NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Sacubitril valsartan for treating heart failure with systolic dysfunction

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Sacubitril valsartan for treating heart failure with systolic dysfunction [ID822]

Contents:

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

Premeeting briefing

Sacubitril valsartan for treating heart failure with systolic dysfunction

This premeeting briefing presents:

- the key evidence and views submitted by the company, the consultees and their nominated clinical experts and patient experts and
- the Evidence Review Group (ERG) report.

It highlights key issues for discussion at the first Appraisal Committee meeting and should be read with the full supporting documents for this appraisal.

Please note that this document includes information from the ERG before the company has checked the ERG report for factual inaccuracies.

Key issues for consideration

Company's decision problem

- The company considers sacubitril valsartan to be most appropriately positioned as a new first-line treatment option. The ERG considers the evidence supports positioning as a second-line treatment option for patients who are symptomatic and who are receiving angiotensin converting enzyme (ACE) inhibitor drug therapy. At what point in the treatment pathway is sacubitril valsartan likely to be offered in England?

Clinical effectiveness issues

- The ERG had concerns regarding the generalisability of the results of the PARADIGM-HF trial to clinical practice in England:

  - The ERG noted differences in age and the proportion of women.
  - Based on the observation in the trial that younger patients had higher mortality than slightly older patients in the trial, the ERG suggested patients in the trial might also include slightly 'different' patients who present with heart problems from a young age.
  - The ERG considered the Western Europe population to be most representative of the UK, and noted that there was a non-statistically significant difference in the Western Europe subgroup for the primary composite outcome, as well both cardiovascular- and all-cause mortality.
  - The ERG considered patients in the trial had a higher tolerability to valsartan than would be expected in clinical practice.
  - The ERG stated that device use in the trial was lower than would be expected in clinical practice.

  How generalisable are the results from the PARADIGM-HF trial to clinical practice in England?

- The ERG concluded that based on the totality of evidence, there is little evidence to support the use of sacubitril valsartan as a first line treatment in newly diagnosed patients:
  - In the PARADIGM-HF trial approximately 78% and 23% of patients had received ACE inhibitors or angiotensin II receptor blocker (ARB) treatment, respectively, before randomisation.
  - Additionally 70% of patients had been diagnosed for over 1 year at baseline and 31% had been diagnosed more than 5 years ago.

Is there sufficient evidence to robustly suggest that sacubitril valsartan is more efficacious and tolerable compared with enalapril (an ACE inhibitor) in the proposed first-line population?

- The ERG regarded the results of the network meta-analysis conducted by the company to compare sacubitril valsartan with an ARB to be uncertain and potentially unreliable based on the heterogeneity in the trials underpinning the network. How robust are the results from the network meta-analysis?

Cost effectiveness issues

- The ERG considers that a first-line ICER for sacubitril valsartan compared with enalapril cannot be plausibly estimated from the PARADIGM-HF trial:
  - The PARADIGM-HF trial population does not reflect a newly diagnosed heart failure population (see clinical effectiveness key issues).
  - The results of the PARADIGM-HF trial are not generalisable to clinical practice in England (see clinical effectiveness key issues).
  - The mortality in the trial (and in the model) portrays a scenario representative of the use of sacubitril valsartan for established patients. Less than 10% of patients in the trial had died by the end of year 1 and only 20% were dead in both treatment arms by the end of the second year. When compared to the NICE clinical guideline 108 prognosis that 30% to 40% of patients diagnosed with heart failure die within a year, the observed mortality in the trial is substantially different (less than half).
  - Given that the PARADIGM-HF trial's patients are symptomatic, despite having been treated with ARBs and ACE inhibitors, the impact of continuing these patients on ACE inhibitors is likely to be a misrepresentation compared to what would happen in treatment-naïve patients.

Can a first-line ICER for sacubitril valsartan compared with enalapril be plausibly estimated from the company's economic model?

- In exploratory analyses the ERG presented a 'second line ICER' which differed from the company base case as follows:
  - Error corrected in the half-cycle adjustment in estimation of utility values.
  - Use of a cardiovascular mortality approach (versus all-cause mortality).
  - Use of a mean cohort model approach (versus the patient-level model).
  - Mean starting age of 75 years (versus mean age in trial of 64 years).
  - Baseline utility value taken from Berg et al. of 0.72 (versus 0.78 from trial).
  - The cost of ramipril (versus enalapril).
  - Adjusted drug costs to reflect target doses consistently.
  - The effectiveness outcomes, costs, QALYs and population characteristics of the Western European subgroup analysis (versus the whole trial).

  - Simplified quality of life modelling approach where the impact of sacubitril valsartan on patients' quality of life was linked to the incidence of adverse events, hospitalisation events and disease progression (versus quality of life regression model).

Are the amendments made by the ERG appropriate for obtaining its second-line ICER?

- The ERG commented that there was a high degree of uncertainty associated with its 'second-line ICER' because of:
  - Generalisability issues (see clinical effectiveness key issues).
  - Evidence of a non-statistically-significant treatment effect in older groups.
  - The inflexibility of the model to truly reflect an older population.
  - The fact that, other than parametric models, different options for modelling mortality such as spline models were not explored.
  - The fact that patients' baseline characteristics were not included in the probabilistic sensitivity analysis and varied stochastically.

What is the potential impact of each of these issues on the robustness of the ICER?

- What are the most plausible ICER estimates for the comparison of sacubitril valsartan with ACE inhibitors and with ARBs?

1 Remit and decision problems

1.1 The remit from the Department of Health for this appraisal was: to appraise the clinical and cost effectiveness of sacubitril valsartan within its marketing authorisation for treating heart failure (NYHA stage II-IV) with systolic dysfunction.

Table 1 Decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Comments from the company	Comments from the ERG
Population	People with chronic heart failure (New York Heart Association [NYHA] class II-IV) with systolic dysfunction.	People with symptomatic heart failure (NYHA II-IV) with reduced left ventricular ejection fraction, referred to as patients with heart failure with reduced ejection fraction.	Population in submission is aligned with the patients studied in the PARADIGM-HF trial.	The population in PARADIGM-HF is relevant to the decision problem. However, the population was younger than those in UK clinical practice.
Intervention	Sacubitril valsartan in combination with standard care (including treatment with a beta blocker and an aldosterone antagonist)		Same as NICE scope	No comments
Comparator(s)	ACE inhibitors in combination with standard care Angiotensin II receptor blocker (ARB) in combination with standard care (for people in whom an ACE inhibitor is unsuitable) Standard care includes treatment with a beta blocker and an aldosterone antagonist		Same as NICE scope	Enalapril is reasonably analogous to the management of CHF in UK clinical practice, and was as specified in the final scope issued by NICE. However, clinical expert advice to the ERG highlighted that enalapril is not the most commonly prescribed ACE inhibitor in the UK.
Outcomes	• Symptoms of heart failure • Hospitalisation for heart failure • All-cause hospitalisation • Mortality • Cardiovascular mortality • Adverse effects of treatment • Health-related quality of life		Same as NICE scope	All clinically relevant outcomes in the final scope issued by NICE were reported in the company submission

Proposed positioning of sacubitril valsartan in clinical practice

1.2 Sacubitril valsartan in combination with standard care (including beta blockers and aldosterone antagonists) is positioned in the company submission as a replacement of current first-line treatment ACE inhibitors in combination with standard care). The company stated that this was based on the "overwhelming clinical benefit sacubitril valsartan demonstrated" compared with enalapril at a dose shown to reduce mortality in the PARADIGM-HF trial. The company further justified this proposed change in the first-line management of people with chronic heart failure because it stated it is a disease area with a high mortality rate and patients require frequent hospitalisations.

ERG comments

1.3 The ERG discussed the company's anticipated positioning of sacubitril valsartan as a first-line treatment option. It stated that the PARADIGM-HF trial population did not reflect a newly diagnosed population. Clinical opinion sought by the ERG indicated that based on the trial design, population and outcomes, the evidence supported positioning as a second-line treatment option for patients who are still symptomatic despite being on an ACE inhibitor drug therapy (see table 3 and sections 4.6, and 4.19) .

2 The technology and the treatment pathway

2.1 Sacubitril valsartan is an angiotensin receptor neprilysin inhibitor. It includes the neprilysin inhibitor, sacubitril (AHU377) and the angiotensin II receptor blocker (ARB), valsartan. Both sacubutril and valsartan lower blood pressure. It is administered orally. The recommended starting dose is 100 mg twice daily (or 50 mg twice daily for patients not currently taking an ACE inhibitor or an ARB, or on low doses of these agents). The dose is to be doubled every 2 to 4 weeks to the target of 200 mg twice daily, as tolerated by the patient.

2.2 NICE clinical guideline 108 ('Chronic heart failure') recommends that all patients with chronic heart failure because of left ventricular systolic dysfunction should be offered beta-blockers and an ACE inhibitor unless contraindicated or not tolerated. ARBs are alternatively recommended for use in people in whom ACE inhibitors are unsuitable. In clinical practice, an aldosterone antagonist is usually administered alongside the other treatments.

Table 2 Technology

	Sacubitril valsartan	**ACE inihibitor**	**Angiotensin receptor blocker (ARB)**
Marketing authorisation	CHMP positive opinion for 'the treatment of symptomatic chronic heart failure with reduced ejection fraction'.	Enalapril (ACE inhibitor used in PARADIGM-HF): • Treatment of symptomatic heart failure • Prevention of symptomatic heart failure in patients with asymptomatic left ventricular dysfunction (ejection fraction ≤35%)	General indication of ARBs (wording of marketing authorisations differ slightly between ACE inhibitors): • Heart failure when ACE inhibitors cannot be used, or in conjunction with an ACE inhibitor when a beta-blocker cannot be used.
Administration method	Oral	Oral	Oral
Average cost per month (Prices estimated in company's model)	• £99.53 List price: 50 mg, 28 pack: £45,78 100 mg, 28 pack: £45.78 100 mg, 56 pack: £91.56 200 mg, 56 pack: £91.56	• Enalapril: £2.10 • Ramipril: £2.70 • Perindopril: £1.58 • Lisinopril: £3.37	• Losartan: £2.97 • Candesartan: £2.39 • Valsartan: £40.03

See summary of product characteristics for details on adverse reactions and contraindications.

3 Comments from consultees

3.1 The following statements were received from 2 clinical experts and by the British Society for Heart Failure (BSHF):

- Chronic heart failure is treated according to standard guidelines across the UK (NICE guidance, and guideline from the European Society of Cardiology [ESC]).
- There is no significant geographical variation in practice due to well established national and international guidelines for heart failure and an exceptionally strong evidence base around standard therapy.
- There were “striking advantages of sacubitril valsartan over current standard medical care in terms of survival, hospitalisations and quality of life” demonstrated in PARADIGM-HF.
- Sacubitril valsartan was effective across all pre-specified sub-groups and although less impressive in older patients (due to increased comorbidities) or in those with NYHA class 3+, it is important that older patients are not denied access to new therapies, and the cut offs for NYHA class are arbitrary and unreliable.
- The relative risk reduction from sacubitril valsartan is of similar magnitude irrespective of baseline risk; if available in clinical practice, it should be considered in all patients with heart failure and reduced ejection fraction.
- ACE inhibition is often limited by renal impairment: the observation in PARADIGM-HF of better renal tolerability of sacubitril valsartan compared with enalapril is welcome.
- As with all heart failure trials, patients enrolled were younger (mean age 64), more likely to be male (78%) and on higher levels of background medication than that of the UK population.
- Once randomised to sacubitril valsartan or enalapril, the side effect profiles were similar.

- Given patients were taking ACE-inhibitors or ARBs at entry to the PARADIGM-HF study, safety information is lacking regarding the introduction of sacubitril valsartan in ACE-naïve patients.
- Despite pre-treatment with enalapril 10 mg twice daily, a further >600 patients (of around 9000 reaching this stage of the trial) had an adverse event or abnormal blood result during the 4 week run-in phase of sacubitril valsartan. The introduction phase of sacubitril valsartan will therefore require very clear guidance to practitioners.
- There were higher rates of angio-oedema in those of African descent exposed to ACE-inhibitors, and extra vigilance would be required because of the low numbers of this cohort included in the trial (5%).

The clinical experts responded differently regarding the expected resource change if sacubitril valsartan becomes the standard of care:

- One clinical expert stated there would be no increased resource will be needed.
- Another clinical expert stated a wholescale switch of heart failure patients from ACE inhibitors to sacubitril valsartan would require a huge resource in heart failure nurse specialist, GP and heart failure consultant time. Even introduction in new heart failure patients would require extra work if the patient needs to be established on ACE-inhibitors before switching to sacubitril valsartan. It would not be feasible to switch the entire UK left ventricular systolic dysfunction (LVSD) heart failure population from ACE-inhibitors to sacubitril valsartan in a 3 month time interval. Provided guidance is explicit the additional training requirement is not great.
- Due to its mode of action, sacubitril valsartan leads to increased plasma levels of B-type natriuretic peptide (BNP), which is paradoxical, in that “high” BNP levels are classically considered undesirable. BSHF stated that consideration may therefore have to be given to provision of N-terminal pro-BNP (NT-proBNP) rather than BNP in clinical services.

BSHF also stated that education will be required in the mode of action of this technology and the need to avoid co-prescription of ACE inhibitors.

3.2 Two patient experts both stated that the treatment gives patients hope because the current gold standard therapies have not changed for years. They stated that a new treatment option is welcome as it will generate optimism and may also enable patients to validate that there is a reason to be positive and develop their self-management skills around heart failure which would lead to better outcomes.

4 Clinical-effectiveness evidence

Overview of the clinical trials

PARADIGM-HF

4.1 PARADIGM-HF was a randomised double-blind controlled phase 3 trial comparing sacubitril valsartan (n=4187) with enalapril (n=4212), both treatment arms in combination with standard care (including beta blockers and aldosterone antagonists). The trial included people with symptomatic heart failure (NYHA II-IV) with reduced left ventricular ejection fraction (LVEF). Enalapril was chosen as a comparator because it is the ACE inhibitor that has been studied in the largest number of trials in this population.

4.2 The trial comprised 4 phases:

1) Screening (for inclusion and exclusion criteria).

2) Enalapril run-in phase: 2 weeks duration. Eligible patients were switched from current medication (that is, ACE inhibitors or ARB) to single-blind treatment with enalapril (10 mg twice daily).

3) Sacubitril valsartan run-in phase: 4 to 6 weeks duration. Patients were eligibile if they had no unacceptable side effects in the enalapril runin phase. Eligible patients were switched to single-blind

treatment with sacubitril valsartan at a dose of 100 mg twice daily, which was increased to 200 mg twice daily. The 2 run-in phases were sequential, with only a brief (approximately 36 hours) washout phase, and both included all eligible patients. The run-in phases ensured an acceptable safety profile of the study drugs at target doses.

4) Patients who had no unacceptable side effects on the target doses of the 2 study medications in the run-in phases were randomly assigned in a 1:1 ratio to double-blinded treatment with either sacubitril valsartan (200 mg twice daily) or enalapril.

4.3 People in the trial had NYHA functional class II to V. Some people had an improvement in their NYHA class between screening and randomisation, so nearly 5% of randomised patients were NYHA class I. The LVEF entry criterion was initially 40% or lower but was subsequently reduced to 35% or lower (961 patients were randomised had LVEF greater than 35%). Mildly elevated B-type natriuretic peptide (BNP) or N-terminal pro-BNP was also required as an inclusion criterion.

4.4 Patient charcteristics at baseline are summarised in Table 3. There were no significant differences between groups regarding baseline patient characteristics. There were some differences between the study population and the general population seen in clinical practice in England, for example, patients in the trial were younger (49% were ≥65 years) and more likely to be men (22% were women). Standard care and background therapies were reported by the company as comparable to clinical practice in England, with 93% in the trial at baseline receiving beta blockers and 56% at baseline receiving aldosterone antagonists.

Table 3: Characteristics of participants in PARADIGM HF across randomised groups (adapted from Table 13 page 54 of company submission)

		Sacubitril valsartan (n=4,187)	Enalapril (n=4,212)
Age	Mean ± SD	63.8 ±11.5	63.8±11.3

	Range years	18.96	21.96
	<65 years, n (%)	2011 (50.4)	2168 (51.5)
	≥65 years, n (%)	2076 (49.6)	2044 (48.5)
Female, n (%)		879 (21.0)	953 (22.6)
Region	North America	310 (7.4)	292 (6.9)
	Latin America	713 (17.0)	720 (17.1)
	Western Europe* , South Africa, Israel	1,026 (24.5)	1,025 (24.3)
	Central Europe	1,393 (33.3)	1,433 (34.0)
	Asia –Pacific	745 (17.8)	742 (17.6)
NYHA class, n (%)	I	180 (4.3)	209 (5.0)
	II	2,998 (71.6)	2,921 (69.3)
	III	969 (23.1)	1,049 (24.9)
	IV	33 (0.8)	27 (0.6)
	Missing data	7 (0.2)	6 (0.1)
Treatments at randomisation (standard care/background therapies), n (%)	Diuretic	3,363 (80.3)	3,375 (80.1)
	Digitalis	1,223 (29.2)	1,316 (31.2)
	BB	3,899 (93.1)	3,912 (92.9)
	AA	2,271 (54.2)	2,400 (57.0)
Medical history, n (%)	Hypertension	2,969 (70.9)	2,971 (70.5)
	Diabetes	1,451 (34.7)	1,456 (34.6)
	AF	1,517 (36.2)	1,574 (37.4)
	Hospitalisation for HF	2,607 (62.3)	2,667 (63.3)
	MI	1,818 (43.4)	1,816 (43.1)
	Stroke	355 (8.5)	370 (8.8)
	Pre-trial use of ACEi	3,266 (78.0)	3,266 (77.5
	Pre-trial use of ARB	929 (22.2)	963 (22.9)

*A total of 242 patients of the 8442 patients randomised were from England.

AA, aldosterone antagonists; ACEi, angiotensin converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin II receptor blocker; BB, beta blocker; HF, heart failure; MI, myocardial infarction; NYHA, New York Heart Association; SD, standard deviation.

ERG comments

4.5 The ERG noted that the PARADIGM-HF trial recruited a large number of patients with chronic heart failure (n=8442) worldwide. The ERG commented that the trial was well conducted. It further commented that the majority of trial participants were taking beta blockers as concomitant therapies, which reflected UK clinical practice.

4.6 The ERG had concerns about whether the population recruited to the PARADIGM-HF trial represents patients with heart failure seen in clinical practice in the UK.

- The ERG noted that the population from the trial had a mean age of 63.8 years and that 32% of patients were below 55 years. It stated that in routine clinical practice average age would be much higher, at between 76 years (men) and 80 years (women). The ERG also noted that the trial included a lower proportion of women (about 22%). The ERG was advised by its clinical experts that these patient characteristics were associated with improved outcomes, although it also noted that this effect would be observed across both treatment arms of the trial.
- The ERG was advised by its clinical experts that a proportion of patients with severe heart failure in the UK would have been fitted with cardiac devices. Although no information was presented on clinical effectiveness in the subgroup of people fitted with a cardiac device in the company submission, the ERG noted that data were presented in the clinical study report (CSR) to show around [redacted] of the trial population used devices.

4.7 The ERG had concerns about the dose of valsartan in combination with sacubitril used in the PARADIGM-HF trial and the comparison with enalapril as it was of the opinion that neither represented UK clinical practice.

- The ERG was advised by its clinical experts that the dose of valsartan in combination with sacubitril in the trial was higher than that typically prescribed in UK clinical practice. The ERG noted that the target dose of sacubitril valsartan was 200 mg twice daily, of which 103 mg is valsartan, which is equivalent to a 160 mg dose of valsartan given alone. The ERG noted that this dose is, according to the summary of product characteristics, the maximum dose allowed in clinical trials for valsartan monotherapy. According to clinical expert opinion provided to

the ERG it is uncommon for patients to tolerate such high doses of valsartan in UK clinical practice. The ERG noted several factors that were likely to have contributed to the increased tolerability of valsartan in the trial:

- Around 78% of patients were receiving ACE inhibitors at baseline.
- Around 23% of patients were receiving ARBs at baseline.
- Around 70% of trial patients had been diagnosed with heart failure for over 1 year.
- The minimum tolerability inclusion criterion in the PARADIGM-HF protocol defined a minimum tolerable dose of valsartan (160 mg daily) which appears to be higher than the average dose tolerated by patients in UK clinical practice.
- The minimum tolerability inclusion criterion in the PARADIGM-HF protocol defined a minimum tolerable dose of enalapril (10 mg daily) which appears to be lower than the average dose tolerated by patients in UK clinical practice.
- Patients in the trial did not have any serious co-morbidities and death was included as a reason for discontinuation in both the trial and the Clinical Practice Research Datalink (CPRD) data analysis.

- The ERG stated that the higher dose of valsartan tolerated by patients in the trial had an impact on the observed discontinuation of study drugs, which it suggested was likely to be higher in UK clinical practice than it was in the trial.
- The company stated that enalapril was chosen because it is the ACE inhibitor that has been studied in the largest number of trials of patients with heart failure and it has a well-documented mortality benefit. However the ERG's clinical experts advised that, in the UK, the standard ACE inhibitor is ramipril. Therefore, comparing sacubitril valsartan with enalapril does not reflect UK clinical practice.

TITRATION

4.8 TITRATION was a randomised, double-blind, parallel group study investigating the safety and tolerability of initiating and up-titrating

sacubitril valsartan from 50 mg twice daily to 200 mg twice daily over 3-weeks compared with over 6-weeks in 498 patients with heart failure with reduced ejection fraction. The majority of patients were receiving varying ACE inhibitor/ARB doses prior to entering the study, although 33 patients (6.6%) enrolled were treatment naïve to ACE inhibitors/ARBs. For further details of the trial methodology and baseline patient characteristics, see pages 101 to 109 of the company's submission).

