-HF trial in the public domain is limited, but it should be noted that in a further breakdown of European subgroup data the use of sacubitril/valsartan in the Western European subgroup was 24.5% compared to 2.7% in the Central/Eastern Europe subgroup and 11% in the overall trial population (McMurray et al. 2019b).

Issue 4: Indirect treatment comparison	
11. Can a class effect be assumed for ACE inhibitors?	In NICE TA388, the appraisal committee agreed that a class effect for ACE inhibitors was an appropriate assumption based on a published systematic review and meta-analysis (Chatterjee et al. 2013). While equal efficacy between ACE inhibitors can be assumed, costs may differ between various ACE inhibitors. However, even under the assumption of a class effect for ACE inhibitors, the comparator arms of the DAPA-HF trial (subgroup with any ACEi) and the PARADIGM-HF trial (enalapril) may have differed in a manner which could potentially limit the validity of the indirect comparison. Different doses of ACEi has been linked to different outcomes (Kahn et al. 2017). In PARADIGM-HF, the mean daily dose of patients in the enalapril arm at the final study visit was 18.9 mg, with 67.5% of patients on the target dose of 20 mg at the end of the study (European Medicines Agency, 2015). In the DAPA-HF study, only 32% of patients were on an ACEi / ARB dose considered equivalent to ≥20 mg enalapril (Docherty et al. 2020). Evidence on the mean daily dose of ACEi in the DAPA-HF study could not be identified. If the mean ACEi dose in the DAPA-HF comparator arm was lower than in the PARADIGM-HF comparator arm, an indirect comparison not accounting for this difference may overestimate the treatment effect of dapagliflozin versus sacubitril/valsartan due to a 'weaker' comparator arm in the DAPA-HF trial. It should also be noted that the indirect treatment comparison did not produce statistically significant results.
12. Can equivalence be assumed for ACEi and ARBs?	In TA388, an NMA was presented in the absence of head to head trial data for sacubitril/valsartan versus ARBs. While the ERG and the appraisal committee concluded that the NMA showed ACEi and ARBs to have broadly similar efficacy, the committee's decision regarding cost-effectiveness

	of sacubitril/valsartan compared to ARBs was based on an economic analysis using effect estimates from the NMA rather than assuming equivalence for ACEi and ARBs.
Issue 5: Use of KCCQ-TSS quartiles in the model	
13. Should the following domains be included in the measurement of HFrEF disease severity? a. physical limitations b. quality of life c. social inference	All relevant domains should be included to fully capture the severity of heart failure. As detailed by the ERG, KCCQ has six different domains and three different summary scores can be generated: Total symptom score (comprising the domains of Symptom burden and Symptom stability), Clinical summary score (which includes the Physical limitations domain as well as Symptoms) and Overall summary score (which includes Social limitations and Quality of Life domains in addition to the Symptom and Physical limitation domains). Physical limitations, social limitations and quality of life are important and integral domains of the KCCQ (Greene 2000). Clinical and Overall Summary Scores are sensitive to changes in disease status and to treatment and are correlated with outcomes such as Heart failure hospitalisations (Greene 2000, Heidenreich 2006, Spertus 2005). Recent analyses mapping between KCCQ and EQ-5D found that Physical limitations, Social limitations and Quality of Life domains were significant variables in mapping to EQ-5D score (Hunger et al. 2020, accepted manuscript to be published in MDM Policy & Practice. Accepted 15 September 2020). Thus, limiting to the TSS which only captures symptom status to define health status will not fully capture disease severity.
Issue 6: Survival extrapolation	
14. Which long-term survival estimates would most accurately reflect what is expected in clinical practice in the NHS?	For base case #1 and #2, survival estimates using the Weibull function appear broadly consistent with those in TA388 derived from PARADIGM-HF, and are also in line with a recent publication by Taylor et al. (2019) evaluating UK survival trends following heart failure diagnosis over time,

whereas estimates derived using the Gompertz function appear notably lower, especially at later timepoints.