Clinical trial results

Primary and secondary endpoints of PARADIGM-HF

4.9 Results were presented based on the full analysis set (FAS) which consisted of all patients except those who did not meet the eligibility criteria or did not receive a single dose of the study drug and these data were used for the efficacy outcomes (8,399 patients; 4,187 in the sacubitril group and 4,212 in the enalapril group).The primary endpoint was a composite of death from cadiovascular causes or a first hospitalisation for heart failure, assessed at every study visit (0 weeks, 2, 4, and 8 weeks, 4 months, and then every 4 months). The composite primary endpoint statistically significantly favoured sacubirtril valsartan compared with enalapril (hazard ratio [HR] 0.80; 95% confidence interval [CI] 0.73 to 0.87; p<0.001); (see Figure 1 and Table 4).

Figure 1: Kaplan-Meier curve for the primary composite outcome of death from CV causes or first hospitalisation for worsening heart failure (figure 5, page 58 of the company submission)

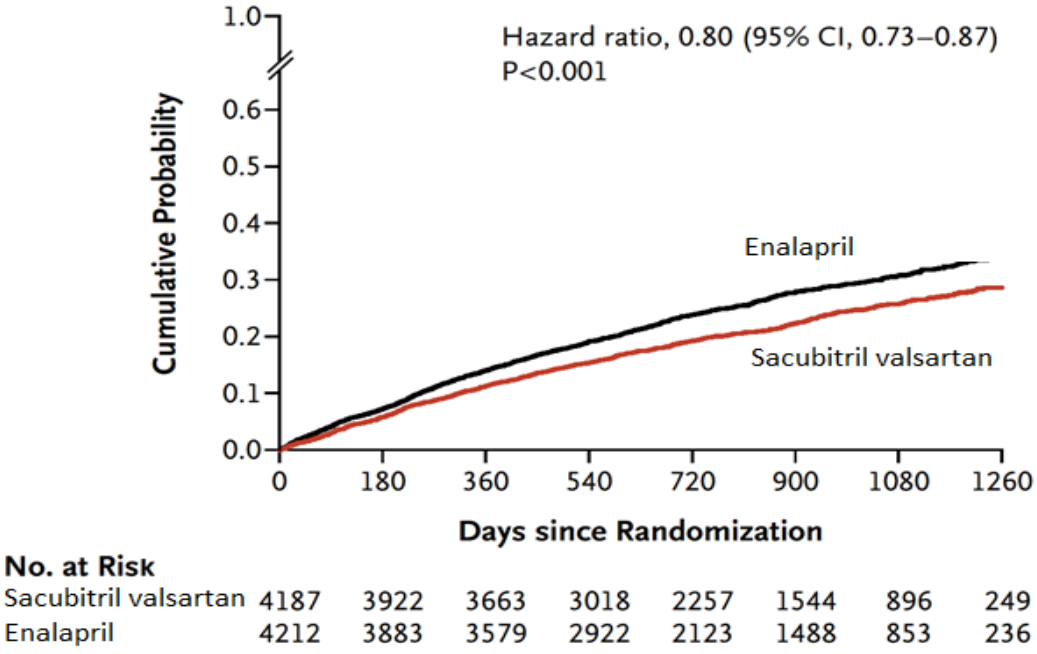


Table 4: Primary composite outcome and component outcomes of PARADIGM-HF (FAS) (reproduced from table 14, page 57 of the company's submission)

	Sacubitril valsartan n=4,187 n, %	Enalapril n=4,212 n, %	HR (95% CI)	p-value
Death from CV causes or first hospitalisation for worsening HF	914 (21.8)	1117 (26.5)	0.80 (0.73–0.87)	<0.001
Death from CV causes	558 (13.3)	693 (16.5)	0.80 (0.71–0.89)	<0.001
First hospitalisation for worsening HF	537 (12.8)	658 (15.6)	0.79 (0.71–0.89)	<0.001
CI, confidence interval; CV, cardiovascular; FAS, full analysis set; HF, heart failure; HR, hazard ratio.				

4.10 The secondary outcomes included time to death from any cause (assessed at all study visits); change from baseline to eight months in the clinical summary score on the Kansas City Cardiomyopathy Questionnaire (KCCQ), whose scores were assessed at baseline/randomisation visit (visit 5), at 4, 8 and 12 months (visits 8, 9 and 10), at 24 and 36 months (visits 14 and17), as well as at the end of study visit; time to a new onset

of atrial fibrillation (AF) (assessed at all study visits); and time to the first occurrence of a decline in renal function. Sacubitril valsartan was associated with statistically signficantly reduced risk of all-cause mortality compared with enalapril (HR 0.84; 95% CI, 0.76 to 0.93, p<0.001). The KCCQ score was reduced for both sacubitril valsartan and enalapril; however, this reduction was less with sacribitril valsartan than with enlapril. For further details of the results for the secondary outcome measures, see pages 59 to 64 of the company submission.

Subgroups

4.11 Patients were stratified by age, gender, race, region, NYHA class, estimated glomerular filtration rate (eGFR), diabetes, systolic blood pressure, LVEF, atrial fibrillation, NT-proBNP, hypertension, prior ACE inhibitors, prior ARB, prior aldosterone antagonist, prior hospitalisation for heart failure, time since diagnosis of heart failure and use of beta blocker, diuretic or digoxin use. Sacubitril valsartan treatment reduced the risk of the primary composite endpoint when compared with enalapril, independent of all pre-defined subgroups. For further details, see the company submission, pages 68 to 70, for a Forest a plot of all subgroup analyses presented from the PARADIGM-HF trial.

4.12 The company stated that age, gender, and NYHA class were important as a result of baseline characteristics being different from the population seen in clinical practice in England. The primary composite outcome was statistically significant in favour of sacubitril valsartan across these subgroups, with the exceptions of people aged 75 years and older (HR 0.86, 95% CI 0.72, 1.04), and people in NYHA class III/IV (HR 0.92, 95% CI 0.79, 1.08).

4.13 The company noted the importance of systolic blood pressure because treatment with sacubitril valsartan was associated with a higher rate of hypotension. The primary composite outcome was statistically significant in favour of sacubitril valsartan in people with lower than median, and people with higher than median systolic blood pressure at baseline.

Finally, the company noted that ejection fraction and NT-proBNP were listed in the inclusion crtieria so could affect trial outcomes. The primary composite outcome was again statistically significant in favour of sacubitril in people with lower than median, and people with higher than median ejection fractions and levels of NT-proBNP.

4.14 For the subgroups based on region, a statistically significant difference in the primary composite outcome in favour of sacubitril valsartan was observed across all regions, with the exception of the Western European subgroup (HR 0.89, 95% CI 0.74 to 1.07), and the Asia/Pacific and Other subgroup (HR 0.85, 95% CI 0.69 to 1.04).

4.15 Regarding the ACE inhibitor naïve subgroup (n= 1867), the primary composite outcome for this subgroup showed a trend favouring sacubitril valsartan but it did not reach statistical significance (hazard ratio 0.92, 95% CI 0.76 to 1.10).

Clinical trial results for TITRATION

4.16 Treatment success, defined as the percentage of patients who achieved and maintained the target dose of sacubitril valsartan (200 mg twice daily) without any dose interruption or down-titration over 12 weeks, was 81.1% of all patients, and was similar for both treatment regimens. Tolerability, defined as the percentage of patients who tolerated the regimen of sacubitril valsartan 200 mg twice daily for at least 2 weeks leading to study completion, regardless of dose interruption or down-titration, was 85.2% of all patients. Tolerability was independent of treatment regimen or whether a patient was treatment naïve or had previously received ACE inhibitor/ARB treatment. For further details of the trial results, see pages 109 to 111 of the company's submission.

ERG comments

4.17 The ERG had concerns regarding the generalisability of the results from the PARADIGM-HF trial to clinical practice in England because the patients recruited to the trial (see section 4.6), the dose of valsartan (in

sacubitril valsartan), and the comparator (enalapril) in the trial (see section 4.7) were not representative of clinical practice in the UK.

4.18 The ERG considered the Western Europe population to be the most representative of the UK (24% of patients in PARADIGM-HF were from Western Europe). Clinical expert opinion sought by the ERG informed that heart failure can have different causes across different geographical regions. It was also noted by the ERG that the place of care was likely to have an effect on the use of medical devices, as for example it is more likely to see implants in Western Europe and North America than Latin America. In response to the clarification questions, the company provided the baseline characteristics of people (n= 2,057) in the Western European population (see table 13, page 56 of the ERG report). The ERG noted that there was a non-statistically significant difference in the Western Europe subgroup for the primary composite outcome, as well both cardiovascular- and all-cause mortality. It considered that the reason for this may relate to people in this subgroup having lower blood pressure, less severe heart failure and more intensive "standard care" (as indicated by a slightly higher consumption of ACE inhibitors). The ERG concluded that the results of the subgroup analysis suggest the effect of sacubitril observed in the trial population might not be observed when used in clinical practice in the UK.

4.19 The ERG considered the results from the PARADIGM-HF and TITRATION trials in relation to the company's proposed positioning of sacubitril valsartan in the treatment pathway. It did not agree with the proposed first-line positioning of sacubitril valsartan by the company:

- The ERG felt the trial population did not reflect a newly diagnosed population (see Table 3).
- The ERG commented that the mortality in the PARADIGM-HF trial portrayed a scenario representative of the use of sacubitril valsartan in patients whose disease is established. It noted that less than 10% of patients in the trial had died by the end of year 1 and 20% were dead in

both treatment arms by the end of the second year (see figure 17, page 145 of the ERG report). The ERG contrasted this with the prognosis in NICE clinical guideline 108 that 30% to 40% of patients diagnosed with heart failure die within a year. The ERG stated that this reinforced its view that the evidence presented in the company submission was most applicable to the use of sacubitril valsartan as a second-line treatment option, given to patients who are still symptomatic despite being on an ACE inhibitor drug therapy.

- The ERG stated that, given the PARADIGM-HF trial's patients were symptomatic, despite having been treated with ARBs and ACE inhibitors, the impact of continuing these patients on ACE inhibitors was likely to misrepresent what would happen in treatment-naïve patients. It further stated that, in principle, the ACE inhibitor treatment regimen has been demonstrated to not improve these patients' symptoms, and therefore randomising them to the same treatment regime is unlikely to show any improvements. The ERG suggested that this has an impact on the observed relative effectiveness of sacubitril valsartan, which might be overestimated in the trial population when compared with treatment-naïve patients.
- The ERG stated that the additional evidence provided from the TITRATION trial did not provide evidence of the effects of sacubitril valsartan in newly diagnosed patients as only 6.6% were treatment naïve.

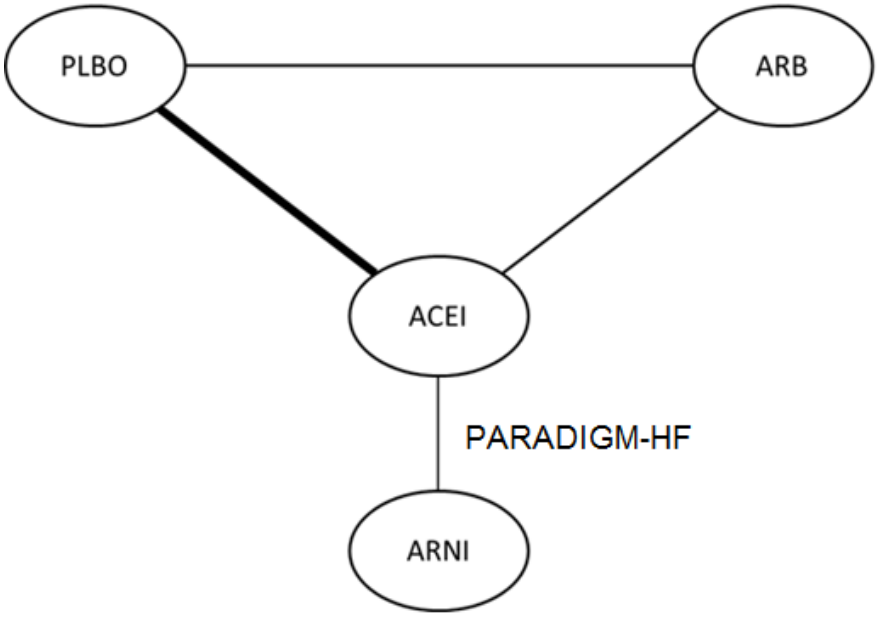
Network meta-analysis

4.20 The final scope issued by NICE specified the comparator, angiotensin II receptor blockers (ARBs) in combination with standard care, for people in whom an ACE inhibitor is unsuitable. As there is no head-to-head evidence comparing sacubitril valsartan with ARBs, the company conducted a network meta-analysis to inform the economic model with estimates of the effectiveness of sacubitril valsartan compared with ARBs, as well as the effectiveness of ARBs compared with ACE inhibitors.

4.21 The core network meta-analysis (see Figure 2) was based on data from 28 randomised controlled trials and provided comparative evidence for all-cause mortality (28 trials, 4 treatment comparisons [see figure 10, page 76 of the company's submission]), cardiovascular mortality (13 trials, 4 treatment comparisons [see figure11, page 77 of the company's submission]) and all-cause hospitalisations (28 trials, 4 treatment comparisons [see figure 12, page 77 of the company's submission]). The company commented that the core network meta-analysis reflected the approach taken by the Cochrane meta-analysis which assessed ACE inhibitors against ARBs with regard to morbidity and mortality irrespective of concomitant treatment with standard care therapies.

4.22 The network meta-analysis categorised treatment by class (angiotensin receptor neprilysin inhibitor [ARNI; sacubitril valsartan], ACE inhibitors, ARBs and placebo), assuming equal efficacy across all molecules within each class. To validate the class-effect assumption of ACE inhibitors, the company referenced a systematic review and network meta-analysis by Chatterjee et al. (2013) which found "there is currently no statistical evidence in support of the superiority of any single agent over the others". The company referenced a Cochrane systematic review by Heran et al. (2012) to validate the assumption of a class effect for ARBs.

Figure 2 Company network meta-analysis evidence network



Abbreviations: ACEi; Angiotensin-converting enzyme inhibitor; ARB: Angiotensin receptor blocker; ARNI: angiotensin receptor neprilysin inhibitor; PLBO: Placebo.

4.23 The company used a Bayesian framework to undertake its network meta-analysis (for further details, see page 87 of the company's submission). The Bayesian network meta-analysis random effects model results are presented in Table 5 below.

Table 5 Summary of random effects results from the company's core network meta-analysis (see table 29, page 88 of the company submission)

Scenario	All-cause mortality HR (95% CrI) P(better)	CV mortality HR (95% CrI) P(better)	All-cause hospitalisation HR (95% CrI) P(better)
ARB vs. ACEi	[redacted]	[redacted]	[redacted]
ARNI vs. ARB	[redacted]	[redacted]	[redacted]

Abbreviations: ;ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; ARNI, angiotensin receptor neprilysin inhibitor; BB, beta blockers; CrI, credible intervals; CV, cardiovascular; HR, hazard ratio; NMA, network meta-analysis; P, probability

4.24 Sensitivity analyses were conducted to 1) adjust for baseline characteristics identified as potential treatment modifiers using meta-

regression and 2) categorise treatments based on investigational therapies in addition to concomitant standard care therapies. For further details see pages 90 to 95 of the company's submission..

ERG comments

4.25 The ERG noted that the company used methods for the network meta-analysis that were in-line with the NICE Decision Support Unit's 'Technical Support Document 2'.

4.26 The ERG noted that, across all outcomes (all-cause mortality, cardiovascular mortality, and all-cause hospitalisation) there were no hazard ratios from the network meta-analysis in which the credible intervals could be considered statistically significantly. The ERG commented that the wide range of drug doses used to manage heart failure and the differences in NYHA classification of patients recruited to the trials in the network meta-analysis were sources of clinical heterogeneity which may have resulted in the wide credible intervals. Overall the ERG regarded the results of the network meta-analysis conducted by the company to be uncertain and potentially unreliable based on the clinical heterogeneity in the trials underpinning the network.

4.27 The ERG discussed the Cochrane systematic review by Heran et al. the company referenced in its assumption of a class effect for ARBs. It noted that the Cochrane review included some trials in which the population studied were not within the scope issued by NICE, for example, because the patients included had heart failure with preserved ejection fraction. The ERG noted that there were similar results observed between the company's network meta-analysis and the meta-analysis from the Cochrane review, and stated that this gave some reassurance that the results were valid. However, it commented that the results needed to be interpreted with caution because of the inclusion of populations that were not within the scope issued by NICE in both meta-analyses.

4.28 Based on the ERG's concerns regarding the company's proposed positioning of sacubitril valsartan as a first line treatment, the ERG considered the clinical effectiveness of sacubitril valsartan compared with ARBs in newly diagnosed patients with heart failure remained an important and yet unanswered question that may require evaluation in a randomised controlled trial.

Adverse effects of treatment

4.29 The overall safety profile of sacubitril valsartan was comparable to that of enalapril during the double-blind trial period of PARADIGM-HF. In the sacubitril valsartan group, fewer patients experienced 1 or more treatment related adverse events, 1 or more serious adverse events, death or discontinued as a result of an adverse event, compared with the enalapril group.

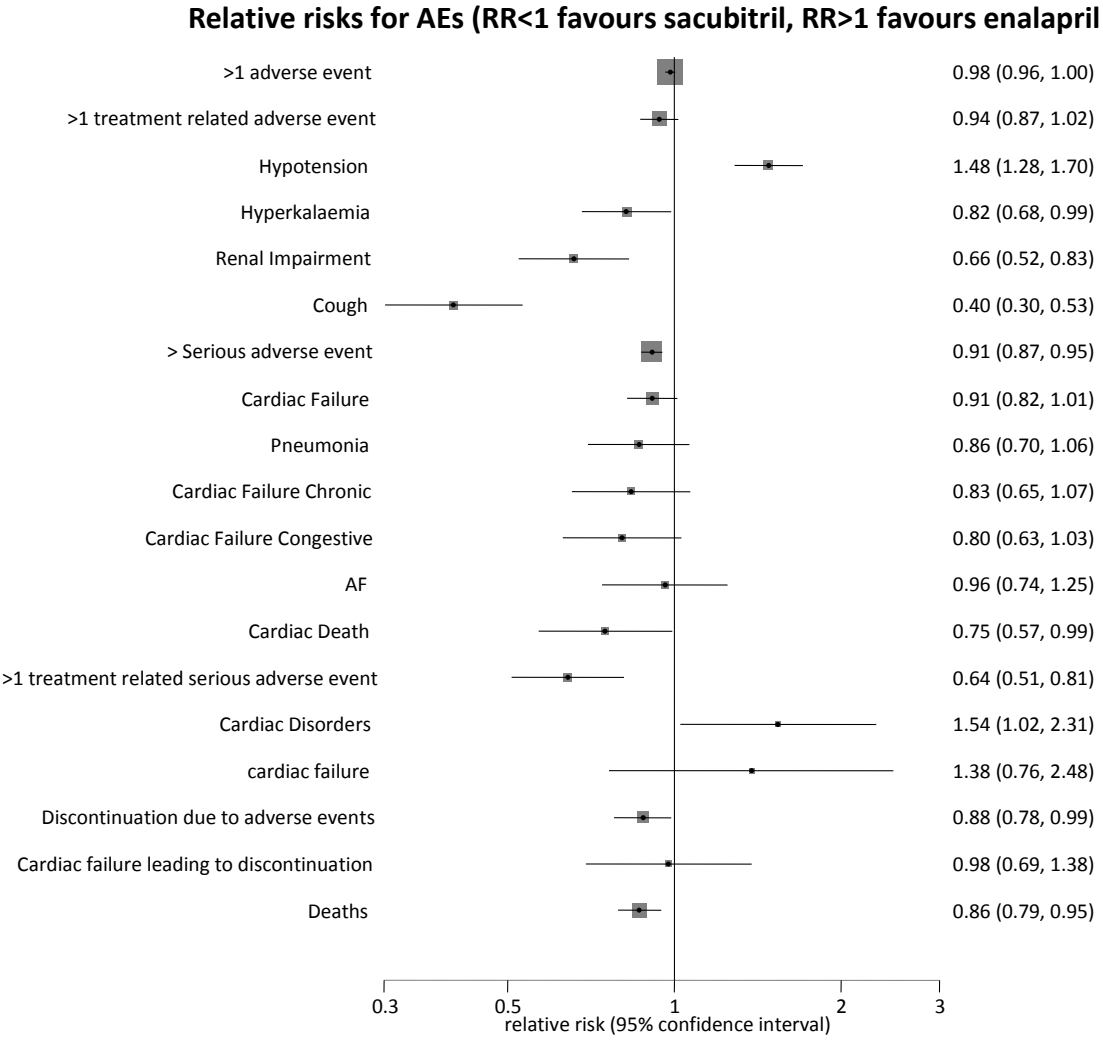
4.30 Treatment with sacubitril valsartan was associated with higher rates of hypotension. The company noted this was a result of sacubitril valsartan's greater vasodilator effect, and that there was no increase in the rate of discontinuation because of possible hypotension-related adverse effects. Fewer patients receiving sacubitril valsartan experienced renal adverse events compared with those receiving enalapril, which was driven by a lower incidence of renal impairment and renal failure in the sacubitril valsartan group (10.14% and 2.66%, respectively) compared with the enalapril group (11.52% and 3.41%, respectively). Other adverse events that were more frequent in the enalapril group compared with the sacubitril valsartan group included hyperkalaemia, cardiac failure, cough, dyspnoea, hypertension, hyperuricemia, and constipation. For further details of the adverse events in the double-blind period of PARADIGM-HF, see table 4, page 98 of the company's submission.

ERG comments

4.31 The ERG noted the company's submission did not report tests of statistical significance for the adverse events. It therefore produced a

forest plot (Figure 3) for all the adverse events listed in the company submission with relative risks and 95% CIs.