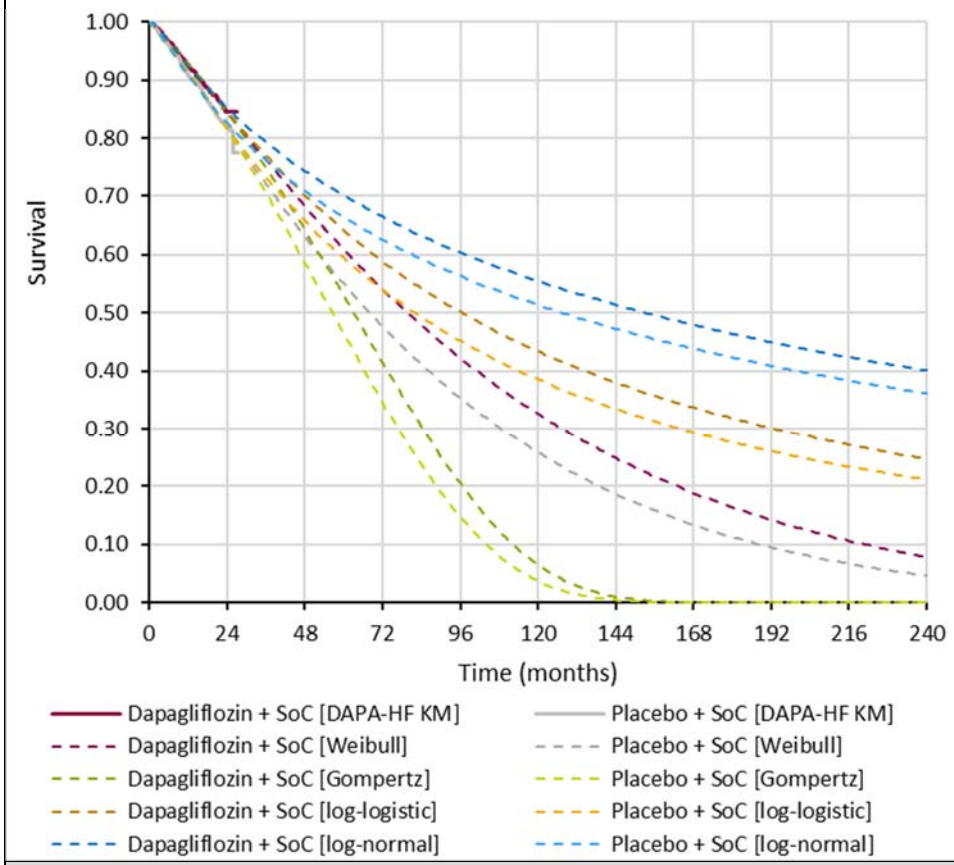
In addition, it is not clear what drives the difference in survival estimates for base case #3 compared to base case #1 and #2 – according to the documentation, survival functions were derived from the overall DAPA-HF trial, with the only difference being that baseline characteristics were taken from the subgroup of patients receiving sacubitril/valsartan in DAPA-HF. However, this results in quite a marked difference in the survival rates shown in the Table, particularly at later timepoints. These results are not consistent with the survival benefit of sacubitril/valsartan demonstrated in the PARADIGM-HF trial (McMurray et al. 2014). Although there may have been differences in patient characteristics between the DAPA-HF patients used for base case #1 and #3, this may not accurately depict the patient characteristics of these populations in clinical practice. The lower survival rates for base case #3 are questionable.

Months		**0**	**12**	**24**	**36**	**60**	**120**	**180**	**240**
Base case #1, people on ACEi or ARB, beta-blocker, ±MRA for whom sacubitril valsartan is suitable									
Weibull	**Dapagliflozin**	100.0%	92.8%	84.5%	76.2%	60.9%	32.60%	16.4%	7.9%
	Standard Care	100.0%	91.4%	81.6%	72.1%	55.0%	25.9%	11.3%	4.7%
Gompertz	**Dapagliflozin**	100.0%	92.8%	84.4%	74.9%	53.0%	6.6%	0.0%	0.0%
	Standard Care	100.0%	91.4%	81.5%	70.6%	46.5%	3.7%	0.0%	0.0%
Base case #2, people on ACEi or ARB, beta-blocker, ±MRA for whom sacubitril valsartan is unsuitable									
Weibull	**Dapagliflozin**	100.0%	92.7%	84.4%	76.2%	61.10%	33.20%	17.1%	8.5%
	Standard Care	100.0%	91.3%	81.6%	72.2%	55.5%	26.8%	12.1%	5.2%
Gompertz	**Dapagliflozin**	100.0%	92.6%	84.3%	74.9%	54.0%	8.9%	0.0%	0.0%
	Standard Care	100.0%	91.3%	81.6%	71.0%	48.2%	5.6%	0.0%	0.0%
Base case #3, people on sacubitril valsartan, beta-blocker, ±MRA									
Weibull	**Dapagliflozin**	100.0%	94.9%	86.2%	76.1%	55.6%	19.1%	4.8%	0.9%