Figure 3 Forest plot of adverse events in the double-blind phase of PARADIGM-HF



5 Cost-effectiveness evidence

Model structure

5.1 The company submitted a 2-state Markov economic model with health states defined as ‘alive’ and ‘dead’. In the base-case, the model captured all-cause mortality, all-cause-hospitalisation rates, EQ-5D and adverse event rates. Models with similar structures have been published

previously, including the model submitted to NICE as part of technology appraisal guidance 267 Ivabradine for treating chronic heart failure. In the main base case analysis hypothetical patients began in the model either in the sacubitril valsartan or in the enalapril treatment arms of the model to reflect the company's anticipated first-line positioning of sacubitril valsartan in the heart failure treatment pathway. A secondary base case model was also developed by the company, where patients for whom ACE inhibitors were not appropriate, entered the model in either the sacubitril valsartan or candesartan treatment arms.

5.2 The company's base case analysis used individual patient-level data from the PARADIGM-HF trial, whereby the model was run the same number of times as the number of patients included in the analysis (8,399). Model outcomes were obtained by averaging across the different 8,399 patients' outcomes. The model used a cycle length of 1-month, and a half-cycle correction was applied to all calculations. The model was conducted over a lifetime horizon (equivalent to 30 years). Both costs and benefits were discounted at a rate of 3.5% and the perspective adopted was that of the NHS and personal social services. Deterministic and probabilistic sensitivity analysis was also undertaken to explore parameter uncertainty in the model

ERG comments

5.3 The ERG stated that the formulae within the economic model were generally sound and the economic model was a good predictor of the trial outcomes. It also commented that the company had conducted scenario and subgroup analyses which were not requested in the NICE final scope but added value to the submission.

5.4 The ERG discussed the use of a patient-level approach adopted by the company, as opposed to a cohort model approach. The ERG stated the need for a patient-level approach was not completely justifiable in this case. The ERG believed that the company should have provided more

details and a clear justification as to why this approach was preferred to a cohort model.

Population

5.5 The model population characteristics were based on the PARADIGM-HF trial population, based on the full analysis set (FAS) population. Patients' baseline characteristics were used as covariates in the regression models used to estimate mortality, hospitalisation and quality of life in the economic analysis.

ERG comments

5.6 Since the model population was based on the population of the PARADIGM-HF trial, the ERG expressed the following concerns regarding the population (which were also raised by the ERG in its critique of the clinical effectiveness evidence for sacubitril valsartan):

- Mean age at baseline: The ERG discussed the impact of the difference in age in the model compared with that typically observed in clinical practice. It noted that NICE Clinical guideline 108 states that 30% to 40% of people diagnosed die in the first year, but thereafter the mortality is less than 10% per year. Based on this, the ERG suggested that the starting age of patients in the economic analysis was a key factor. The ERG constructed hypothetical survival curves for mortality based on patients entering the model at 64 years or 75 years (see figures 11 and 12 of the ERG report, page 121). Comparing the difference in the areas under the superimposed survival curves, the ERG showed there were considerable survival gains over time for the younger population, and this had implications for the costs and benefits collected during that time.
- The ERG stated it was uncertain if the effectiveness of sacubitril valsartan in preventing hospitalisation differed across different age groups. The ERG discussed a study by Jhund et al. (see pages 138 to 139 of the ERG report) which concluded that the effect of sacubitril valsartan compared with enalapril was consistent across age groups

even though hazard ratios were non-statistically-significant in older groups. The ERG suggested the non-statistically significant result in older people was consistent with expert opinion provided to the ERG advising that for patients who are around 80 years of age, clinicians expect treatment to improve patients' quality of life, but not mortality. The ERG commented that this was particularly relevant to the UK given that the average age of patients seen in clinical practice is between 75 and 80 years.

- Previous heart failure treatment received and time from diagnosis: The company's anticipated positioning of sacubitril valsartan in the heart failure treatment pathway was as a first-line treatment in newly diagnosed patients. However the population in the PARADIGM-HF trial was not reflective of newly diagnosed patients with heart failure (see table 3 in this document and page 122 of the ERG report for further details). Therefore the model population does not accurately reflect a population with heart failure for whom sacubitril valsartan would be given as a first-line treatment.
- Tolerability of valsartan (in sacubitril valsartan): The target dose of valsartan (in sacubitril valsartan) in the PARADIGM-HF trial was the maximum dose allowed for valsartan. However, the ERG stated that it seems to be uncommon for patients to tolerate such high doses of valsartan in clinical practice (see section 4.7 of this document, and pages 122-126 of the ERG report for further details). The ERG further stated that taking this into consideration, it seems that the trial (and therefore the model) population presents a higher tolerability to the intervention drugs, especially valsartan (in sacubitril valsartan) than the typical population with heart failure seen in clinical practice in the UK. This has an impact on the observed discontinuation of study drugs, which is likely to be higher in UK clinical practice than it is in the trial.
- Region: Clinical expert opinion sought by the ERG informed that heart failure can have different causes across different geographical regions. It was also noted that the place of care is likely to have an effect on the use of medical devices, as for example it is more likely to see implants

in Western Europe and North America than Latin America. The ERG's clinical experts also advised that differences in mortality across North America, Western Europe and the UK could be expected given that the UK has previously used fewer implantable cardioverter-defibrillators (ICDs) than the rest of Europe or North America.

- Device use: The ERG's clinical experts advised that the cardiac device use observed at baseline in PARADIGM-HF was lower than what would be expected in UK clinical practice. The ERG's clinical experts commented that the use of devices at baseline is an important prognostic factor for heart failure (see section 4.6 of this document and table 47, pages 126-128 of the ERG report for further details).

Intervention and Comparators

5.7 The ACE inhibitor comparator arm in the base case model was informed by efficacy data from the enalapril arm of PARADIGM-HF. The company stated that enalapril was selected as the comparator in PARADIGM-HF because it is the ACE inhibitor which has been most studied. The company assumed that enalapril was clinically representative of all ACE inhibitors.

5.8 In a secondary analysis, the company compared sacubitril valsartan with ARBs for people for whom ACE inhibitors are not appropriate. The ARB considered in the economic analysis was candesartan, and a class effect for ARBs was assumed.

5.9 In both treatment and comparator arms of the model, a proportion of patients received standard care (and other background therapies) in addition to sacubitril valsartan or enalapril (or candesartan). Standard care was defined as beta blockers and aldosterone antagonists. Additional background therapies consisted of diuretics, digoxin, anticoagulants, aspirin, adenosine diphosphate antagonists and lipid lowering drugs.

ERG comments

5.10 Regarding the use of enalapril as a comparator treatment in the PARADIGM-HF trial, the ERG's clinical experts advised that, in the UK, the standard ACE inhibitor is ramipril. The company commissioned a CPRD analysis in order to characterise the burden of illness in the UK for patients with heart failure. The ERG analysed the CPRD data commissioned by the company which showed that ramipril is the most commonly used ACE inhibitor in the UK. Therefore, the ERG stated that comparing sacubitril valsartan with enalapril did not reflect clinical practice in England.

5.11 The ERG stated the comparison with candesartan representing ARB treatment appeared to be appropriate.

5.12 The ERG discussed the modelled treatment regimens. It stated that these broadly reflected the PARADIGM-HF trial, even though there was some inconsistency in the chosen treatment doses (see section 5.36). The ERG was concerned with the representativeness of the modelled treatment regimens to clinical practice. It noted that the modelled dose of sacubitril valsartan was 400 mg per day was unlikely to accurately represent the average dose of valsartan tolerated typically observed in clinical practice (see section 5.6). The ERG noted that the dose of candesartan modelled in the economic analysis (32 mg daily) which was dissimilar to the average dose of candesartan reported in the CPRD analysis ([redacted]). Clinical opinion sought by the ERG advised that the observed daily mean dose of candesartan in UK clinical practice was around 16 mg. Finally, the ERG noted a discrepancy in the observed average daily dose for enalapril of 18.9 mg in the PARADIGM-HF trial compared with the CPRD data of about [redacted].

5.13 The ERG stated that the difference in intervention doses compared with clinical practice had an impact on the observed discontinuation of study drugs. The ERG noted that the base case economic model did not consider drug discontinuation, but the company had carried out a scenario

analysis in which the inclusion of discontinuation over the lifetime time horizon had only a modest impact, with a 1% increase in the ICER (see Table 8, section 5.43).

Treatment effectiveness

Base case analysis: comparison with ACE inhibitors

Hospitalisation

5.14 The company's base case analysis modelled the likelihood of a patient experiencing a hospitalisation event using a negative binomial regression model. Predicted all-cause hospitalisation rates were determined by the treatment received by the patient (sacubitril valsartan or enalapril) and patients' baseline characteristics, taken from the PARADIGM-HF trial. These were used to model the number of hospitalisations occurring in the initial period of the economic analysis but also allowed extrapolation beyond the follow-up of the PARADIGM-HF trial. The rate of hospitalisation was assumed constant over time, therefore assuming that hospitalisation was not related with disease progression over time.

ERG comments

5.15 The ERG noted that the company modelled the within trial period with predicted data from the hospitalisation model instead of using observed trial data. It stated this approach was less robust as it used estimated data instead of real data. However, the ERG noted that the company had provided results using the ERG's suggested approach in its response to a clarification request from NICE and the ERG which showed relatively small variations in the final ICER.

5.16 Clinical expert opinion sought by the ERG confirmed that the assumption of constant hospitalisation over time was not reflective of UK clinical practice. For example, a higher proportion of interventional procedures and shorter length of stay would be expected for younger patients than for older patients. The impact of this assumption on the cost of hospitalisation

is discussed by the ERG (see section 5.37 below). The impact was also explored in a scenario analysis by the company in which the baseline annual hospitalisation rate was assumed to increase by 10% of the original baseline rate each year, and this analysis proved the model was relatively insensitive to this variation (see Table 8 in section 5.435.43 below).

Mortality

5.17 Transition probabilities between the alive and dead health states were obtained from all-cause mortality data from PARADIGM-HF in the base case. All-cause mortality was estimated with survival regression analysis. The company chose the Gompertz distribution for the base case, noting that it was preferred by clinical experts, it provided the most conservative (shortest) estimate of survival benefit, and it was used in technology appraisal guidance 267 'Ivabradine for treating chronic heart failure'. Predicted all-cause mortality was determined by the treatment received by the patient (sacubitril valsartan or enalapril) and patients' baseline characteristics, taken from the PARADIGM-HF trial. The mortality model was run using the FAS population of the PARADIGM-HF trial and the model outputs provided daily hazard rates. These were used to model the probability of patients dying in the initial period of the economic analysis but also allowed extrapolation beyond the end of the PARADIGM-HF trial for the remainder of the modelled time horizon.

5.18 In an alternative analysis, the company derived transition probabilities between the alive and dead health states from cardiovascular-related mortality. The Gompertz distribution was also used for this analysis.

ERG comments

5.19 The ERG had concerns about the modelling of mortality in the model. The ERG reiterated that the modelled population did not reflect patients typically observed in clinical practice, and nor did it reflect a newly diagnosed population. Each of these factors impacted on the estimated mortality in the model. The ERG did not run any additional analyses to try

and replicate the mortality of newly diagnosed patients as it stated too many assumptions would have had to be made to approximate a treatment-naïve population. The ERG noted the potential bias arising from the early stop observed in the PARADIGM-HF trial, at which point the data observed might have been a "random high" effect, favouring sacubitril valsartan. For further details see figures 16-19, pages 143 to 146 of the ERG report.

5.20 The ERG noted the company's decision to use a Gompertz distribution was based on this distribution presenting the most plausible survival time. The ERG believed that the company should have presented different modelling options, such as spline models. The ERG noted the company had not tried other approaches outside parametric curves, and it stated that this might have produced suboptimal results. Even though the Gompertz distribution produced the most plausible survival curves among the group of alternative distributions considered, the ERG considered that it could represent an overestimate of treatment effects compared with different (and potentially more appropriate) approaches.

5.21 The ERG discussed the use of the all-cause mortality model used in the company's base case, as opposed to the use of cardiovascular mortality. The ERG noted that the company had chosen the all-cause mortality model as this was considered the most conservative approach (that is, it produced the higher ICER). The ERG believed that the cardiovascular mortality approach was likely to have been more robust from a theoretical point of view. It stated that there were issues in using an all-cause mortality approach as it included non-cardiovascular mortality observed in the trial. Clinical opinion sought by the ERG explained that non-cardiovascular mortality was likely to be overestimated in the trial (when compared to the UK life tables) given that the trial included a considerable proportion of patients from countries where other causes of death, such as infection, are much more prevalent than in Europe and North America.

5.22 The ERG commented that even though the modelled effect of age at baseline in cardiovascular mortality seems to be appropriate to capture the PARADIGM-HF trial data, the unexpected shape of the mortality curve (see figure 22, page 153 of the ERG report) leads to other issues in the economic analysis, such as the lack of face validity of the predicted life expectancy in the model. The ERG highlighted that the predicted life expectancy by the mortality survival model indicated that 21-year-old patients have the same life expectancy as 87-year-old patients and that equally implausible, 72-year-old patients have a much higher life expectancy than 18 year olds. The ERG appreciated that this was a direct implication of the modelled effect of age at baseline on cardiovascular mortality (see figure 22, page 153 of the ERG report), which in turn was a direct consequence of the PARDIGM-HF trial data (See figure 23, page 153 of the ERG report).

Utility values

5.23 The company used a linear mixed regression model based on EQ-5D trial data from PARADIGM-HF to predict the utility scores for patients in the base case analysis. Since the economic model did not explicitly include mutually exclusive health states (other than the alive and the dead states), mean utility values over time were calculated for each patient profile. Predicted EQ-5D scores were based on treatment received, baseline characteristics (including baseline EQ-5D), and risk of hospitalisation and adverse events.

5.24 A small but significant EQ-5D treatment effect in favour of sacubitril valsartan was assumed even after controlling for the effects of hospitalisations and adverse events. This was assumed to persist for the duration of the time horizon. EQ-5D scores were assumed to decline at a constant rate of -0.008 over the modelled time horizon (30 years), which was based on data from PARADIGM-HF and a longitudinal study by Berg et al. (2015) which reported an annual decline in EQ-5D of -0.006. The decline rate was not dependent on baseline characteristics.

5.25 The company applied utility decrements when a patient was hospitalised, with a decrement of -0.105 during days 0 to 30, and -0.054 during days 30 to 90. The company also applied adverse event utility decrements for hypotension (-0.029) and cough (-0.028) over an average duration of 64.9 and 73.3 days respectively. The effect of serious adverse events requiring hospitalisation on quality of life was assumed to be captured in the utility decrements associated with hospitalisation.

ERG comments

5.26 The ERG was concerned with the validity of the health-related quality-of life analysis undertaken by the company. Firstly, the ERG could not be certain if there was a baseline statistically significant difference, or not, in patients' EQ-5D scores between the 2 treatment groups. It noted there was a [redacted], and it suggested the statistical test performed by the company ([redacted]) might not be appropriate given the [redacted] shape of the quality of life distribution at baseline. The ERG stated that the trial and consequently the model outcomes could potentially be biased if there was a clinically significant difference in patients' disease severity and quality of life across the treatment groups. The ERG suggested that, if one assumed patients in a healthier state would have better outcomes, the potential imbalance in disease severity ([redacted]) might have favoured the sacubitril valsartan group.

Secondary analysis: Comparison with ARBs for people for whom ACE inhibitors are not appropriate

5.27 For the comparison with ARBs, all-cause mortality and all-cause hospitalisation models used the network meta-analysis results to estimate the effectiveness of sacubitril valsartan compared with candesartan. For the all-cause hospitalisation model the company applied a hazard ratio of [redacted] for ARBs compared with ACE inhibitors (that is, candesartan was

assumed to be [redacted] more effective than enalapril in preventing hospitalisations). Utility values in the ARB treatment arm of the model were assumed to be equivalent to the ACE inhibitor treatment arm as modelled in the base case analysis.

ERG comments

5.28 The ERG was concerned with the clinical heterogeneity in the trials underpinning the network, and it considered the clinical effectiveness of sacubitril valsartan compared with ARBs in newly diagnosed patients with heart failure remained an unanswered question.

Adverse events

5.29 Adverse events included in the base case model were based on the FAS population (as opposed to the safety analysis set) which the company stated was to ensure consistency with the modelling of clinical and quality of life outcomes which were also based on the FAS population. The company modelled the adverse events by assuming a constant probability of a specific adverse event occurring each cycle. It assumed that all-cause hospitalisation included all the relevant serious adverse events, including the associated costs and impact on patients' quality of life. The "less serious adverse events" were modelled independently from hospitalisation. These consisted of hypotension, elevated serum creatinine, elevated serum potassium, cough and angioedema.

5.30 Adverse events in the secondary analysis in the ARB treatment arm of the model were assumed to be equivalent to the sacubitril valsartan treatment arm.

ERG comments

5.31 The ERG's clinical experts advised that some of the considered less serious adverse events can have a substantial impact on patients' quality of life, depending on their severity. The ERG therefore stated that the more severe versions of these adverse events should have been included in the all-cause hospitalisation regression model. The ERG noted that the

monthly probabilities of elevated serum creatinine and elevated serum potassium were quite different across the full analysis set and the safety analysis set populations, but, given the very small frequency of these events, the ERG was not concerned with this issue.

5.32 The ERG noted that adverse events were estimated as 'one-off' events each cycle, with the exception of hypotension and cough. It stated that clinical opinion sought by the ERG advised that cough symptoms will usually persist until drug discontinuation which was not accounted for in the economic model.

Resources and costs

5.33 Resource use and costs considered in the model consist mainly of:

- Intervention and comparator's costs (including background therapies)
- Treatment initiation costs
- Hospitalisation cost
- Heart failure management costs
- Adverse event costs.

5.34 The company based the daily costs of ACE inhibitors and sacubitril valsartan on observed doses from PARADIGM-HF. The cost of hospitalisation was based on Healthcare Resource Groups (HRGs) mapped from physician-reported diagnoses, surgeries and interventional procedures that could be classified, and medical management hospitalisations with > 30 instances considered. Typical costs of standard care (including beta blockers and aldosterone antagonists) and background medications were based on recommended doses. Estimates of background resource use, including A&E referrals, outpatient contacts and GP visits, were taken from relevant national sources. The CPRD analysis was used as the main source for resource use in the base case.

ERG comments

5.35 The ERG agreed with the company that real-world data from CPRD was more robust and more reflective of the UK population than literature studies. However the ERG was concerned with the appropriateness of the use of the CPRD data to estimate the resource use for the patient profiles observed in the trial as there were differences in the population observed in the CPRD analysis and the population in the PARADIGM-HF trial.

5.36 The ERG noted that the assumptions by the company regarding the daily drug doses were not consistent across different treatments. For some treatments, the doses were estimated as the average between the minimum and maximum dose and for other drugs, the doses were based on maximum doses. The ERG carried out exploratory analysis (see section 5.48) to reflect consistent drug dose assumption and using the cost of ramipril instead of enalapril. Based on advice from its clinical experts, it assumed a reduced cost for ramipril reflecting the fact that in clinical practice ramipril is given as a single daily dose, rather than as 2 daily doses (see table 59, pages 165 to 166 of the ERG report).

5.37 Clinical expert opinion sought by the ERG confirmed that the assumption of constant hospitalisation over time was not reflective of clinical practice in the UK. The ERG stated the hospitalisation cost would be expected to depend on starting age and time. The ERG's clinical experts advised that the incidence of hospitalisation caused by renal failure in the trial appeared to be lower than expected, and that the cause could be due to the population being younger and healthier than in UK clinical practice. The ERG therefore had concerns that the starting age in the model impacted the cost savings caused by the reduction in hospitalisations.

Company's base-case results and sensitivity analysis

5.38 The base case deterministic incremental cost effectiveness ratio (ICER) for sacubitril valsartan compared with ACE inhibitors was £17,939 per QALY gained (Table 6), and the probabilistic ICER was £18,818 per

QALY gained. The probabilities of sacubitril valsartan being cost-effective at thresholds of £20,000 and £30,000 were 64% and 93%, respectively.

Table 6 Company's primary base case results (reproduced from table 1, company's Addendum - Update to cost effectiveness results)

	ACE inhibitors + standard care	Sacubitril valsartan + standard care	Incremental value
Total costs (£)	£13,287	£20,801	£7,514
QALYs	4.60	5.02	0.42
ICER			**£17,939**

5.39 Deterministic one-way sensitivity analysis showed that for the comparison with ACE inhibitors the ICER was most sensitive to all-cause mortality, with the greatest effects on the ICER coming from the treatment effect of sacubitril valsartan on all-cause mortality, the baseline risk of all-cause mortality, and age (as a result of its impact on expected survival). Variables which had a modest effect included the improvements in health-related quality of life and reduction in hospitalisations.

5.40 For sacubitril valsartan compared with ARBs, the deterministic ICER was £16,481 per QALY gained (Table 7), and the probabilistic ICER was £17,599 per QALY gained. The probabilities of sacubitril valsartan being cost-effective at the lifetime time horizon at thresholds of £20,000 and £30,000 were 60% and 77%, respectively. Results of the one-way deterministic sensitivity analysis were consistent with the analysis compared with ACE inhibitors, except the all-cause mortality hazard ratio for ARB compared with ACE inhibitors from the network meta-analysis was the most influential parameter. This parameter was subject to a high degree of uncertainty as a result of the wide credible intervals generated by the network meta-analysis.

Table 7 Company's secondary analysis results (reproduced from table 4, company's Addendum - Update to cost effectiveness results)

	ARBs + standard care	Sacubitril valsartan + standard care	Incremental value
Total costs (£)	£12,288	£20,801	£8,513
QALYs	4.50	5.02	0.52
ICER			**£16,481**

5.41 The company also presented results obtained using cardiovascular-mortality (rather than overall mortality in the base case) and in this analysis the deterministic ICERs for sacubitril valsartan were £16,678 per QALY gained compared with ACE inhibitors and £16,569 compared with ARBs.

ERG comments

5.42 The ERG was concerned that parameter uncertainty in the economic analysis was not appropriately accounted for. The ERG stated that patients' baseline characteristics should have been included in the deterministic and probabilistic sensitivity analysis given the concerns discussed throughout regarding the lack of generalisability of the PARADIGM-HF trial population to clinical practice. The ERG also commented that the baseline characteristics were key parameters in the economic model given that these were included as prognostic factors of mortality, hospitalisation, quality of life and costs in the regression analyses.

Company scenario analyses

Deterministic scenario analyses

5.43 In order to provide estimates of cost-effectiveness more representative of clinical practice, the company carried out deterministic scenario analyses for the comparison of sacubitril valsartan with ACE inhibitors, the results of which are presented in Table 8.

Table 8 Scenario analyses performed by the company (reproduced from table 22, company's Addendum - Update to cost effectiveness results)

Scenario name	Sacubitril valsartan		ACEi		ICER	% change from base case
	Costs	QALYs	Costs	QALYs		
Base case analysis	£20,801	5.02	£13,287	4.60	£17,939	–
Discount rates altered to reflect historic NICE discount rates of 6% for costs and 1.5% for outcomes	£18,581	5.54	£11,977	5.05	£13,390	-25%
Weibull distribution used in all-cause mortality model	£27,080	6.40	£17,009	5.81	£17,135	-4%
Exponential distribution used in model of all-cause mortality	£29,714	6.95	£18,709	6.33	£17,698	-1%
Annual rate of decline in EQ-5D halved	£20,801	5.15	£13,287	4.71	£17,236	-4%
Annual rate of decline in EQ-5D doubled	£20,801	4.75	£13,287	4.37	£19,535	9%
No decline in EQ-5D over time	£20,801	5.28	£13,287	4.83	£16,588	-8%
No decline in EQ-5D after 5 years	£20,801	5.11	£13,287	4.67	£17,238	-4%
No decline in EQ-5D after 10 years	£20,801	5.04	£13,287	4.61	£17,688	-1%
Effect of sacubitril valsartan on EQ-5D (beyond differences in hospitalisation / adverse event rates) assumed to be zero	£20,801	4.95	£13,287	4.60	£21,516	20%
Effect of sacubitril valsartan on hospitalisation rates assumed to apply to HF hospitalisation only	£21,556	5.01	£13,287	4.60	£19,895	11%
Effect of sacubitril valsartan on hospitalisation rates assumed to apply to CV hospitalisation only	£21,217	5.01	£13,287	4.60	£19,013	6%
Effect of hospitalisation on EQ-5D assumed to be zero	£20,801	5.05	£13,287	4.63	£18,032	1%
Sacubitril valsartan treatment effects assumed to cease at year 5	£20,521	4.82	£13,287	4.60	£31,808	77%
Sacubitril valsartan treatment effects assumed to cease at year 10	£20,677	4.95	£13,287	4.60	£20,941	17%
Treatment discontinuation considered over lifetime time horizon	£18,623	4.89	£13,293	4.60	£18,150	1%
Treatment discontinuation considered up to year 3	£19,548	4.95	£13,290	4.60	£17,932	0%
Treatment discontinuation assumed to result in reduced therapy costs; efficacy estimates as in trial	£18,660	5.02	£13,293	4.60	£12,814	-29%
Hospitalisation costs doubled	£27,620	5.02	£20,726	4.60	£16,458	-8%
Hospitalisation costs halved	£17,391	5.02	£9,567	4.60	£18,680	4%
Proportions of hospitalisation types derived using Western Europe population	£21,503	5.02	£14,053	4.60	£17,787	-1%
All adverse event rates set to zero	£20,703	5.02	£13,195	4.60	£17,909	0%
Primary therapies costed assuming target doses from PARADIGM-HF	£20,801	5.02	£13,296	4.60	£17,918	0%
Cost of ramipril applied to ACEi arm	£20,801	5.02	£13,330	4.60	£17,835	-1%
Cost of titration included	£21,062	5.02	£13,287	4.60	£18,564	3%
Increased risk of hospitalisation over time	£28,500	4.99	£21,193	4.57	£17,443	-3%

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; CV, cardiovascular; HF, heart failure; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

CPRD-based re-weighting scenario analysis

5.44 The company carried out a scenario analysis to adjust the trial population characteristics to those of the UK population with heart failure by using the results from the CPRD analysis. The company built the scenario analysis using a raking (or sample balancing) method, such that weights were attributed to each patient in order to adjust for differences between the observed and the target population. Two raking-based analyses were performed: the first analysis took into account only age and gender, while the second analysis included (in addition to age and gender) prior stroke, eGFR levels, and current smokers. Estimates of cost-effectiveness of sacubitril valsartan compared with ACE inhibitors for the re-weighted cohort were consistent with the base-case ICER irrespective of the weighting scheme used. The company noted that while there were only modest effects on the ICERs, the total costs and QALYs varied more noticeably, and suggested this was because the reduced survival reduced both the number of QALYs and the costs in similar proportions. For further details, see tables 18 to 21, page 21 of the company's Addendum - update to cost effectiveness results.

ERG comments

5.45 The ERG noted the company did not describe the raking procedure undertaken in the CPRD-based re-weighting scenario analysis. The ERG commented that the raking procedure was effective in fitting the CPRD distribution and led to a convergence of the trial data to the target values. It stated that even though this scenario analysis was designed based on the need to provide estimates representative of the UK population with heart failure, the final weights attributed to the profiles of patients from outside Western Europe was substantial. The ERG stated this was an issue given that the majority of baseline characteristics were not able to be adjusted to reflect CPRD data.

Deterministic subgroup analyses

5.46 The company presented a large number of deterministic subgroup analyses. The subgroup analyses were based on the patient-level modelling approach, and were performed by selecting only the results of the patient profile-based cohorts corresponding to certain baseline characteristics out of the 8,399 cohorts. For details of the results of the subgroup analyses see table 74, page 184 of the ERG report.

5.47 In response to a clarification request, the company also provided a subgroup analysis of the Western European population in the PARADIGM-HF trial. For further details of the subgroup analysis see pages 185-193 of the ERG report.

ERG exploratory analyses

5.48 The scenario analyses carried out by the ERG were ran for a population with a mean starting age of 64 years (as per the company's base case) and for a mean starting age of 75 years to reflect the UK heart failure population. The ERG used the cardiovascular mortality approach and the mean cohort model (as opposed to the all-cause mortality approach and the patient-level model used by the company in the base case). The additional scenario analysis ran for the 64-year-old population included the following.

- The ERG changed the cardiovascular mortality hazard ratio in the model to reflect the Jhund et al. point estimate and confidence interval limits for the 55 to 64 year category. The hazard ratio used was 0.79 (CI 0.64 to 0.98);
- The ERG used the baseline utility score of 0.72 reported by Berg et al.
- The ERG used the baseline utility score of 0.660 reported by Austin et al.
- Given the issues found in the modelling approach of quality of life in the model, the ERG adopted a simplified approach, where the impact of sacubitril valsartan on patients' quality of life was linked to the

incidence of adverse events and hospitalisation events and disease progression in both treatment arms. Therefore, the quality of life regression model was not used, even though some of its estimates were used as these were validated by clinical experts. The impact of sacubitril valsartan alone on quality of life was also removed to reflect the lack of robust evidence to support a measurable improvement in patients' quality of life caused by sacubitril other than through hospitalisation, mortality and adverse events. The impact of treatment regimens on quality of life was assessed by the ERG through:

  - Adverse events and hospitalisation events: the ERG applied the same utility decrements used by the company to estimate the loss in quality of life due to the incidence of adverse events and hospitalisation.
  - Disease progression: the ERG applied the same utility decrement used by the company to reflect the loss of quality of life as time progressed.
- The ERG changed the drug doses used in the model to reflect a consistent approach to the estimation of drug costs.
- The ERG included the cost of ramipril (using the ERG drug dose assumption) as to reflect clinical practice in the UK
- The ERG used the option included in the company's economic model to run the ERG corrected model considering treatment discontinuation
- The ERG used the company's subgroup analysis results to run the ERG corrected model considering the Western European population.

The additional scenario analysis ran for the 75-year-old population included the following:

- The ERG changed the cardiovascular mortality hazard ratio in the model to reflect the Jhund et al. HR point estimates and confidence interval limits for the ≥75 year category. The HR used was 0.84 (95% CI: 0.67 to 1.06).

- As the hazard ratio of cardiovascular mortality in the ≥75years was non-statistically significant the ERG ran the model with a hazard ratio of 1.

The incremental costs, QALYS and ICERs for both sets of scenario analyses are presented in Table 9.

Table 9 ERG exploratory scenario analyses

Scenario	Inc. cost	Inc. QALY	ICER
Base case (CV approach, mean cohort model) with ERG corrections			
64 years	£8,653	0.58	£15,026
75 years	£6,936	0.44	£15,843
HR for CV mortality changed to reflect Jhund et al			
64 years; CV mortality HR = 0.79	£8,859	0.62	£14,246
75 years; CV mortality HR = 0.84	£6,610	0.37	£18,021
HR for CV mortality changed to reflect Jhund et al upper CI limit			
64 years; CV mortality HR = 0.98	£6,631	0.12	£53,803
75 years; CV mortality HR = 1.06	£4,759	-0.04	Dominated
HR for CV mortality changed to reflect Jhund et al lower CI limit			
64 years; CV mortality HR = 0.64	£11,052	1.11	£9,977
75 years; CV mortality HR = 0.67	£8,362	0.75	£11,192
HR for CV mortality changed to 1			
75 years	£5,225	0.06	£81,329
Change in baseline utility to reflect Berg et al utility (0.72)			
64 years	£8,525	0.55	£15,407
75 years	£6,846	0.42	£16,190
Change in baseline utility to reflect Austin et al utility (0.66)			
64 ears	£8,398	0.53	£15,821
75 years	£6,757	0.41	£16,571
Change in QoL modelling approach			
64 years	£8,653	0.50	£17,413
75 years	£6,936	0.38	£18,357
Change in pharmaceutical costs to reflect drug target doses			
64 years	£8,655	0.58	£15,030
75 years	£6,937	0.44	£15,845
Including the cost of ramipril			
64 years	£8,704	0.58	£15,115
75 years	£6,979	0.44	£15,940
Including discontinuation (with ERG correction)			
64 years			

75 years	£4,876	0.31	£15,628
Western Europe subgroup (corrected)			
[redacted] years	£6,841	0.33	£20,550
75 years	£5,744	0.28	£20,321
Abbreviations: Inc., incremental; QALY, Quality adjusted life year; ICER, incremental cost effectiveness ratio			

5.49 The ERG noted that the additional analysis presented for the 64 year-old population was consistent with the company's sensitivity analysis in showing that the model results were most sensitive to changes in the mortality hazard ratio, with cardiovascular mortality the key model driver.

ERG second-line ICER

5.50 The ERG presented ICERs for sacubitril valsartan compared with enalapril assuming that sacubitril valsartan was used as a second-line treatment in clinical practice. The ICERs estimated by the ERG were based on the PARADIGM-HF population and clinical effectiveness results. The ERG assumed the following:

- Mean starting age of the model population is 75 years old.
- Baseline utility value taken from Berg et al.
- The cost of ramipril instead of enalapril to reflect clinical practice in the UK.
- The effectiveness outcomes, costs, QALYs and population characteristics of the Western European subgroup analysis.
- Additionally the ERG used its alternative quality of life modelling approach and adjusted drug costs to reflect target doses consistently across the economic analysis. The second-line ICERs estimated by the ERG are presented in Table 10.

Table 10 ERG's second-line ICER (recreated from the ERG report: table 86, pages 205 to 206)

Results per patient	Sacubitril+SoC (1)	Enalapril+SoC (2)	Incremental value (1 – 2)
Company's base case with ERG corrections			

Total costs (£)	£22,961	£14,308	£8,653
QALYs	5.40	4.82	0.58
ICER			£15,026
Mean age at baseline of 75 years			
Total costs (£)	£19,498	£12,562	£6,936
QALYs	4.43	3.99	0.44
ICER (compared with base case)			£15,843
ICER with all changes incorporated			£15,843
Change in baseline utility to reflect Berg et al utility (0.72)			
Total costs (£)	£22,824	£14,299	£8,525
QALYs	5.11	4.55	0.55
ICER (compared with base case)			£15,407
ICER with all changes incorporated			£16,190
Change in QoL modelling approach			
Total costs (£)	£22,961	£14,308	£8,653
QALYs	5.30	4.80	0.50
ICER (compared with base case)			£17,413
ICER with all changes incorporated			£19,697
Change in pharmaceutical costs to reflect drug target doses			
Total costs (£)	£23,085	£14,430	£8,655
QALYs	5.40	4.82	0.58
ICER (compared with base case)			£15,030
ICER with all changes incorporated			£19,701
Change in pharmaceutical costs to reflect the cost of ramipril			
Total costs (£)	£22,961	£14,257	£8,704
QALYs	5.40	4.82	0.58
ICER (compared with base case)			£15,115
ICER with all changes incorporated			£19,843
Western Europe subgroup			
Total costs (£)	£24,182	£17,341	£6,841
QALYs	4.86	4.52	0.33
ICER (compared with base case)			£20,550
ICER with all changes incorporated			£29,478
Abbreviation used in the table: Abbreviations used in the table; SoC, standard of care; ICER, incremental cost-effectiveness ratio; HR, hazard ratio; QALYs, quality-adjusted life years; QoL, quality of life.			

5.51 The second-line ICER estimated by the ERG was £29,478 per QALY gained for sacubitril valsartan compared with enalapril, using a cardiovascular mortality approach and a mean cohort model. The results for sacubitril valsartan compared with candesartan (ARB) were consistently similar, with the final second-line ICER resulting in £30,140 per QALY gained. The ERG considered that the second-line ICERs

reported must be interpreted with caution regarding uncertainty around the effectiveness of sacubitril valsartan compared with enalapril when analysed in the context of UK clinical practice (for more information regarding these uncertainties, see pages 206 to 208 of the ERG report). The ERG also presented further scenario analyses which demonstrated the variance in values when different hazard ratios and mortality approaches (cardiovascular or all-cause) were taken (see Table 11).

Table 11 ERG's additional scenario analyses (recreated from the ERG's addendum report)

Scenario	CV mortality approach HR	ICER	All-cause mortality approach HR	ICER
Second-line ICER estimated by ERG (using Western European HRs)				
[redacted] years	0.86	£30,190	0.94	£53,299
75 years		£29,478		£47,699
HR for CV mortality changed to reflect Jhund et al				
64 years; CV mortality	0.79	£22,025	0.87	£28,851
75 years; CV mortality	0.84	£26,605	0.87	£25,396
HR for CV mortality changed to reflect Jhund et al upper CI limit				
64 years; CV mortality	**0.98**	**£143,265**	1.06	Dominated
75 years; CV mortality	1.06	Dominated	1.07	Dominated
HR for CV mortality changed to reflect Jhund et al lower CI limit				
64 years; CV mortality	0.64	£14,942	0.72	£15,959
75 years; CV mortality	0.67	£15,584	0.71	£14,059
HR for CV mortality changed to 1				
64 years	1	£533,646	1	£533,646
75 years		£492,438		£492,438
Western Europe subgroup upper CI limit				
[redacted] years	1.11	Dominated	1.17	Dominated
75 years		Dominated		Dominated
Western Europe subgroup lower CI limit				
[redacted] years	0.67	£15,739	0.76	£17,479
75 years		£15,474		£16,015
Abbreviations: Inc., incremental; QALY, Quality adjusted life year; ICER, incremental cost effectiveness ratio				

Innovation

5.52 Justifications for considering sacubitril valsartan to be innovative:

- Sacubitril valsartan has a unique mechanism of action: it is an angiotensin receptor neprilysin inhibitor (ARNI), acting as a neprilysin inhibitor and an ARB simultaneously, resulting in complementary effects on the cardiovascular system that are beneficial in patients with heart failure. The company state that it is the first time in over a decade, since the introduction of aldosterone antagonists, that a new first-line treatment for heat failure offers significant benefits over the current standard of care. Sacubitril valsartan has been granted a promising innovative medicine (PIM) designation by the MHRA.

6 Equality issues

6.1 It was noted in a statement from a clinical expert that there were higher rates of angio-oedema in those of African descent exposed to ACE-inhibitors, and that extra vigilance would be required because of the low numbers of this cohort included in the trial (5%). NICE considers that this is not an equalities issue that can be addressed within a technology appraisal and any recommendations made would not result in a difference in access to treatment for people of African descent.

7 Authors

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Appendix A: Clinical efficacy section of the draft European public assessment report

[redacted]

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Proposed Health Technology Appraisal

Sacubitril valsartan for treating chronic heart failure

Final scope

Remit/appraisal objective

To appraise the clinical and cost effectiveness of sacubitril valsartan within its marketing authorisation for treating heart failure (NYHA stage II-IV) with systolic dysfunction.

Background

Heart failure is a complex clinical syndrome of signs and symptoms, generally defined as the inability of the heart to supply sufficient blood flow to meet the body's needs. It is caused by structural or functional abnormalities of the heart, commonly resulting from coronary artery disease. Heart failure may be associated with left ventricular systolic dysfunction (that is, reduced left ventricular ejection fraction, where the left pumping chamber's ability to pump is impaired) but may also be associated with preserved ejection fraction (minimum ejection fraction of 45%). Severe systolic dysfunction is usually associated with an ejection fraction of 35% or lower.

Symptoms of heart failure are classified by the New York Heart Association (NYHA) system from class I (no limitations) to class IV (inability to carry out any physical activity without discomfort), and commonly include breathlessness, fatigue and ankle swelling. Quality of life is affected by the physical limitations imposed by the symptoms.

Around 900,000 people in the UK have heart failure. Approximately 42,000 people were admitted to hospital in England with heart failure in 2012/13 and 72% of these people had a reduced left ventricular ejection fraction[1]. Both the prevalence and incidence of heart failure increase with age. Thirty to forty percent of patients diagnosed with heart failure die within the first year.

NICE clinical guideline 108 ('Chronic heart failure') recommends that all patients with chronic heart failure due to left ventricular systolic dysfunction should be offered beta-blockers and an angiotensin-converting enzyme (ACE) inhibitor unless contraindicated or not tolerated. Angiotensin II receptor inhibitors are alternatively recommended for use in people in whom ACE inhibitors are unsuitable. In clinical practice, an aldosterone antagonist is usually administered alongside the other treatments.

The technology

Sacubitril valsartan (brand name unknown, Novartis) is an angiotensin receptor neprilysin inhibitor. It includes the neprilysin inhibitor sacubitril

(AHU377) and the angiotensin II receptor inhibitor valsartan. Both sacubutril and valsartan lower blood pressure. It is administered orally.

Sacubitril valsartan does not currently have a marketing authorisation in the UK. It has been studied in a clinical trial compared with the ACE inhibitor enalapril in adults with heart failure (New York Heart Association (NYHA) class II-IV) with a left ventricular ejection fraction of 35% or lower. It is being assessed in an ongoing trial in adults with heart failure with a preserved left ventricular fraction of 45% or more, compared with valsartan.