	Standard Care	100.0%	92.8%	81.1%	68.0%	43.7%	9.6%	1.4%	0.1%
Gompertz	**Dapagliflozin**	100.0%	94.8%	85.9%	71.5%	26.7%	0.0%	0.0%	0.0%
	Standard Care	100.0%	92.8%	80.8%	62.3%	15.6%	0.0%	0.0%	0.0%

15. Based on the company's goodness of fit criteria estimates (AIC/BIC) the log-logistic and log-normal curves could be a suitable fit to the data but predict more optimistic extrapolations that the Weibull (as shown in the graph below). Would you expect improved survival in clinical practice compared to what is estimated using the Weibull extrapolation curve (see table from question 14)?	Of note, it is not clear how the extrapolations presented in the Figure relate to the base cases. We have interpreted the below as the DAPA-HF trial population therefore, as stated in the response to question 14 above, the survival estimates using the Weibull extrapolation curve seem broadly aligned with previously published estimates for HFrEF patients (Taylor et al. 2019).

Company's alternative all-cause mortality survival curves (scenario analyses) (CS p109)



Issue 7: Treatment waning effect	
16. **NHS England:** Would a stopping rule apply for dapagliflozin in the NHS?	There does not appear to be any evidence available to support a stopping rule for dapagliflozin.

17. Would treatment effect be expected to continue after stopping dapagliflozin? a. If yes, how long after stopping treatment would this effect last? b. Is this observed in patients having sacubitril valsartan?	We are not currently aware of any evidence regarding whether a continued treatment effect could be expected after stopping dapagliflozin or sacubitril/valsartan in HFrEF patients.

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in collaboration with:

ERASMUS UNIVERSITEIT ROTTERDAM
INSTITUTE OF HEALTH POLICY & MANAGEMENT

Maastricht University

Dapagliflozin for treating heart failure with reduced ejection fraction

Comment on response to technical engagement

Produced by Kleijnen Systematic Reviews (KSR) Ltd. in collaboration with Erasmus University Rotterdam (EUR) and Maastricht University

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Date completed 26/10/2020, modified 30/10/2020 (following PMB)

Use of dapagliflozin in the clinical pathway for treating patients with heart failure and initiation of treatment

The Evidence Review Group (ERG) noticed several stakeholder comments received during technical engagement (TE).

The ERG noted comments by Klaus Witte of the University of Leeds as well by the British Society for Heart Failure (BSHF) highlighting the need for further clarification on how "treatment response" should be assessed.

While Klaus Witter described the positioning proposed by the company as "reasonable", other stakeholder were more critical of the proposed treatment pathway. For example, the Pumping Marvellous Foundation wondered whether one treatment option has been missed while the statement by the South Asian Health Foundation described the algorithm as *"unnecessarily confusing"*. One competitor company, Novartis, highlighted that *"the company's positioning of dapagliflozin, particularly as a replacement therapy for sacubitril/valsartan in population #1, is not aligned to the pivotal trial evidence from DAPA-HF. The clinical evidence supports dapagliflozin as an add-on therapy to standard of care (SOC), as reflected in the NICE scope"*.

Several stakeholders, including Klaus Witte, the BSHF and Cardiomyopathy UK, stated that it might be possible to prescribe dapagliflozin for treatment of heart failure (HF) in primary care. The British Cardiovascular Society (BCS) appeared to agree by stating that *"whilst it does seem reasonable to require initiation to be done by a heart failure specialist, this may not involve hospital doctors"*.

While the comments made in the ERG report, see e.g. sections 3.2 and 7.4 still stand, the comments by the stakeholders should be considered by the committee.

The use of KCCQ-TSS quartiles to inform the model structure

In its report, the ERG commented on the use of the Kansas City Cardiomyopathy Questionnaire (KCCQ) Total Symptom Score (TSS) rather than the KCCQ quality of life domain (KCCQ-QoL), the KCCQ clinical summary score (KCCQ-CSS) or the overall summary score (KCCQ-OSS) to characterise/ define the health states. Mainly highlighting the company's justification (provided in the company submission and in response to question B1 of the request for clarification) is limited. Therefore, it was unclear to the ERG whether other metrics than the KCCQ-TSS are preferred and what the impact of using alternative metrics would be.