Intervention(s)	Sacubitril valsartan in combination with standard care (including treatment with a beta blocker and an aldosterone antagonist)
Population(s)	People with chronic heart failure (NYHA class II-IV) with systolic dysfunction.
Comparators	• ACE inhibitor in combination with standard care • Angiotensin II receptor blocker in combination with standard care (for people in whom an ACE inhibitor is unsuitable). Standard care includes treatment with a beta blocker and an aldosterone antagonist.
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 • health-related quality of life

Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. Standard care includes treatment with a beta blocker and an aldosterone antagonist. The cost of background therapies, such as diuretics, should also be included in cost effectiveness analyses.
Other considerations	Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.
Related NICE recommendations and NICE Pathways	Related Technology Appraisals: Technology Appraisal No. 267, Nov 2012 'Ivabradine for treating chronic heart failure'. Review proposal date Nov 2015. Technology appraisal No. 314, Jun 2014 'Implantable cardioverter defibrillators and cardiac resynchronisation therapy for arrhythmias and heart failure (review of TA95 and TA120)'. Review proposal date May 2017. Related Guidelines: Clinical Guideline No. 108, Aug 2010, 'Chronic heart failure: Management of chronic heart failure in adults in primary and secondary care'. Review in progress. Anticipated publication date to be confirmed. Related Interventional Procedures: Interventional Procedure No. 463, Aug 2013, 'Insertion and use of implantable pulmonary artery pressure monitors in chronic heart failure. Related Quality Standards: Quality Standard No. 9, Jun 2011 'Chronic heart failure'. Update in progress. Related NICE Pathways:

	NICE pathway: Chronic heart failure, pathway last updated July 2014.
Related National Policy	Department of Health National service framework: coronary heart disease. Published Mar 2000. https://www.gov.uk/government/publications/quality-standards-for-coronary-heart-disease-care Department of Health, NHS Outcomes Framework 2014-2015, Nov 2013. Domains 1,2, 3 and 4 https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/256456/NHS_outcomes.pdf

[1]The National Heart Failure Audit April 2012-March 2013. Available from: http://www.hqip.org.uk/assets/NCAPOP-Library/NCAPOP-2013-14/UCL-HF-2013-Report-2013-ONLINE-v2.pdf

Appendix C

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Sacubitril valsartan for treating chronic heart failure [ID822]

Matrix of consultees and commentators

Consultees	**Commentators (no right to submit or appeal)**
Company • Novartis (Sacubitril valsartan) Patient/carer groups • Afiya Trust • Atrial Fibrillation Association • Arrhythmia Alliance • Black Health Agency • Blood Pressure UK • British Cardiac Patients Association • Cardiac Risk in the Young • Cardiomyopathy Association • Cardiovascular Care Partnership • Equalities National Council • HEART UK • Muslim Council of Britain • Network of Sikh Organisations • Pumping Marvellous Foundation • Somerville Foundation • South Asian Health Foundation • Specialised Healthcare Alliance Professional groups • British Association for Nursing in Cardiovascular Care • British Cardiovascular Intervention Society • British Cardiovascular Society • British Geriatrics Society • British Heart Foundation • British Heart Rhythm Society • British Hypertension Society • British Nuclear Cardiology Society • British Society of Cardiovascular Imaging	General • Allied Health Professionals Federation • Board of Community Health Councils in Wales • British Cardiovascular Industry Association • British National Formulary • Care Quality Commission • Department of Health, Social Services and Public Safety for Northern Ireland • Healthcare Improvement Scotland • Medicines and Healthcare products Regulatory Agency • National Association of Primary Care • National Pharmacy Association • NHS Alliance • NHS Commercial Medicines Unit • NHS Confederation • Scottish Medicines Consortium Possible comparator companies • AbbVie (eprosartan) • Actavis UK (candesartan, losartan potassium, lisinopril, telmisartan, valsartan) • Accord healthcare (losartan, irbesartan) • AstraZeneca (lisinopril) • Aurobindo Pharma-Milpharm (losartan, irbesartan, lisinopril, enalapril maleate) • Bayer (telmisartan) • Boehringer Ingelheim (telmisartan) • Bristol laboratories (captopril, losartan, lisinopril) • Bristol-Myers Squibb (captopril) • Daiichi Sankyo (olmesartan) • Dexcel pharma (losartan)

Consultees	**Commentators (no right to submit or appeal)**
• British Society for Heart Failure • British Thoracic Society • College of Emergency Medicine • Royal College of General Practitioners • Royal College of Nursing • Royal College of Pathologists • Royal College of Physicians • Royal Pharmaceutical Society • Royal Society of Medicine • Society for Cardiological Science & Technology • Society for Vascular Nurses • Society for Vascular Technology • UK Health Forum • UK Clinical Pharmacy Association • Vascular Society of Great Britain and Ireland <u>Others</u> • Department of Health • NHS Doncaster CCG • NHS England • NHS Surrey Heath CCG • Welsh Government	• Martindale Pharma (captopril) • Merck Sharpe Dohme (enalapril maleate, losartan potassium, lisinopril) • Mylan (losartan, quinapril, valsartan) • Pfizer (losartan, quinapril) • Sanofi (captopril, irbesartan, ramipril) • Servier (perindopril arginine) • Takeda (azilsartan, candesartan cilexetil) • Teva (candesartan, losartan, lisinopril, quinapril, telmisartan, valsartan) • Wockhardt (losartan) <u>Relevant research groups</u> • <u>Antithrombotic Trialists' (ATT) Collaboration</u> • British Society for Cardiovascular Research • Cardiac and Cardiology Research Dept, Barts • Central Cardiac Audit Database • Cochrane Heart Group • Cochrane Peripheral Vascular Diseases Group • European Council for Cardiovascular Research • MRC Clinical Trials Unit • National Centre for Cardiovascular Preventions and Outcomes • National Heart Research Fund • National Institute for Health Research • Wellcome Trust <u>Evidence Review Group</u> • BMJ Group • National Institute for Health Research Health Technology Assessment Programme <u>Associated Guideline Groups</u> • National Clinical Guidelines Centre <u>Associated Public Health Groups</u> • Public Health England • Public Health Wales

Appendix C

NICE is committed to promoting equality, eliminating unlawful discrimination and fostering good relations between people who share a protected characteristic and those who do not. Please let us know if we have missed any important organisations from the lists in the matrix, and which organisations we should include that have a particular focus on relevant equality issues.

PTO FOR DEFINITIONS OF CONSULTEES AND COMMENTATORS

Definitions:

Consultees

Organisations that accept an invitation to participate in the appraisal; the company that markets the technology; national professional organisations; national patient organisations; the Department of Health and the Welsh Government and relevant NHS organisations in England.

The company that markets the technology is invited to make an evidence submission, respond to consultations, nominate clinical specialists and has the right to appeal against the Final Appraisal Determination (FAD).

All non-company consultees are invited to submit a statement[1], respond to consultations, nominate clinical specialists or patient experts and have the right to appeal against the Final Appraisal Determination (FAD).

Commentators

Organisations that engage in the appraisal process but that are not asked to prepare an evidence submission or statement, are able to respond to consultations and they receive the FAD for information only, without right of appeal. These organisations are: companies that market comparator technologies; Healthcare Improvement Scotland; the relevant National Collaborating Centre (a group commissioned by the Institute to develop clinical guidelines); other related research groups where appropriate (for example, the Medical Research Council [MRC], National Cancer Research Institute); other groups (for example, the NHS Confederation, NHS Alliance and NHS Commercial Medicines Unit, and the *British National Formulary*.

All non-company commentators are invited to nominate clinical specialists or patient experts.

Evidence Review Group (ERG)

An independent academic group commissioned by the National Institute for Health Research (NIHR) Health Technology Assessment Programme (HTA Programme) to assist the Appraisal Committee in reviewing the company evidence submission to the Institute.

[1]Non-company consultees are invited to submit statements relevant to the group they are representing.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Sacubitril Valsartan for Heart Failure with Systolic Dysfunction

[ID822]

Novartis Pharmaceuticals UK Ltd

[17 August 2015]

File name	Version	Contains confidential information	Date
Company submission STA	3.0	Yes	27 November 2015

Instructions for companies

This is the template for submission of evidence to the National Institute for Health and Care Excellence (NICE) as part of the single technology appraisal (STA) process. Please note that the information requirements for submissions are summarised in this template; full details of the requirements for pharmaceuticals and devices are in the user guide.

This submission must not be longer than 250 pages, excluding appendices and the pages covered by this template.

Companies making evidence submissions to NICE should also refer to the NICE guide to the methods of technology appraisal and the NICE guide to the processes of technology appraisal.

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Abbreviations

A	Asian
A&E	Accident and emergency
AA	Aldosterone antagonist
AC	Any cause
ACEi	Angiotensin converting enzyme inhibitor
ACS	Acute coronary syndrome
ADL	Activities of daily living
ADP	Adenosine diphosphate
AE	Adverse event
AF	Atrial fibrillation
AIC	Akaike information criterion
ANCOVA	Analysis of covariance
ARB	Angiotensin II receptor blocker
ARNI	Angiotensin receptor neprilysin inhibitor
[redacted]	[redacted]
AT1	Angiotensin II type-1
BB	Beta blocker
BIC	Bayesian information criterion
bid	Twice daily
BL	Baseline
BMI	Body mass index
BNF	British National Formulary
BNP	B-type natriuretic peptide
BP	Blood pressure
C	Caucasian
CAD	Coronary artery disease
CADTH	Canadian Agency for Drugs and Technologies in Health
CC	Complication and comorbidity
CCS	Clinical composite score
CEA	Cost-effectiveness analysis
CEAC	Cost-effectiveness acceptability curve
CEP	Cost-effectiveness plane

CFB	Change from baseline
CHF	Chronic heart failure
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
Coef	Coefficient
COPD	Chronic obstructive pulmonary disease
CPRD	Clinical Practice Research Datalink
CrI	Credible intervals
CRT	Cardiac resynchronisation therapy
CRT-D	Cardiac resynchronisation therapy defibrillator
CRT-P	Cardiac resynchronisation therapy pacemaker
CSR	Clinical study report
CSS	Clinical summary score
CV	Cardiovascular
DBL	Database lock
df	Degrees of freedom
DIC	Deviance information criterion
DSU	Decision support unit
EAMS	Early access to medicine scheme
ECG	Electrocardiogram
ECHO	Echocardiography
ECHOES	Echocardiographic Heart of England Screening
EF	Ejection fraction
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
EPAR	European Public Assessment Report
ESC	European Society of Cardiology
ESRD	End-stage renal disease
FAS	Full analysis set
FDA	US Food and Drug Administration
GCP	Good clinical practice
GP	General practitioner
H	Hispanic
HD	High dose
HF	Heart failure

HFpEF	Heart failure with preserved ejection fraction
HFrEF	Heart failure with reduced ejection fraction
HFSA	Heart Failure Society of America
Hosp	Hospitalisation
HR	Hazard ratio
HRG	Healthcare Resource Group
HRQoL	Health-related quality of life
HSUV	Health state utility value
HTA	Health Technology Assessment
i.v.	intravenous
IC	Ischaemic cardiomyopathy
ICD	Implantable cardioverter-defibrillator
ICER	Incremental cost-effectiveness ratio
ICU	Intensive care unit
IF	I*f* (“funny” current) channel inhibitor
IQR	Interquartile range
IRR	Incidence rate ratio
ITT	Intention-to-treat
IVRS	Interactive voice response system
KCCQ	Kansas City Cardiomyopathy Questionnaire
LD	Low dose
ll	Log-likelihood*
ll	Lower limit*
LSM	Least squares mean
LV	Left ventricular
LVAD	Left ventricular assist device
LVEF	Left ventricular ejection fraction
LVSD	Left ventricular systolic dysfunction
LYG	Life years gained
MA	Marketing authorisation
MD	Medium dose
MeSH	Medical subject headings
MHRA	Medicines and Healthcare products Regulatory Agency
MI	Myocardial infarction
MTP	Multiple testing procedure

NA	Not applicable
NB	Negative binomial
NHS	National Health Service
NHS-EED	NHS Economic Evaluation Database
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
NOAC	Novel oral anticoagulant
NR	Not reported
NT-proBNP	N-terminal pro-brain natriuretic peptide
NYHA	New York Heart Association
O	Other
Obs	Observations
OD	Once daily
OECD	Organisation for economic co-operation and development
OR	Odds ratio
P	Probability
PARADIGM-HF	Prospective comparison of ARNI with ACEi to Determine Impact on Global Mortality and morbidity in Heart Failure
PBAC	Pharmaceutical Benefits Advisory Committee
PbR	Payment by results
PCI	Percutaneous coronary intervention
PDE-5	Phosphodiesterase-5
PIM	Promising Innovative Medicine
PK	Pharmacokinetics
PLBO	Placebo
PP	Per protocol
PSA	Probabilistic sensitivity analysis
PSS	Personalised social services
PSSRU	Personal Social Services Research Unit
QALY(s)	Quality adjusted life year(s)
QoL	Quality of life
RAAS	Renin angiotensin aldosterone system
RCT	Randomised controlled trial
RePEc	Research Papers in Economics
RR	Relative risk

SAE	Serious adverse event
SAF	Safety population
SAP	Statistical analysis plan
SBP	Systolic blood pressure
SD	Standard deviation
SE	Standard error
SG	Standard gamble
SIGN	Scottish Intercollegiate Guidelines Network
SmPC	Summary of product characteristics
SMC	Scottish Medicine Consortium
SMQ	Standardised MedDRA query
SR	Systematic review
STA	Single technology appraisal
TA	Technology appraisal
TIA	Transient ischaemic attack
TTO	Time trade off
ul	Upper limit
VAS	Visual analogue scale
W	White
WHO	World Health Organization

* Specified in tables where used which abbreviation applies

1 Executive summary

1.1 *Background and context*

1.1.1 *Heart Failure*

Heart failure (HF) is a complex clinical syndrome in which the heart fails to pump enough blood to meet the body's demands. Approximately 550,000 people in the UK are living with HF (1). Heart failure is associated with poor survival rates, frequent hospitalisations and a significant reduction in quality of life (2, 3). Approximately 50% of patients with HF die within five years of diagnosis and nearly one in six patients with HF die within 30 days of admission or 30 days post discharge (10.8% and 6.4% respectively) (3). In relation to other disease areas, a recent study demonstrated that a first admission for HF is associated with lower survival rates compared with some common types of cancer (e.g. prostate cancer in men and breast cancer in women) (4). The progression of HF is characterised by deterioration in symptoms, which leads to repeated hospitalisations and death. HF imposes a significant burden on individuals, families, and the health services (5). The most commonly recognised type of HF is HF with reduced left ventricular ejection fraction (LVEF; 72% of HF patients have LVEF) (6). This is also referred to as HF with reduced ejection fraction (HFrEF).

1.1.2 *Current Care Pathway*

The current first-line treatment for the management of HFrEF in England is an angiotensin converting enzyme inhibitor (ACEi) in combination with a beta blocker (BB). In case of insufficient efficacy, an aldosterone antagonist (AA) may be added. An angiotensin II receptor blocker (ARB) may be substituted in case of ACEi intolerance (7). Despite the widespread use of these existing treatment options (in greater than 90% of patients) HF remains a progressive syndrome with a high mortality rate, frequent hospitalisations (6) and with an unmet need for new therapies to improve health outcomes.

1.2 *Statement of the decision problem*

The decision problem addressed in this submission is largely in line with the scope issued by NICE (National Institute for Health and Care Excellence). The key difference is that the scope states systolic dysfunction while in this submission we consider patients with HFrEF. This is aligned with the population in the pivotal Phase III trial (PARADIGM-HF, see Table 1) as well as the anticipated marketing authorisation and population for which clinicians would prescribe sacubitril valsartan. Table 1 provides an overview of the decision problem addressed in this submission in relation to the scope.

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	People with chronic HF (New York Heart Association [NYHA] class II-IV) with systolic dysfunction	People with symptomatic HF (NYHA II-IV) with reduced LVEF, referred to as patients with HFrEF	Aligned with population from PARADIGM-HF pivotal trial– primary evidence source in submission and anticipated license.
Intervention	Sacubitril valsartan in combination with standard care (including treatment with a BB and an AA)	Sacubitril valsartan in combination with standard care (including treatment with a BB and an AA)	Same as final NICE scope
Comparator(s)	ACEi in combination with standard care ARB in combination with standard care (for people in whom an ACEi is unsuitable) Standard care includes treatment with a BB and an AA	ACEi in combination with standard care ARB in combination with standard care (for people in whom an ACEi is unsuitable) Standard care includes treatment with a BB and an AA	Same as final NICE scope
Outcomes	• Symptoms of HF • Hospitalisation for HF • All-cause hospitalisation • Mortality • Cardiovascular (CV) mortality • Adverse effects of treatment • Health-related quality of life (HRQoL)	• Symptoms of HF • Hospitalisation for HF • All-cause hospitalisation • Mortality • CV mortality • Adverse effects of treatment • HRQoL	Same as final NICE scope
Economic analysis	The cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year	The cost effectiveness of treatments is expressed in incremental cost per quality-adjusted life year	Same as final NICE scope
	The time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared	The time horizon for estimating clinical and cost effectiveness is lifetime	
	Costs will be considered from an NHS and Personal Social Services perspective	Costs are considered from an NHS and Personal Social Services perspective	

	Standard care includes treatment with a beta blocker and an aldosterone antagonist	Standard care includes treatment with a beta blocker and an aldosterone antagonist	
	The cost of background therapies, such as diuretics, should also be included in cost effectiveness analyses	The costs of background therapies, such as diuretics, are included in cost effectiveness analyses	
Subgroups to be considered	Not specified	The PARADIGM-HF study demonstrates consistently superior clinical endpoints (primary and secondary) for sacubitril valsartan compared with ACEi across all pre-specified trial sub-groups (Section 4.8). Cost-effectiveness is determined by absolute benefit, and as such the incremental cost-effectiveness ratio (ICER) may be expected to vary across subgroups – this has been explored and the impact on the ICER is minimal (Section 5.9).	Not specified in final NICE scope
Special considerations including issues related to equity or equality	Not specified	No equality issues identified	Not specified in final NICE scope

Abbreviations: AA, aldosterone antagonist; ACEi, Angiotensin converting enzyme inhibitor; ARB, Angiotensin II receptor blocker; BB, beta blocker; CV, cardiovascular; HF, heart failure; HFrEF, HF with reduced ejection fraction; HRQoL, health-related quality of life; ICER, incremental cost-effectiveness ratio; LVEF, left ventricular ejection fraction; MA, marketing authorisation; NHS, national health service ; NICE, National Institute for Health and Care Excellence; NYHA, New York Heart Association; SAP, statistical analysis plan

1.3 *Description of the technology being appraised*

Table 2: Technology being appraised

UK approved name and brand name	Sacubitril valsartan (previously known as LCZ696) Brand name is to be confirmed.
Marketing authorisation/CE mark status	The Committee for Medicinal Products for Human Use (CHMP) has granted accelerated assessment to sacubitril valsartan. CHMP opinion was received on 24 September 2015. An EMA (European Medicines Agency) decision on marketing authorisation is therefore expected in December 2015.
Indications and any restriction(s) as described in the summary of product characteristics	The anticipated indication for sacubitril valsartan is to reduce the risk of cardiovascular mortality and morbidity in adult patients with symptomatic heart failure and reduced ejection fraction. Contraindications are: • Hypersensitivity to the active substance, sacubitril, valsartan, or to any of the excipients listed • Concomitant use with ACEi. Sacubitril valsartan must not be administered until 36 hours after discontinuing ACEi therapy • Known history of angioedema related to previous ACEi or ARB therapy • Concomitant use with aliskiren-containing products in patients with diabetes mellitus or in patients with renal impairment (eGFR <60 ml/min/1.73 m^2) • Severe hepatic impairment, biliary cirrhosis and cholestasis • Pregnancy.
Method of administration and dosage	Oral administration. The recommended starting dose, for patients previously treated with an ACEi or ARB is 100 mg twice daily titrating up to a target maintenance dose of 200 mg twice daily after 2-4 weeks. For patients not currently taking an ACEi or ARB, and those previously taking low doses of these agents, a starting dose of 50mg twice daily is recommended doubling the dose every 2-4 weeks up to the target maintenance dose of 200mg twice daily.

Abbreviations: ACEi, Angiotensin converting enzyme inhibitor; ARB, Angiotensin II receptor blocker; CHMP, Committee for Medicinal Products for Human Use; eGFR, estimated glomerular filtration rate; EMA, European Medicines Agency.

1.4 *Summary of the clinical effectiveness analysis*

In this submission, sacubitril valsartan in combination with standard care (including beta blockers and aldosterone antagonists) is being positioned to replace current first-line treatment (ACEis in combination with standard care) in patients with HFrEF. This is based on the overwhelming clinical benefit sacubitril valsartan demonstrated versus the ACEi enalapril at a dose shown to reduce mortality (8, 9) in the pivotal head-to-head randomised active-controlled Phase III trial PARADIGM-HF (10).

The PARADIGM-HF study (n=8,399), the largest HF study ever conducted, evaluated the efficacy of sacubitril valsartan compared with the ACEi enalapril (both in combination with standard care (10)). PARADIGM-HF included a run-in phase to ensure an acceptable safety profile of the study drugs at target doses, for enalapril this was a dose that has been demonstrated to reduce mortality in HF patients (8, 9). Enalapril was chosen as a comparator because it is the ACEi that has been studied in the largest

number of trials with HFrEF patients (8, 9). The proportion of patients on various HF standard care and background therapies was reflective of English clinical practice. Patient characteristics in PARADIGM-HF were mostly reflective of the English HF population. However, patients were, on average, younger than the average patients in England (approximately 65 versus 75 years) and more patients were male. However, in PARADIGM-HF, 49% of patients were ≥65 years of age (n=4120) and 18.6% of patients were ≥75 years of age (n=1563) with the oldest patient aged 96 at randomisation (11), and 21.8% (n=1,832) were female (10). The PARADIGM-HF study was terminated early due to the compelling efficacy; sacubitril valsartan demonstrated superior clinical benefit in reducing mortality, hospitalisation and HF symptom progression over enalapril at a dose previously demonstrated to reduce mortality.

Primary outcome

- The composite primary outcome, as well as its individual components, significantly favoured sacubitril valsartan over enalapril (10)
    - Hazard ratio (HR) for death from CV causes or first hospitalisation for worsening HF was 0.80 (95% confidence interval [CI] 0.73–0.87), p<0.001 (20% reduction)
    - Sacubitril valsartan significantly reduced the risk of mortality from CV causes by 20% (HR 0.80 (0.71–0.89), p<0.001)
    - Sacubitril valsartan significantly reduced the risk of first hospitalisation for worsening HF by 21% (HR 0.79 (0.71–0.89), p<0.001)

Secondary outcomes

- There was a significant reduction in all-cause mortality with sacubitril valsartan compared with enalapril (HR 0.84; 95% CI, 0.76 to 0.93, p<0.001; 16% reduction)
- HF symptoms and physical limitations were measured by the mean change from baseline (CFB) to Month 8 in the Kansas City Cardiomyopathy Questionnaire (KCCQ) clinical summary score (CSS)
    - Sacubitril valsartan was superior to enalapril with a reduction of 2.99 ±0.36 points versus reduction of 4.63 ±0.36 points with enalapril (between-group difference, 1.64 points; 95% CI, 0.63 to 2.65, p=0.001) (10)

The superior outcomes for sacubitril valsartan compared with enalapril were consistent across all subgroups, including subgroup analysis of older patients (patients over 75 years). In addition, exploratory outcomes were aligned with the primary and secondary endpoints, demonstrating superiority of sacubitril valsartan over enalapril with regards to:

- HRQoL, assessed by total score and individual scores of the sub-domains from the KCCQ and total score of the EQ-5D health questionnaire for health status
- Reduction in all-cause hospitalisation by 12%
- Reduction in CV hospitalisation by 12%
- Reduction in non-CV hospitalisation by 13%

In addition, sacubitril valsartan was associated with a safety profile that is comparable to that of the ACEi enalapril. Due to greater vasodilator effect, treatment with sacubitril valsartan was associated with a higher rate of hypotension. However, there was no

increase in the rate of discontinuation because of possible hypotension-related adverse events. Overall, discontinuations due to adverse events were less frequent in the sacubitril valsartan group compared with the enalapril group (10.7% vs. 12.3% (10)).

As a result of the superior clinical efficacy compared with current first-line treatment in PARADIGM-HF, sacubitril valsartan has been granted accelerated EMA regulatory review, with marketing authorisation anticipated in December 2015. The US Food and Drug Administration (FDA) approved sacubitril valsartan for the treatment of HF on 6th July 2015. Furthermore, sacubitril valsartan has been granted a Promising Innovative Medicine (PIM) designation in the UK and has positive opinion for the Early Access to Medicine Scheme (EAMS) by the Medicines and Healthcare products Regulatory Agency (MHRA). It is the first non-oncology medicine to receive the PIM designation, which recognises medicines likely to offer a major advantage over current therapies used in the UK to treat a particular condition.

A systematic review (SR) and network meta-analysis (NMA) was conducted to inform an indirect comparison versus ARBs, given the lack of head-to-head evidence between sacubitril valsartan and ARBs in the population of interest. The SR identified 108 studies that fitted the inclusion criteria and 64 of these studies were eligible for the NMA. The core NMA (based on data from 28 RCTs) provided comparative evidence on the outcomes of interest (all-cause mortality, CV mortality and all-cause hospitalisations) for input into the economic model. The NMA categorised treatment by class: angiotensin receptor neprilysin inhibitor [ARNI; sacubitril valsartan], ACEi, ARB, or placebo. Trials of 7 different ACEis and 4 different ARBs were included in the core NMA. There was uncertainty associated with the relative treatment effects obtained from the NMA as shown by wide credible intervals. The NMA demonstrated that (12):

- ARBs and ACEis were broadly equivalent.
- Sacubitril valsartan was superior to ARBs with regards to all-cause and CV mortality and broadly equivalent with regards to all-cause hospitalisation outcomes.
- Sacubitril valsartan was superior to ACEis with regards to all-cause and CV mortality and superior with regards to all-cause hospitalisation which is aligned with the results from PARADIGM-HF.

1.5 *Summary of the cost-effectiveness analysis*

An economic evaluation was performed comparing sacubitril valsartan with ACEi (both in combination with standard care, including beta blockers and aldosterone antagonists) in the treatment of individuals with HFrEF, primarily based on data from PARADIGM-HF. A secondary analysis was performed comparing sacubitril valsartan with ARBs, based on indirect evidence from the NMA, given the lack of direct evidence comparing sacubitril valsartan with ARBs in a population with HFrEF. The economic model was structured as a two-state Markov model (with health states defined as alive and dead), with hospitalisation rate, EQ-5D and adverse event rates estimated within the alive health state.

The primary base case analysis (modelling all-cause mortality directly from PARADIGM-HF) shows that sacubitril valsartan is cost-effective for the treatment of HFrEF at a willingness-to-pay threshold of £20,000 per QALY, compared with the evidence-based

dose of ACEis shown to reduce mortality versus placebo in patients with HF (£18,187 per quality-adjusted life year [QALY] gained). This cost-effectiveness result is observed despite all ACEis being generic compounds. A similar result was observed for the alternative analysis (where CV mortality was modelled directly from PARADIGM-HF) in which sacubitril valsartan is also cost-effective at a £20,000 per QALY willingness-to-pay threshold (£16,894 per QALY gained). The secondary comparison of sacubitril valsartan versus ARBs resulted in a cost per QALY gained of £16,753.

The cost-effectiveness findings were robust to changes in most structural assumptions. The only scenarios associated with ICERs over £30,000 per QALY gained were 1) sacubitril valsartan treatment effect assumed to persist for durations of <5 years, which represents a conservative assumption, and 2) modelled time horizon reduced to <5 years, which is not an adequate time horizon to model the costs and benefits associated with a lifelong treatment for a chronic condition.

Deterministic sensitivity analysis suggests that cost-effectiveness is driven principally by reductions in mortality associated with sacubitril valsartan, but also by superior HRQoL and reduction in hospitalisations.

Probabilistic sensitivity analysis demonstrated that the probability of sacubitril valsartan being cost-effective versus ACEi at a £20,000 per QALY threshold is 61% increasing to 93% at £30,000 per QALY. The probabilistic ICER is £18,955 (95% CI: £8,599, £37,222). The probability that sacubitril valsartan is cost-effective versus ARB at a £20,000 per QALY threshold is 56%, and 76% at £30,000 per QALY. The probabilistic ICER is £18,180 (the 95% CI was undefined). There was a higher level of uncertainty associated with the results of the ARB analysis based on the NMA, compared to the treatment effect from the head-to-head ACEi analysis from PARADIGM-HF

Comparisons vs ACEis and ARBs were performed separately, as there is an established hierarchy in the use of ACEi as first-line therapy, and the use of ARBs in patients intolerant to ACEi. As specified in NICE guidelines (CG108 (7)), ARBS are only recommended for patients intolerant to ACEi and are not a substitute for ACEi in the first-line position.

Table 3: Cost-effectiveness results for base case analysis vs. ACEi

Technology (and comparators)	Total costs	Total life years	Total QALYs	Inc. costs	Inc. life years	Inc. QALYs	Inc. cost per QALY
ACEi	£13,286	6.03	4.46	-	-	-	-
Sacubitril valsartan	£20,734	6.51	4.87	£7,448	0.48	0.41	£18,187

Abbreviations: ACEi: Angiotensin converting enzyme inhibitor; inc., incremental; QALY, quality adjusted life year

Table 4: Cost-effectiveness results for base case analysis vs. ARB

Technology (and comparators)	Total costs	Total life years	Total QALYs	Inc. costs	Inc. life years	Inc. QALYs	Inc. cost per QALY
ARB	£12.281	5.89	4.37	-	-	-	-
Sacubitril valsartan	£20,734	6.51	4.87	£8,453	0.62	0.50	£16,753

Abbreviations: ARB, angiotensin receptor blocker; inc., incremental; QALY, quality adjusted life year

Table 5: Cost-effectiveness results for alternative CV mortality analysis vs. ACEi

Technology (and comparators)	Total costs	Total life years	Total QALYs	Inc. costs	Inc. life years	Inc. QALYs	Inc. cost per QALY
ACEi	£14,823	6.73	4.93	-	-	-	-
Sacubitril valsartan	£23,405	7.34	5.44	£8,583	0.62	0.51	£16,894

Abbreviations: ACEi: Angiotensin converting enzyme inhibitor; inc., incremental; QALY, quality adjusted life year

Based on the calculations in the budget impact model, the estimated eligible patient population for sacubitril valsartan in England in 2016 is 227,849 patients with HFrEF. The expected uptake of sacubitril valsartan is [redacted] in 2016 rising to [redacted] by 2020. The key drivers of the budget impact analysis are the cost of sacubitril valsartan and savings incurred by reduction of hospitalisations leading to an estimated net budget impact of [redacted] in 2016 and to [redacted] in 2020. It is estimated that in 2020 alone, based on an uptake of [redacted] in the eligible HF population, sacubitril valsartan would prevent [redacted] CV-related deaths and [redacted] hospitalisations.

In this submission, it has been demonstrated that sacubitril valsartan in combination with standard care is a cost-effective treatment in patients with HFrEF. This is based on an overwhelming mortality, hospitalisation, and HRQoL benefit over the current first-line treatment in England, ACEis, at a dose that has been shown to reduce mortality. These results support sacubitril valsartan replacing ACEi as first-line therapy in patients with HFrEF.

2 The technology

2.1 *Description of technology under assessment*

Sacubitril valsartan (previously known as LCZ696) is an angiotensin receptor neprilysin inhibitor (ARNI), a salt complex comprising two active moieties, sacubitril and valsartan, which have been co-crystallised in a 1:1 molar ratio.

Sacubitril valsartan is a novel first-in-class therapy proposed for the treatment of HFrEF. Following oral administration, sacubitril valsartan dissociates into the pro-drug sacubitril (also known as AHU377), which is further metabolised to the neprilysin inhibitor (LBQ657), and valsartan, an ARB. Sacubitril valsartan has the mechanism of action of an neprilysin inhibitor and an ARB (angiotensin receptor neprilysin inhibitor; ARNI), by simultaneously inhibiting neprilysin via LBQ657 and blocking the angiotensin II type-1 (AT1) receptor via valsartan, resulting in complementary effects on the CV system that are beneficial in HF patients.

Sacubitril valsartan represents a breakthrough in the treatment for patients with symptomatic HF with reduced ejection fraction (HFrEF).

In this submission, the patient population will be referred to as HFrEF, which corresponds to people with symptomatic HF (New York Heart Association [NYHA] class II-IV) with reduced left ventricular ejection fraction (LVEF). In addition, sacubitril valsartan is reviewed in combination with standard care. When referring to standard care, this is defined as beta blockers (BB) and aldosterone antagonists (AA). Additionally, when referring to first line treatment, this is defined as ACEi in combination with standard care. When referring to background medication, this is defined as any of the following: diuretics, digoxin, anticoagulants, aspirin, adenosine diphosphate (ADP) antagonists and lipid lowering medications.

2.2 *Marketing authorisation/CE marking and health technology assessment*

2.2.1 *Indicate whether the technology has a UK marketing authorisation/CE marking for the indications detailed in this submission. If so, give the date on which this was received. If not, state the current UK regulatory status, with relevant dates (for example, date of application and/or expected date of approval from the Committee for Human Medicinal Products).*

The marketing authorisation application for sacubitril valsartan was submitted on 16 December 2014. The CHMP has granted accelerated assessment to sacubitril valsartan. An EMA decision on marketing authorisation is expected in December 2015.

2.2.2 ***Give the (anticipated) indication(s) in the UK. For devices, provide the date of (anticipated) CE marking, including the indication for use. If a submission is based on the company's proposed or anticipated marketing authorisation, the company must advise NICE immediately of any variation between the anticipated and the final marketing authorisation approved by the regulatory authorities.***

The anticipated indication for sacubitril valsartan is in adult patients with symptomatic heart failure and reduced ejection fraction.

2.2.3 ***Summarise any (anticipated) restrictions or contraindications that are likely to be included in the (draft) summary of product characteristics (SmPC).***

The contraindication in the draft SmPC are:

- Hypersensitivity to the active substance, sacubitril, valsartan, or to any of the excipients listed
- Concomitant use with ACEi. Sacubitril valsartan must not be administered until 36 hours after discontinuing ACEi therapy
- Known history of angioedema related to previous ACEi or ARB therapy
- Concomitant use with aliskiren-containing products in patients with diabetes mellitus or in patients with renal impairment (eGFR <60 ml/min/1.73 m^2)
- Severe hepatic impairment, biliary cirrhosis and cholestasis
- Pregnancy.

2.2.4 ***Include the (draft) SmPC for pharmaceuticals or information for use (IFU) for devices in an appendix.***

Please see Section 8.1.1 (Appendix 1).

2.2.5 ***Provide the (draft) assessment report produced by the regulatory authorities (that is, the European public assessment report for pharmaceuticals) and a (draft) technical manual for devices in an appendix.***

Please see Section 8.1.2 (Appendix 1).

2.2.6 ***Summarise the main issues discussed by the regulatory authorities (preferably by referring to the [draft] assessment report [for example, the European public assessment report]). State any special conditions attached to the marketing authorisation (for example, if it is a conditional marketing authorisation).***

Not applicable at this time as the European Public Assessment Report (EPAR) is still in development.

2.2.7 ***If the technology has not been launched, supply the anticipated date of availability in the UK.***

Sacubitril valsartan will be available in the UK in January 2016.

2.2.8 *State whether the technology has regulatory approval outside the UK. If so, please provide details.*

The FDA assigned priority review designation for sacubitril valsartan and approved it for the treatment of HF in July 2015.

2.2.9 *State whether the technology is subject to any other health technology assessment in the UK. If so, give the timescale for completion.*

Sacubitril valsartan has been submitted for review by SMC in October 2015, , with guidance estimated to be published in March 2016.

2.3 *Administration and costs of the technology*

Table 6: Costs of the technology being appraised

	Details/cost	Source
Pharmaceutical formulation	Each 50 mg film-coated tablet contains 24 mg of sacubitril and 26 mg of valsartan. Each 100 mg film-coated tablet contains 49 mg of sacubitril and 51 mg of valsartan. Each 200 mg film-coated tablet contains 97 mg of sacubitril and 103 mg of valsartan.	SmPC (Section 8.1.1)
Acquisition cost (excluding VAT)	List price 50mg, 28 pack: £45,78 100mg, 28 pack: £ 45.78 100mg, 56 pack: £91.56 200mg, 56 pack: £91.56	Novartis confidential information
Method of administration	Oral administration, with or without food.	SmPC (Section 8.1.1)
Doses	The recommended starting dose is 100 mg twice daily. A starting dose of 50 mg twice daily is recommended for patients not currently taking an ACEi or an ARB, or on low doses of these agents. The dose is to be doubled every 2-4 weeks to the target of 200 mg twice daily, as tolerated by the patient.	SmPC (Section 8.1.1)
Dosing frequency	Twice daily	SmPC (Section 8.1.1)
Average length of a course of treatment	Lifelong	The condition is chronic
Average cost of a course of treatment	Average annual treatment cost is £1194.37	
Anticipated average interval between courses of treatments	NA	
Anticipated number of repeat courses of treatments	NA	
Dose adjustments	If patients experience tolerability issues (symptomatic hypotension, hyperkalaemia and renal dysfunction) consideration should be given to adjustment of concomitant medications, or to temporary down-titration of sacubitril valsartan.	SmPC (Section 8.1.1)
Anticipated care setting	Home	–

Abbreviations: ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; NA, not applicable; SmPC, summary of product characteristics.

2.3.1 *Provide details of any patient access scheme that has been referred to NICE for inclusion in the technology appraisal by ministers and formally agreed by the company with the Department of Health before the date of evidence submission to NICE for the technology.*

No patient access scheme has been submitted for sacubitril valsartan.

2.4 *Changes in service provision and management*

2.4.1 *State whether additional tests or investigations are needed (for example, diagnostic tests to identify the population for whom the technology is indicated in the marketing authorisation) or whether there are particular administration requirements for the technology.*

No additional tests or investigations are needed for sacubitril valsartan.

2.4.2 *Identify the main resource use to the NHS associated with the technology being appraised. Describe the location or setting of care (that is, primary and/ or secondary care, commissioned by NHS England specialised services and/or clinical commissioning groups), staff costs, administration costs, monitoring and tests. Provide details of data sources used to inform resource estimates and values.*

When initiating sacubitril valsartan in patients previously treated with ACEi or ARB, one titration visit with either a General Practitioner (GP) (£35 per visit (13)), cardiologist (£130.86 per visit (14)) or HF specialist nurse (£33 per visit (13)) will be required (to the target dose of 200 mg) as patients would be initiated on 100 mg. In newly diagnosed patients, titration may require two visits, to titrate patients from 50 mg to100 mg and then from 100 mg to the 200 mg target dose (15).

As part of current standard practice initiation of ACEi or ARB treatment requires titration and this cost should therefore not be considered incremental for sacubitril valsartan over and above standard care provided with ACEi or ARB treatment.

No additional tests or monitoring are required with sacubitril valsartan above those that are already part of current clinical practice. Therefore, it is anticipated that no further additional NHS resources will be required.

Sacubitril valsartan is used in the home setting and will be commissioned by clinical commissioning groups.

2.4.3 *Specify if the technology requires additional infrastructure in the NHS to be put in place.*

No additional NHS infrastructure is required to accommodate sacubitril valsartan.

2.4.4 *State if and to what extent the technology will affect patient monitoring compared with established clinical practice in England.*

No effect on patient monitoring is expected above that which is already established in current clinical practice.

2.4.5 *State whether there are any concomitant therapies specified in the marketing authorisation or used in the key clinical trials (for example, for managing adverse reactions) administered with the technology.*

There are no concomitant therapies specified in the marketing authorisation or SmPC. Patients in both the sacubitril valsartan and enalapril arms of PARADIGM-HF received standard care and background medications (see Section 4.3.1, Table 11), in line with NICE clinical guidelines (7) and current clinical practice (16).

2.5 *Innovation*

Sacubitril valsartan is a salt complex of co-crystallised valsartan (an ARB) and sacubitril (a prodrug, which is metabolised to a neprilysin inhibitor). This salt complex is novel in the treatment of HF and has a unique mode of action (see Section 2.1).

Sacubitril valsartan is intended to be used as a first-line treatment, replacing ACEi, for patients with HFrEF. As demonstrated in the pivotal clinical trial PARADIGM-HF, sacubitril valsartan represents a breakthrough in the treatment of HF, offering patients an overwhelming mortality, hospitalisation, and HRQoL benefit compared with the current first-line treatment ACEi. This is the first time in over a decade, since the introduction of aldosterone antagonists, that a new first-line treatment for HF offers significant benefits over the current standard of care.

Sacubitril valsartan has been granted a PIM designation and a positive opinion for the EAMS in the UK by the MHRA, making it the first non-oncology medicine and only CV medicine to receive the PIM distinction. The EMA has also granted accelerated assessment to sacubitril valsartan.

3 Health condition and position of the technology in the treatment pathway

3.1 *Provide a brief overview of the disease or condition for which the technology is being used. Include details of the underlying course of the disease.*

Heart failure is a complex clinical syndrome in which the heart fails to pump enough blood to meet the body's demands. The global prevalence of HF is over 23 million and represents a major public health issue (17), with an estimated one in five individuals developing HF in their lifetime (17). There are approximately 550,000 patients in the UK who suffer from HF (1). The most commonly recognised and studied type of HF is caused by compromised systolic heart function and is characterised by reduced LVEF termed HFrEF. HFrEF is due to the left ventricle losing its ability to contract normally.

Heart failure is associated with poor survival rates, repeated hospitalisations (3) and a significant reduction in quality of life compared with the general population (2, 3). Approximately 50% of patients with HF will die within five years of diagnosis (3). One-year mortality estimates for patients from England diagnosed with HF vary, ranging from 9% (18) to 38% (19). Heart failure imposes a significant burden on individuals, families, and healthcare systems, and patients with HF experience higher rates of disability, geriatric conditions, and nursing home admissions (5). Typical symptoms of chronic HF include breathlessness, orthopnoea, paroxysmal nocturnal dyspnoea, reduced exercise tolerance, fatigue, tiredness, increased time to recover after exercise and ankle swelling (20). The course of HF includes deterioration in symptoms, which leads to repeated hospitalisations for acute decompensations, and eventually death from progressive pump failure (21).

Heart failure related hospital admissions are projected to rise by 50% over the next 25 years – largely as a result of the ageing population (7). Patients with HF are also at high risk of sudden (usually arrhythmic) death at any time during the course of their illness. Despite a decline of the age-adjusted hospitalisation rate at 1–1.5% per annum since 1992/93 (22) improving implementation of NICE clinical guidelines and recommended HF treatment options over the past five years, mortality and hospitalisation rates are still high among patients, indicating an unmet need in the management of HF in England (6).

Patients

Heart failure is associated with poor survival rates (3), and lower survival compared with some common types of cancer (e.g. prostate cancer in men and breast cancer in women) (4). Patients also suffer from a significant reduction in HRQoL and significantly increased hospitalisations compared with the general population (2, 3). Compared with subjects without HF, HF patients experience significant impairment with regard to activities of daily living (ADL) (5). A study of >500 English HF patients indicates that breathlessness and/or fatigue are common, followed by chest pain, nausea, sleep disruption, and confusion (23). In addition to disease severity and comorbidities reducing HRQoL for patients with HF (23), it may be further decreased by low socioeconomic status and the lack of informal care (24). Patients with HF also experience significantly higher rates of disability, geriatric conditions, and nursing home admissions (compared

with people without HF) (5). [redacted]

Carers

Although data are scarce, it is assumed that the majority of HF patients are cared for by their partner or a family member (26). Due to the chronic nature of the condition and the often complex treatment regimen (especially when there are comorbidities), the involvement of a family member in care is considered essential. Caregivers' quality of life (QoL) has been shown to be dependent on patient-related factors, like symptom severity or comorbidities (24). Male caregivers tend to have a QoL comparable to men living with a healthy partner, whereas female carers of HF patients show reduced QoL compared with controls (27). Although many caregivers feel positive about their role (28), the impact on their physical and mental wellbeing should not be underestimated (26, 28). [redacted]

Society

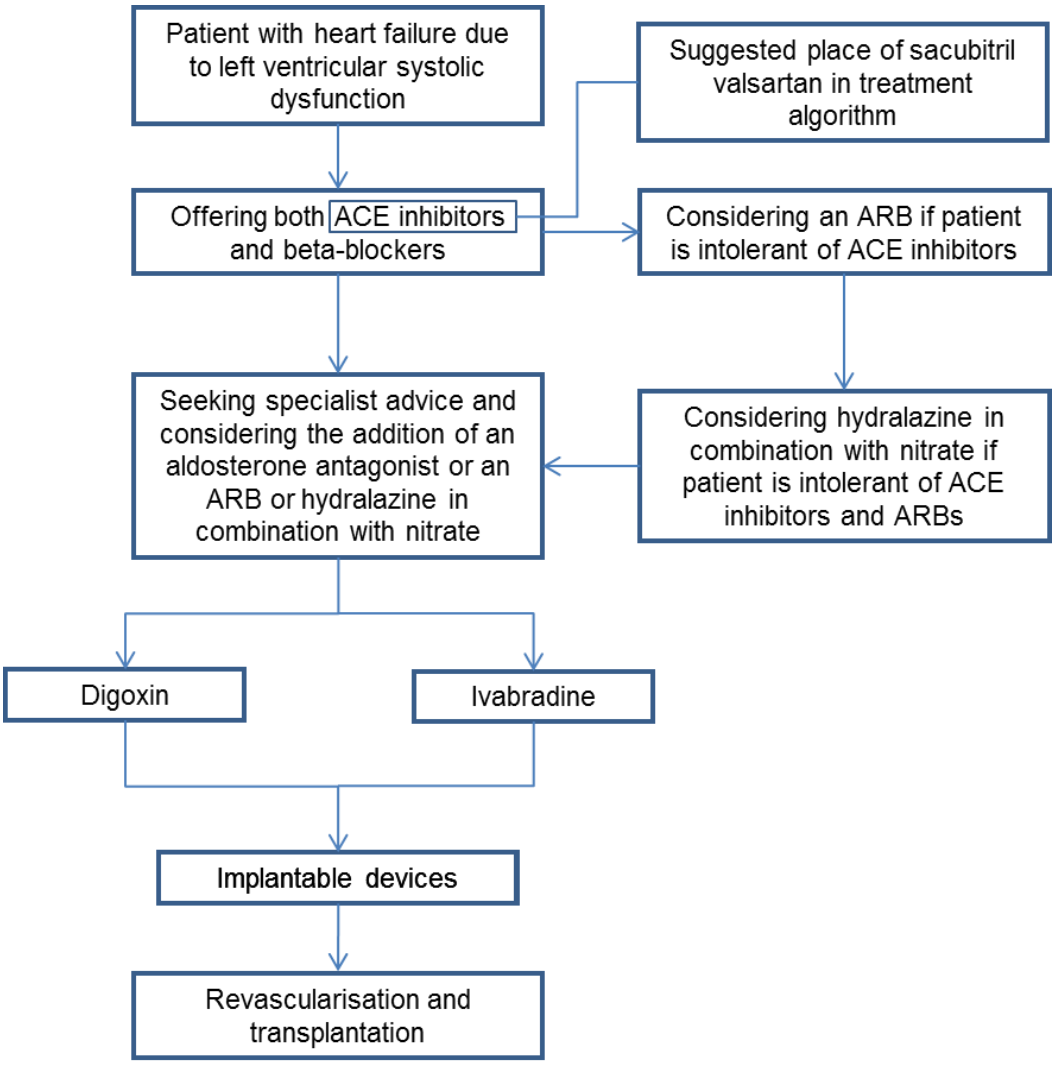
The direct cost burden of HF to society consists of GP and cardiology outpatient visits and hospital admissions based on Scottish data (29), no English data was identified in published literature. An estimate from NICE indicates that the NHS spends approximately 2% of its total budget on HF (approximately £2.3 billion); 70% of this is due to hospitalisation (30). Globally, indirect costs of HF to society are caused by informal (i.e. unpaid) care costs, premature mortality and lost productivity (31) and have been estimated to account for approximately 40% of the total costs of HF (31). [redacted]

3.2 *Present the clinical pathway of care that shows the context of the proposed use of the technology.*

The NICE chronic heart failure (CHF) clinical guideline specifies that patients with HFrEF should be offered both ACEis and beta blockers first line. In case of intolerance to treatment with ACEi, an ARB can be considered, or, in case of ARB contraindication, hydralazine in combination with nitrate. In case of insufficient efficacy, an aldosterone antagonist may be added to existing therapy, before digoxin or ivabradine are considered (Figure 1) (7).