In section 2 of the company's response to TE, New York Heart Association (NYHA) class was considered as an alternative metric. Although NYHA class was not suggested by the ERG as an alternative (given the poor inter-rater concordance and poor reproducibility), the ERG agrees with the justification provided by the company and believes it is reasonable to prefer the KCCQ above NYHA to inform the model structure.

In section 5e of the company's response, the company is requested to provide scenario analyses that use KCCQ-CSS/ KCCQ-OSS as alternative metrics. Unfortunately, the company does not provide these scenario analyses, hence the impact of using an alternative approach based on KCCQ-QoL/ KCCQ-CSS/ KCCQ-OSS remains uncertain. However, the company now more clearly justifies the use of KCCQ-TSS rather than KCCQ-CSS/ KCCQ-OSS and this seems reasonable. The company illustrated the overlap between the summary scores (see Figure 7 in the company response to TE), summarized discussions with the FDA and stated that analyses of clinically meaningful improvements/ deterioration show the results to be highly consistent across KCCQ-TSS, KCCQ-CSS and KCCQ-OSS. Therefore, according to the company, cost-effectiveness results from models based on these metrics are not

expected to substantially differ. The ERG does not fully agree with this latter statement as 1) the required scenario analyses are not provided and 2) the evidence provided to support the consistent findings across the metrics is very limited (e.g. the win ratios in Table 12 of the company response do not provide information on the magnitude of effect). However, the ERG believes that, given the additional justification provided by the company, the use of the KCCQ-TSS to inform the model structure is a reasonable approach. It is however worth mentioning that the KCCQ-TSS is limited to HF symptom burden and frequency while KCCQ-CSS and KCCQ-OSS also capture other domains that might be considered relevant such as physical limitations, social limitations and/ or quality of life. This underscores the relevance of the requested scenario analyses that are unfortunately not provided.

Use in patients with acute decompensated heart failure and discontinuation due to lack of efficacy

The ERG has no specific comments regarding the response by the company to issues #3 and #4 of the TE response.

ITC analyses based on European subgroup

In order to comply with the request from the National Institute for Health and Care Excellence (NICE) Technical Team, an indirect treatment comparison (ITC, Bucher method) of the Europe subgroup from DAPA-HF versus the Western Europe subgroup from PARADIGM-HF was conducted (see section 5c1 of the company's response to TE). However, the company lists several reasons why an ITC is not appropriate.

Section 4.2.1 of the ERG report discussed the rationale for highlighting differences regarding both efficacy as well as safety in the European subgroup compared to the overall trial population. However, the ERG acknowledges the concerns voiced by the company regarding an ITC (Europe subgroup from DAPA-HF versus the Western Europe subgroup from PARADIGM-HF), e.g. greater uncertainty due to smaller number of participants and differences of countries covered in DAPA-HF and PARADIGM-HF, respectively.

In addition, it should be noted that neither trial stratified the randomisation by region. Therefore, using these subgroup results mean that the balance from the randomisation is being lost, which is an assumption of the ITC. Having said that, any results from these ITCs should be interpreted with some degree of caution and the results presented in Table 4 of the company's response to TE could be included in the PMB slides for illustration when discussing this issue as these might be of some use.

Pooled Europe and North America analyses)

These analyses were not requested by the ERG. In the request for clarification (question A17), the ERG asked the company to provide results of efficacy and safety outcomes for the DAPA-HF trial by geographic region which included Europe. For the reasons outlined in the ERG comment on section 4.2.1 of the ERG report (see page 38), the ERG decided to present the results of the European subgroup alongside the whole study population in the clinical effectiveness section of the report. Similarly, the ERG adopted the relative effectiveness as estimated based on the European subgroup in the cost effectiveness section (see section 7.1.3 of the ERG report).

Overall, the ERG values validity higher than (im)precision. Having said that, the ERG prefers an estimate for the "right" population/ intervention/ comparator/ outcome with a smaller sample size to the other way around, i.e. higher sample size but slightly different population/ intervention/ comparator/ outcome. Therefore, there seems to be no clear advantage in combining patients from only North America with those from Europe, i.e. either the whole intention-to-treat (ITT) population should be

preferred on the basis of precision or the European subgroup should be used on the basis of applicability to the UK. The ERG still believes the European subgroup to be more relevant to this submission.

Estimated cost-effectiveness

The ERG successfully reproduced the results provided in Table 15 of the TE responses provided by the company. Moreover, the ERG has submitted (in a separate document), the revised company submission (CS) base-case results (both deterministic as well as probabilistic) incorporating the confidential CMU price for sacubitril valsartan.