Evidence from the PARADIGM-HF trial supports the position of sacubitril valsartan as a first-line treatment for patients with HFrEF. Sacubitril valsartan demonstrates significant improvements in mortality and hospitalisation outcomes compared with optimal doses of the current first-line treatment, ACEi. Both treatments were used in combination with standard care therapies (e.g. beta blockers and aldosterone antagonists) reflecting clinical guidelines and clinical practice see Section 4.5.2). Therefore patients with HFrEF should be offered sacubitril valsartan as a first-line therapy and as replacement for ACEi.

Figure 1: CHF treatment and monitoring. NICE pathways.



Abbreviations: ACE, angiotensin converting enzyme; ARB, angiotensin II receptor blocker.
Source: NICE (32)

3.3 *Provide information about the life expectancy of people with the disease or condition in England and the source of the data.*

One-year mortality estimates for English patients diagnosed with HF vary, ranging from 9% (18) to 38% (19). In the NICE quality standard on chronic HF, it is stated that 30% to 40% of patients diagnosed with HF die within one year (33). In the ECHOES (Echocardiographic Heart of England Screening) study including 6,162 subjects, recruited from GP practices/hospitals in England, five year mortality was 47.5% (104/219) in the cohort of patients with a diagnosis of HFrEF (mean age of 70.5 years) compared with 9.7% (546/5604) in those patients without a diagnosis of HFrEF (mean age of 63.3 years, (18)). People with HF have an increased risk of death compared to age and sex matched people without HF (HR 1.19 (95% CI 1.06–1.33)), and the risks of death increased with HF symptoms and limitations of physical activity, patients with NYHA II, III or IV class respectively (compared with NYHA I class) were found to be 1.22 (95% CI 1.09–1.35), 1.57 (95% CI 1.35–1.82) and 1.64 (95% CI 1.36–1.97, (18)).

3.4 *Provide details of any relevant NICE guidance, pathways or commissioning guides related to the condition for which the technology is being used. Specify whether any subgroups were explicitly addressed.*

In 2010, NICE published a clinical guideline (CG108) entitled 'Chronic heart failure: Management of chronic heart failure in adults in primary and secondary care' (7). The guideline gives the following recommendations for the treatment of patients with chronic HF:

- Both ACEis and beta blockers should be offered to all patients with HFrEF.
    - If the patient remains symptomatic in spite of ACEi and beta blocker therapy, consider adding an aldosterone antagonist, an ARB or hydralazine in combination with nitrate.
    - Digoxin is recommended for worsening or severe HF with left ventricular systolic dysfunction (LVSD) despite first and second-line treatment.
- In patients with HF due to valve disease, ACEi should not be initiated until the patient has been assessed by a specialist.

In 2012 NICE recommended ivabradine (Procorolan®), a heart-rate-lowering agent, for the treatment of chronic heart failure (TA267) (34).

NICE has also published a care pathway "Chronic heart failure pathway" (Figure 1 (32)), visually outlining the recommended pathway of diagnosis and treatment of patients with chronic HF.

In order to drive quality improvements in the management of chronic HF, NICE has also published a quality standard (33).

3.5 *Provide details of other clinical guidelines (for example, UK guidance from the royal societies or European guidance) and national policies.*

Both the Scottish Intercollegiate Guidelines Network (SIGN) (35) and European Society of Cardiology (ESC) (20) guidelines, of which an overview is presented below, broadly align with NICE guidance on the pharmacological treatment of HF patients.

There are no significant differences between the three guidelines (NICE, SIGN and ESC). In all three cases, sacubitril valsartan is expected to replace ACEi as first-line treatment for patients with HFrEF.

Scottish Intercollegiate Guidelines Network – Management of chronic heart failure (35)

With regard to pharmacological treatments, the SIGN guidelines recommend the following:

- For all patients with HFrEF, irrespective of NYHA functional class
    - ACEis should be considered
    - Beta blocker therapy should be started as soon as their condition is stable
- Patients with HFrEF alone, or HF, reduced ejection fraction or both following myocardial infarction (MI), who are intolerant of ACEis, should be considered for an ARB
- Patients with HFrEF who are still symptomatic despite therapy with an ACEi and a beta blocker may benefit from the addition of candesartan (an ARB), following specialist advice
- Following specialist advice, patients with moderate to severe HFrEF should be considered for spironolactone (an aldosterone antagonist), unless contraindicated by the presence of renal impairment or a high potassium concentration
- Patients who have suffered a MI and with LVEF ≤40% and either diabetes or clinical signs of HF should be considered for eplerenone (an aldosterone antagonist) unless contraindicated by the presence of renal impairment or a high potassium concentration
- Diuretic therapy should be considered for HF patients with dyspnoea or oedema
- Digoxin should be considered as an add-on therapy for HF patients in sinus rhythm who are still symptomatic after optimum therapy
- African-American patients with advanced HFrEF should be considered for treatment with hydralazine and isosorbide dinitrate in addition to standard therapy
- Patients who are intolerant of an ACEi and an ARB due to renal dysfunction or hyperkalaemia should be considered for treatment with a combination of hydralazine and isosorbide dinitrate

ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012 (20)

Briefly, the ESC recommends that all patients receive an ACEi (or an ARB, in case of intolerance to ACEi) in combination with diuretics (to relieve symptoms of congestion). In case of insufficient or no improvement, a beta blocker may then be added, followed by an aldosterone antagonist, if required, and, finally, by ivabradine.

3.6 *Describe any issues relating to current clinical practice, including any variations or uncertainty about established practice.*

Information collected by the National Heart Failure Audit (2013) (6) indicates that, although in-hospital and one-year mortality were reduced since the previous audit (one year earlier), prescription rates for disease-modifying drugs (ACEi/ARB and beta blockers), as recommended by NICE guidelines (7), although very high, could still be improved (i.e. 85% prescribed ACEi and/or ARB (6)).

Overall, although considerable improvements have been made in the management of HF, mortality rates remain variable and relatively high (6). This variation is due to variations in care (6), and could, for example, reflect variations in the availability of HF nurses and access to specialist services (36).

3.7 *Provide an assessment of whether the use of this technology is likely to raise any equality issues.*

No equality issues with sacubitril valsartan have been identified.

4 Clinical effectiveness

Summary

PARADIGM-HF study

Study design and patient characteristics

- The evidence for sacubitril valsartan is obtained from the pivotal head-to-head trial, PARADIGM-HF, comparing sacubitril valsartan with current first-line treatment in England, the ACEi enalapril, both in combination with standard care (including beta blockers and aldosterone antagonists).
- A sequential run-in phase maximised the number of randomised patients able to tolerate the sacubitril valsartan and enalapril target doses and allowed for use of an evidence based dose of enalapril that has been shown to reduce mortality.
- 8,399 randomised patients with LVEF≤40%and NYHA II-IV.
- Inclusion criteria to ensure an adequate event rate:
    - LVEF: An amendment was made from ≤40% to ≤35%
    - B-type natriuretic peptide (BNP): Mildly elevated BNP or N-terminal pro-BNP (NT-proBNP)

Clinical efficacy

- The overwhelmingly significant benefit of sacubitril valsartan compared with first-line ACEi therapy led to the premature termination of PARADIGM-HF
- The composite primary outcome, as well as its individual components and secondary efficacy outcomes, significantly favour sacubitril valsartan over enalapril:
    - Hazard ratio (HR) for death from CV causes or first hospitalisation for worsening HF was 0.80 (95% CI 0.73–0.87), p<0.001 (20% reduction)
    - Sacubitril valsartan reduced the risk of CV mortality, all-cause mortality, first all-cause hospitalisation and first HF hospitalisation in patients with HFrEF compared with enalapril, by 20%, 16%, 12%, 21% respectively.
- In addition, sacubitril valsartan was significantly superior to enalapril with regard to HF symptoms and physical limitations, as measured by KCCQ and NYHA class shift, and HRQoL, measured by EQ-5D and KCCQ.

Clinical safety

- The overall safety profile of sacubitril valsartan is comparable to that of enalapril.
- With sacubitril valsartan fewer patients experienced ≥1 treatment related adverse event (AE), ≥1 serious adverse event (SAE), death or discontinued due to an AE.
- Due to greater vasodilator effect, treatment with sacubitril valsartan was associated with a higher rate of hypotension. However, there was no increase in the rate of discontinuation because of possible hypotension-related adverse effects. In addition, treatment effect was not different in the subgroup analysis of SBP

Conclusion and relevance to English clinical practice

- The magnitude of the advantages of sacubitril valsartan over enalapril was highly statistically significant and clinically meaningful, particularly since sacubitril valsartan was compared with an evidence based dose of enalapril that has been shown to reduce mortality in patients with HF, as compared with placebo.
- The superior outcomes were consistent in all subgroups, which included age, gender, NYHA, LVEF, NT-pro-BNP, and systolic blood pressure (SBP).
- The standard care and background therapies used in PARADIGM-HF are comparable to standard background therapies used in England.
- Compared with the English HFrEF population, subjects in PARADIGM-HF were younger, more likely to be male and distributed into milder NYHA classes.
    - In PARADIGM-HF 49% of patients were ≥65 years of age (n=4120) and 19% of patients were ≥75 years of age (n=1563) with the oldest patient aged 96 at randomisation, and 22% (n=1,832) were female. No difference in treatment effects were seen in subgroup analysis of these patient groups.
- Results demonstrated in PARADIGM-HF support the positioning of sacubitril valsartan as a replacement for first-line therapy for HFrEF patients in England.

TITRATION study

- A randomised, double-blind, parallel group study investigating the safety and tolerability of initiating and up-titrating sacubitril valsartan from 50 mg bid to 200 mg bid over 3-weeks (Condensed) vs. 6-weeks (Conservative) in 498 HFrEF patients
- Patients enrolled were treatment naïve to or receiving varying ACEi/ARB doses (renin angiotensin-aldosterone system [RAAS] inhibition) prior to entering the study
- *Proportion of patients experiencing pre-specified AEs*: the condensed (n=247) and conservative (n=251) treatment regimens showed comparable incidence of AEs. AEs for the RAAS naive (n=33) patients were comparable to other patients in the low RAAS stratum.
- *Treatment success:* 81.1% of all patients achieved treatment success, which was similar for both treatment regimens (condensed and conservative).
- *Tolerability:* 85.2% of all patients tolerated the dosing regimen independent of treatment regimen or ACEi/ARB treatment, including treatment-naive, at baseline.

Conclusion and relevance to English clinical practice

- Contrary to PARADIGM-HF, the TITRATION study included treatment naïve patients. It is anticipated that sacubitril valsartan would be initiated in these patients given the superior clinical effectiveness over enalapril as shown in PARADIGM-HF. The TITRATION study provides evidence of the tolerability and treatment success in these patients.

NMA for comparison against ARBs

- No head-to-head evidence exists for a comparison against ARBs, which are used in cases of ACEi intolerance in England. A SR and NMA were conducted to inform an

indirect comparison.

- Data from 64 RCTs identified in the systematic review were eligible for the NMA. The core NMA (based on data from 28 RCTs) provided comparative evidence on the outcomes of interest (all-cause mortality, CV mortality and all-cause hospitalisations) for input into the economic model. The NMA categorised treatment by class (ARNI [sacubitril valsartan], ACEi, ARB and placebo). Trials of 7 different ACEis and 4 different ARBs were included in the core NMA.
- There was uncertainty associated with the relative treatment effects obtained from the NMA as shown by wide credible intervals.
- The NMA demonstrated that:
  - ARBs and ACEis were broadly equivalent.
  - Sacubitril valsartan was superior to ARBs with regards to all-cause and CV mortality and broadly equivalent with regards to all-cause hospitalisation outcomes.
  - Sacubitril valsartan was superior to ACEis with regards to all-cause and CV mortality and superior with regards to all-cause hospitalisation which is aligned with the results from PARADIGM-HF.

4.1 *Identification and selection of relevant studies*

4.1.1 *Advise whether a search strategy was developed to identify relevant studies for the technology.*

A systematic review was conducted to identify from the published literature:

- Randomised controlled trial (RCT) evidence on the efficacy and safety of sacubitril valsartan and relevant comparators for people with chronic HF (NYHA class II-IV) with reduced LVEF

For RCT evidence, original searches were initially conducted in 2011, covering the period from 2000 to 2011. This was followed by a supplementary search in 2013, covering the period from 1987 to 2000, as well as that from 2011 to 2013 (with an adequate overlap). Two further updates were then performed: one covers the period from July 2013 to September 2014, and the other one in April 2015, covers September 2014 to April 2015. In April 2015, slightly modified (less restrictive) inclusion/exclusion criteria were applied to the search (see Table 7). These criteria were also retrospectively applied to the previous search outputs, resulting in updated, merged search results, covering the period from 1987 to September 2014. Merged search results for all individual searches are presented here.

Search strategy

4.1.2 *Describe the search strategies used to retrieve relevant clinical data.*

Full details of the search are provided in the Appendix, Section 8.2.

Study selection

4.1.3 *Describe the inclusion and exclusion selection criteria, language restrictions and the study selection process in a table.*

Studies identified were initially assessed based on title and abstract. Papers not meeting the inclusion criteria were excluded, and allocated a "reason code" to document the rationale for exclusion. Papers included after this stage were then assessed based on the full text; further papers were excluded, yielding the final data set for inclusion. The final included data set consisted of clinical studies for sacubitril valsartan and those for comparator treatments. The full text of these comparator studies was screened and those suitable for indirect comparison were selected.

Inclusion and exclusion selection criteria (i.e. the revised criteria, applied to the latest update and retrospectively applied to the previous searches) are shown in Table 7.

Table 7: Eligibility criteria used in search strategy for the RCT systematic review

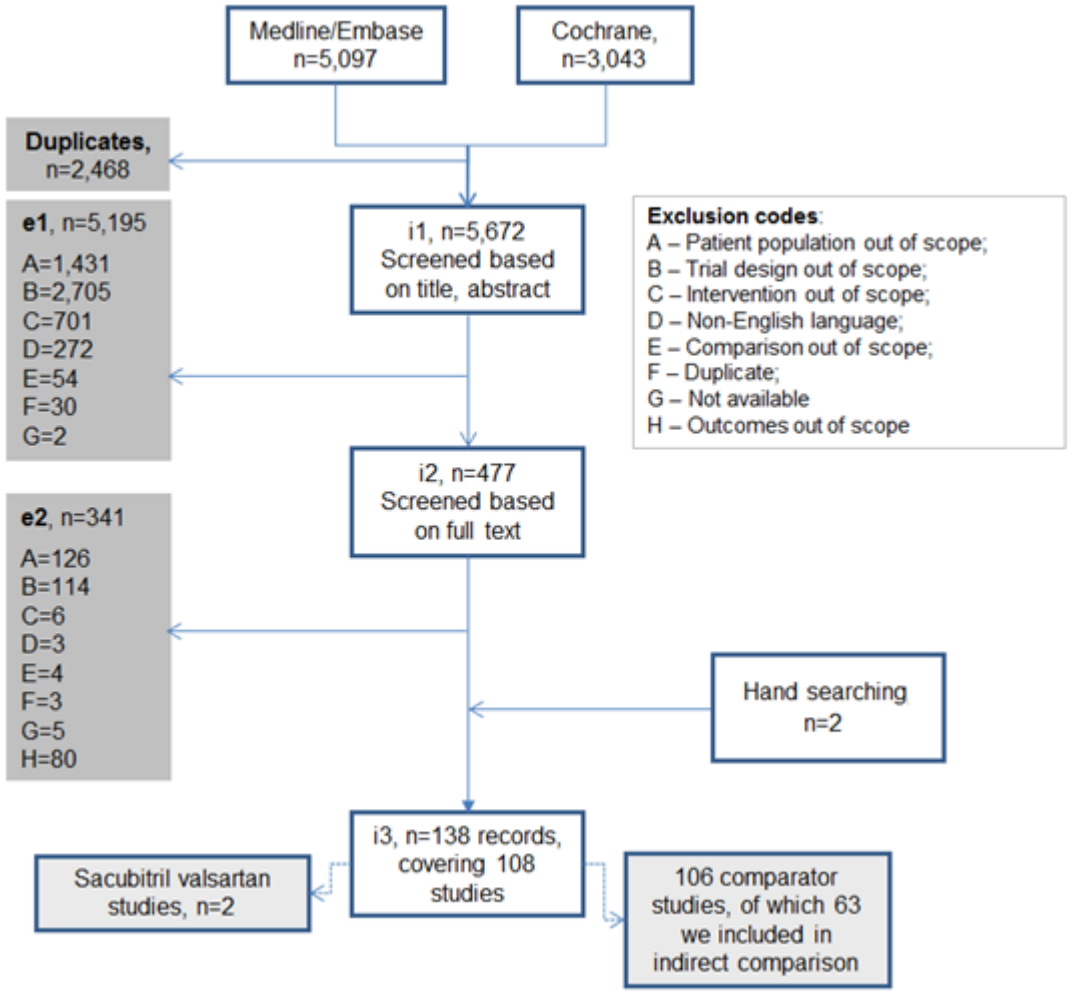
Clinical effectiveness	Inclusion criteria	Exclusion criteria
Population	Adult patients with chronic HFrEF (defined by LVEF below 40-45% or simply reported as "reduced") and NYHA class II-IV	Studies including 100% patient populations with the following characteristics will be excluded: • Acute HF • Non-North American, non-European • NYHA class I • Preserved EF
Interventions	In addition to ARNI [sacubitril valsartan], all guideline recommended treatment classes will be included: ACEi, ARB, BB, AA, and IF channel inhibitors administered alone or in combination.	
Comparators	Comparators of interest are placebo or any active interventions, except interventions limited to different doses or routes of administration of the active agent.	
Outcomes	Outcomes of interest include: • Deaths due to any cause, CV events (or cardiac events), and HF • hospitalisations due to all causes, CV events (or cardiac events), and HF • NYHA class CFB • LVEF CFB • Withdrawals • Withdrawals due to adverse events	
Study design	RCTs (Phase II and III).	Substudies of RCTs providing only prognostic or subgroup data
Language restrictions	English-language publications	Non-English language publications

Abbreviations: AA, aldosterone antagonist; ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; ARNI, angiotensin receptor neprilysin inhibitor; BB, beta blockers; CFB, change from baseline; CV, cardiovascular; EF, ejection fraction; HF, heart failure; HFrEF, HF with reduced ejection fraction; IF, I*f* ("funny" current) channel inhibitor; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; RCT, randomised controlled trial

4.1.4 *A flow diagram of the numbers of studies included and excluded at each stage should be provided using a validated statement for reporting systematic reviews and meta-analyses, such as the PRISMA flow diagram.*

Following assessment and exclusion of studies based on title, abstract and full text, 107 studies (136 publications) were included in the final data set (8-10, 37-169). Of the 107 included studies, one trial (PARADIGM-HF (10, 129) examined the intervention of interest (sacubitril valsartan). The remaining 106 studies reported on comparator interventions that are of relevance to the decision problem. These studies are reported further in Section 4.10. Hand searching identified a further sacubitril valsartan study, named TITRATION (170, 171) (leading to a total of 108 studies and 138 publications). Our search of trial registries identified two relevant clinical trials, which are both currently ongoing. The SR schematic is shown in Figure 2.

Figure 2: Schematic for the systematic review of clinical RCT evidence



4.1.5 *Provide a complete reference list for excluded studies in an appendix.*

Please see Section 8.2.7.

4.2 *List of relevant randomised controlled trials*

4.2.1 *In a table, present the list of relevant RCTs comparing the intervention with other therapies (including placebo) in the relevant patient group. Highlight which studies compare the intervention directly with the appropriate comparator(s) with reference to the decision problem. If there are none, state this. A suggested table format is presented below.*

Table 8 summarise the relevant RCTs conducted for sacubitril valsartan.

In the pivotal PARADIGM-HF trial (see Section 4.7), which compares the efficacy and safety of sacubitril valsartan with that of the ACEi enalapril, sacubitril valsartan has shown superior efficacy and a comparable safety profile. The overwhelming benefit of sacubitril valsartan compared with enalapril led to a premature termination of the trial. It is therefore expected that sacubitril valsartan will replace ACEi as first-line therapy in this patient group and ACEi are considered the most relevant comparator. The HF standard care and background therapies used in PARADIGM-HF reflect English clinical practice (see Sections 4.7 and 3.5).

A further RCT was identified (TITRATION), which provides data in patients naïve to or receiving varying doses of ACEi/ARB, showing that the safety and tolerability of sacubitril valsartan is similar in these patient groups to that in the treatment-experienced patient group of PARADIGM-HF. As the TITRATION study is a safety study, it is summarised in Section 4.12, where the methods as well as the results are reported.

Table 8: The relevant RCTs

Trial no. (acronym)	Population	Intervention	Comparator	Study reference
PARADIGM-HF	Patients with HFrEF	Sacubitril valsartan	Enalapril	Clinical Study Report (11) McMurray et al, 2013 (172) McMurray et al, 2014a (173) McMurray et al, 2014b (10) McMurray et al, 2014c (174) Packer et al, 2015 (129) Desai et al, 2015 (175)
TITRATION	Patients with HFrEF	Sacubitril valsartan (titration regimen 1)	Sacubitril valsartan (titration regimen 2)	Clinical study report (176) Senni et al, 2015a (170) Senni et al, 2015b (171)

Abbreviations: HFrEF, heart failure with reduced ejection fraction

4.2.2 *When the RCTs listed above have been excluded from further discussion, justification should be provided to ensure that the rationale for doing so is transparent. For example, when RCTs have been identified, but there is no access to the level of data required, this should be stated.*

NA

4.3 *Summary of methodology of the relevant randomised controlled trials*

4.3.1 *Provide a comparative summary of the methodology of the RCTs in a table. A suggested table format is presented below.*

- See Figure 3 for a visual representation of the study design of PARADIGM-HF.
- The rationale of the Run-in phase and the choice of ACEi as the comparator are described below.
- Eligibility criteria are summarised in Table 9.
- For details of the outcome measures listed in the PARADIGM-HF trial protocol, see Table 10.
- The detailed methodology of the RCT, PARADIGM-HF (10, 11, 129, 172, 173, 175) is summarised in Table 11.

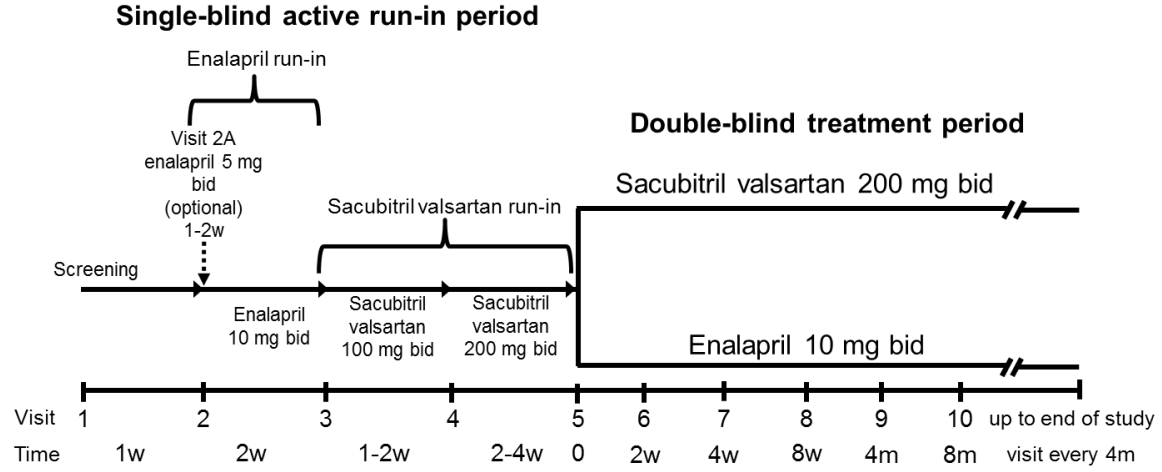
Study design

PARADIGM HF was a randomised, double-blind, parallel group, active controlled, two-arm, event driven trial comparing sacubitril valsartan to enalapril.

The trial comprised four phases (see Figure 3):

1) Screening (for inclusion and exclusion criteria see Table 9)
2) Enalapril run-in phase: two weeks duration, eligible patients were switched from current medication (i.e. ACEi or ARB) to single-blind (patients were blinded) treatment with enalapril (10 mg bid)
3) If no unacceptable side effects occurred, this was followed by a sacubitril valsartan run-in phase: single-blind (patients were blinded) treatment with sacubitril valsartan for 4 to 6 weeks at a dose of 100 mg bid, which was increased to 200 mg bid
    a. The two run-in phases were sequential, with only a brief (approximately 36 hours) washout phase, and both included all eligible patients.
4) Patients who had no unacceptable side effects on the target doses of the two study medications in the run-in phases were randomly assigned in a 1:1 ratio to a double-blind, randomised treatment phase: subjects were randomised to either sacubitril valsartan (200 mg bid) or to enalapril (10 mg bid).

Figure 3: PARADIGM HF study schematic, from McMurray et al, 2013 (172)



Abbreviation: bid, twice daily.

Run-in phase

This sequential design was chosen so that all patients had received enalapril and sacubitril valsartan to ensure an acceptable safety profile of the study drugs at target doses (10). This study design also maximised the number of randomised patients able to tolerate the target dose of both sacubitril valsartan and enalapril during the long-term follow-up period. As a result of including the active run-in period in the study design, it was anticipated that the average dose of enalapril achieved in the long-term randomised follow-up period of this study would be similar to or exceed the evidence-based average dose of 16.6 mg/day, providing head-to-head data of sacubitril valsartan against enalapril at an evidence based dose that has been shown to reduce mortality in patients with HF, compared with placebo (9, 11). Another reason for this design was the lack of Phase II data in this patient population.

ACEi as the comparator

Enalapril was chosen because it is the ACEi that has been studied in the largest number of trials (see systematic review, Section 4.1) of patients with HFrEF and it has well-documented mortality benefits in HF (9). The dose of enalapril was based on an evidence based dose of enalapril demonstrated in clinical trials to reduce mortality in patients with HF, as compared with placebo (9).

The selection of ACEis as a comparator is justified and supported by the following:

- ACEi remains the cornerstone of management of HFrEF. In England, the National Heart Failure Audit (2013) states that 73% of patients discharged for HFrEF are treated with ACEi, while 18% are treated with an ARB (6)[a].

[a] Note, the total population receiving ACEis and/or ARBs is 85% as some patients receive both ACEis and ARBs.

- NICE clinical guidelines recommend ACEi as the first-line therapeutic option in HFrEF (7)

Eligibility criteria

A summary of the key inclusion and exclusion criteria in PARADIGM HF is provided in Table 9. The inclusion criteria for NHYA, LVEF and BNP are summarised below.

  - NYHA: All patients screened at study admittance were NYHA functional class II-IV, however, a small number of patients had an improvement in their NYHA class between screening and randomisation, and so nearly 5% of randomised patients were NYHA class I (10).

- LVEF: An amendment to the study was made to amend the LVEF entry criterion from ≤40% to ≤35%. This modification was essential to ensure an adequate event rate in the study population where use of evidence-based, disease-modifying agents was increasing. 961 patients who were randomised had LVEF >35% (10).
- BNP: Mildly elevated BNP or NT-proBNP was required as an inclusion criterion to ensure that patients enrolled were at risk for CV events in order to ensure a reasonable event incidence rate over the duration of the trial (10). The patient characteristics were similar to those of study populations in other relevant trials and patients in the community (173, 177, 178).

Table 9: Eligibility criteria of the RCTs

PARADIGM-HF	
Key inclusion criteria	**Key exclusion criteria**
• ≥18 years old • NYHA functional class II-IV (some patients had an improvement in NYHA class between screening and randomisation; therefore ≤5% of randomised patients were NYHA class I at baseline, see Table 13) • LVEF ≤35% • Plasma BNP ≥150 pg/mL (or NT-proBNP ≥600 pg/mL) at screening visit or a BNP ≥100 pg/mL (or NT-proBNP ≥400 pg/mL) and a hospitalisation for heart failure within the last 12 months • Stable dose of ACEi or ARB equivalent to enalapril 10 mg/day for ≥4 weeks before screening visit • Stable dose of BB for ≥4 weeks before screening visit (unless contraindicated or not tolerated) • Stable dose of AA for ≥4 weeks before screening visit (if prescribed) • Patients not tolerating enalapril 10 mg bid during the run-in phase were considered run-in failures, did not enter the sacubitril valsartan run-in phase and were withdrawn from the study • Patients not tolerating sacubitril valsartan 200 mg bid during the run-in phase were considered run-in failures and were withdrawn from the study	• Any contraindications to study drugs or other drugs required in the inclusion criteria • History of angioedema • Treatment requirement for both ACEi and ARB • Current acute decompensated HF • Symptomatic hypotension or systolic BP <100 mmHg at Visit 1 or <95 mmHg at Visit 3 or 5 • eGFR <30 mL/min per 1.73 m^2 at Visit 1, 3 or 5 or >35% decline in eGFR between Visit 1 and 3 or 5 • ACS, stroke, TIA, major CV surgery, PCI or carotid angioplasty within 3 months prior to Visit 1 • CAD likely to require surgical or percutaneous intervention within 6 months after Visit 1 • CRT device implanted within 3 months of screening visit or plan to implant • History of/planned heart transplant • History of severe pulmonary disease • Peripartum or chemotherapy induced cardiomyopathy (within 12 months) • Untreated ventricular arrhythmia with syncopal episodes (within 3 months) • Haemodynamically significant obstructive lesions of the LV outflow tract • Any surgical or medical condition which might significantly alter the absorption, distribution, metabolism or excretion of study drugs • Any disease with life expectancy <5 years

Abbreviations: AA, aldosterone antagonist; ACEi, angiotensin converting enzyme inhibitor; ACS, acute coronary syndrome; ARB, angiotensin II receptor blocker; BB, beta blocker; BNP, B-type natriuretic peptide; BP, blood pressure; CAD, coronary artery disease; CRT, cardiac resynchronisation therapy; CV, cardiovascular; eGFR, estimated glomerular filtration rate; HF, heart failure; LV, left ventricular; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; SBP, systolic blood pressure; TIA, transient ischaemic attack.

Table 10: Primary and secondary outcomes of PARADIGM-HF

Primary outcome(s) and measures	Reliability/validity/current use in clinical practice
• A composite of death from CV causes or a first hospitalisation for HF. An Endpoint Adjudication Committee was responsible for classifying all deaths and for determining whether pre-specified endpoint criteria are met for the non-fatal events.	• As CV death and HF hospitalisation both reflect disease-specific endpoints related to progressive worsening of the HF syndrome, they should both be modifiable by treatments that improve this condition. This has generally proved to be the case with both drugs (ACEis, AA, and BB) (20) and devices (CRT) (179). This understanding of HF and its treatment has led to the disease-specific composite outcome of CV death or HF hospitalisation becoming the most commonly used primary endpoint in current HF outcomes trials (78, 151, 180). Importantly, this study is powered sufficiently to detect a reduction in CV mortality.
Secondary outcome(s) and measures	**Reliability/validity/current use in clinical practice**
• Time to death from any cause. • CFB to 8 months in the clinical summary score on the KCCQ (on a scale from 0 to 100, with higher scores indicating fewer symptoms and physical limitations associated with HF). The CSS symptoms and functional limitation. • Time to a new onset of AF. • Time to the first occurrence of a decline in renal function (which was defined as ESRD or as a decrease in the eGFR of at least 50% or a decrease of more than 30 mL/min per 1.73 m^2 from randomisation to <60mL/min per 1.73 m^2).	• Whilst death from CV causes is the most relevant endpoint, it is important to show that sacubitril valsartan does not lead to an increase in deaths from any cause (e.g. an increase in deaths from a certain type of cancer). • The KCCQ is a valid, reliable and responsive health status measure for patients with HF and may serve as a clinically meaningful outcome in CV clinical research, patient management and quality assessment (181). The questionnaire is available in a number of validated translations, which makes it suitable for multinational clinical trial use. • Both AF and ESRD are complications of HF that develop over time. They are associated with their own complications, requiring further treatments/interventions. Delaying the onset of AF or ESRD is therefore likely to reduce resource use and maintain patient QoL.

Abbreviations: AA, aldosterone antagonists; ACEi, angiotensin converting enzyme inhibitor; AF, atrial fibrillation; BB, beta blockers; CRT, cardiac resynchronisation therapy; CFB, change from baseline; CRT, cardiac resynchronisation therapy; CSS, clinical summary score; CV, cardiovascular; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; HF, heart failure; KCCQ, Kansas City Cardiomyopathy Questionnaire.

Table 11: Comparative summary of methodology of PARADIGM HF

Trial (References)	PARADIGM HF (10, 11, 172, 173)
Study objective	**Primary:** To test whether sacubitril valsartan is superior to enalapril in delaying time to first occurrence of the composite endpoint (defined as either CV death or HF hospitalisation) in patients with CHF (NYHA class II to IV) and reduced ejection fraction. **Secondary:** To test whether sacubitril valsartan • improves the CSS for HF symptoms and physical limitations (as assessed by KCCQ) at 8 months, compared with enalapril • is superior to enalapril in delaying the time to all-cause mortality • is superior to enalapril in delaying time to new onset AF • is superior to enalapril in delaying the time to first occurrence of either (1) a 50% decline in eGFR relative to baseline, (2) >30 mL/min per 1.73 m^2 decline in eGFR relative to baseline to a value below 60 mL/min per 1.73 m^2, or (3) reaching ESRD
Trial design	Randomised, double-blind, parallel group, active controlled, two-arm, event driven trial. The trial comprised four phases (see Figure 3): • Screening. • Enalapril run-in phase: 2 weeks duration, patients were switched from current medication (i.e. ACEi or ARB) to single-blind (patients were blinded) treatment with the evidence-based dose of enalapril shown to reduce mortality versus placebo in patients with HF (10 mg bid). • This was followed by a sacubitril valsartan run-in phase: single-blind (patients were blinded) treatment with sacubitril valsartan for 4 to 6 weeks at a dose of 100 mg bid, which was increased to 200 mg bid. • Main double-blind, randomised treatment phase: subjects were randomised to either sacubitril valsartan (200 mg bid) or to enalapril (10 mg bid).
Trial design – run-in phase	The two run-in phases were sequential, with only a brief (approximately 36 hours) washout phase, and both included all eligible patients. This sequential design was chosen so that the study could compare patients who are both ACEi and sacubitril valsartan tolerant making it a true head to head comparison. Another reason for this design was the lack of Phase II data in this patient population.
Trial design – key changes	The LVEF entry criterion was changed from ≤40% to ≤35% after approximately 1,285 patients had been randomised This modification was essential to ensure an adequate event rate in the study population where use of evidence-based, disease-modifying agents was increasing
Location	985 sites in 47 countries • Forty-nine centres and 242 patients in England • 24.37% of patients were recruited in Western Europe (33.61% in Eastern Europe, 17.63% in Asia/Pacific and other, 17.27% in Latin America, and 7.13% in North America)

Trial (References)	PARADIGM HF (10, 11, 172, 173)
Intervention(s) and comparator(s)	Main double-blind treatment phase, target dose: • Sacubitril valsartan, 200 mg bid (n=4,187) • Enalapril, 10 mg bid (n=4,212) Patients not tolerating the target dose were titrated down to lower dose levels (i.e. 100 mg bid or 50 mg bid for sacubitril valsartan and 5 mg bid or 2.5 mg bid for enalapril) at the discretion of the treating physician. The enalapril target dose of 10 mg bid in PARADIGM-HF was selected on the basis of evidence from the SOLVD-Treatment study, in which it was shown to reduce the risk of death or hospitalisation. It is noted that PARADIGM-HF patients were titrated to a comparable level as patients enrolled in SOLVD (average daily enalapril doses in PARADIGM-HF and SOLVD were 18.9 mg (10) and 16.6 mg (182), respectively).
Permitted and disallowed concomitant medications	An optimal medical regimen of standard care HF medications was obligatory. • This included an individually optimised dose of a BB (i.e., maximally tolerated dose) at a stable dose for ≥4 weeks prior to study entry, unless contraindicated or not tolerated. • Use of an AA was encouraged as indicated by local guidelines and as tolerated. In self-identified black patients, the use of isosorbide dinitrate/hydralazine hydrochloride was to be considered. Dose levels of these background disease-modifying HF medications were to be kept stable throughout the entire study, if possible. Diuretics were used and could be adjusted throughout study. PDE-5 inhibitors and any medications known to raise potassium levels were to be used with caution. The concomitant administration of sacubitril valsartan with nesiritide and i.v. nitrates had not been studied, and, if such treatment was required, blood pressure was to be monitored carefully. Bile acid sequestering agents, such as cholestyramine and colestipol, were prohibited. Patients were to notify the study site staff of any changes in concomitant medications. The patient's pre-study ACEis/ARBs were replaced with study medications. Open-label ACEis or ARBs were strictly prohibited.
Primary outcome	A composite of death from CV causes or a first hospitalisation for heart failure, assessed at every study visit (0 weeks, 2, 4, and 8 weeks, 4 months, and then every 4 months)
Secondary outcomes	Secondary outcomes were: • Time to death from any cause, assessed at all study visits. • CFB to 8 months in the CSS on the KCCQ 25 (on a scale from 0 to 100, with higher scores indicating fewer symptoms and physical limitations associated with HF). KCCQ scores were assessed at baseline/randomisation visit (Visit 5), at four, eight and 12 months (Visits 8, 9 and 10), at 24 and 36 months (Visits 14 and17), as well as at the end of study visit (Visit 778).

Trial (References)	PARADIGM HF (10, 11, 172, 173)
	• Time to a new onset of AF, assessed at all study visits. • Time to the first occurrence of a decline in renal function (which was defined as ESRD or as a decrease in the eGFR of at least 50% or a decrease of more than 30 mL/min per1.73 m^2 from randomisation to <60 mL/min per 1.73 m^2). This was determined by eGFR measurements, performed at baseline and then every 12 months and at the end of study visit.

Exploratory outcomes (including scoring methods and timings of assessments)	• Time to first occurrence of a composite event of CV death, hospitalisation for HF, nonfatal MI, non-fatal stroke or resuscitated sudden death
	  ○ Time to first occurrence of a composite event of CV death, non-fatal MI, non-fatal stroke or resuscitated sudden death
	  ○ Time to first occurrence of a composite event of CV death, non-fatal MI, and non-fatal stroke
	  ○ Time to first occurrence of MI and stroke (fatal and non-fatal)
	  ○ Time to first occurrence of MI (fatal and non-fatal)
	  ○ Time to first occurrence of stroke (fatal and non-fatal)
	  ○ Time to first occurrence of resuscitated sudden death
	• Time to first all-cause hospitalisation
	• Time to first cause-specific hospitalisation, such as CV hospitalisation
	• Number of hospital admissions (all-cause and cause-specific)
	• Number of days alive out of the hospital at Month 12
	• Rate of change in eGFR from double-blind phase baseline to last available value
	• Time to study treatment failure defined as: addition of a new drug for treatment of worsening HF, IV treatment requirement, or increase of diuretic dose (e.g., more than 80 mg furosemide) for persistent use for more than one month
	• Change in the clinical composite assessment at Month 8
	• Change in NYHA class from randomisation
	• Changes in HF signs and symptoms from randomisation
	• Time to new onset diabetes mellitus
	• Changes in HRQoL (assessed by total score and individual scores of the subdomains from the KCCQ and assessments of the EQ-5D for health status)
	• Time to first coronary revascularisation procedures
	• Changes from double-blind phase baseline to pre-defined time-point in pre-selected biomarkers (e.g., vascular, renal, collagen, metabolism, and inflammatory biomarkers)

Trial (References)	PARADIGM HF (10, 11, 172, 173)
	• Number of days/stays in ICU, number of re-hospitalisations, and number of A&E visits for HF • Variables for measuring the PK parameters of valsartan, sacubitril, and LBQ657 at steady state in patients receiving sacubitril valsartan using population modelling and/or non-compartmental based methods • Recurrent HF hospitalisations; recurrent composite events of CV mortality and HF hospitalisations; recurrent composite events of CV death, HF hospitalisation, MI, stroke, and resuscitated sudden death; recurrent composite events of CV mortality, MI, and stroke; recurrent composite events of MI and stroke (these analyses were not specified in the protocol but were included in the analysis plan prior to DBL). • Indicator of re-hospitalisation for any cause (for HF) within 30 days of discharge of previous hospitalisation for any cause (for HF) (These analyses were not specified in the protocol, but were included in the analysis plan prior to DBL)
Duration of follow-up	The mean duration of follow-up was 27 months (no significant between-group differences).

Abbreviations: AA, aldosterone antagonist; ACEi, angiotensin converting enzyme inhibitor; A&E, accident and emergency; AF, atrial fibrillation; ARB, angiotensin II receptor blocker; BB, beta blocker; bid, twice daily; CFB, change from baseline; CHF, chronic heart failure; CSS, clinical summary score; CV, cardiovascular; DBL, database lock; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; HF, heart failure; HRQoL, health-related quality of life; ICU, intensive care unit; i.v., intravenous; KCCQ, Kansas City Cardiomyopathy Questionnaire; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NYHA, New York Heart Association; PDE-5, phosphodiesterase-5.; PK, pharmacokinetics.

4.4 *Statistical analysis and definition of study groups in the relevant randomised controlled trials*

4.4.1 *PARADIGM-HF*

Populations used for the statistical analyses

The **full analysis set (FAS)** consisted of all randomised patients, except those who did not qualify for randomisation and have not received a dose of a study drug, but have been inadvertently randomised. Following the intention-to-treat (ITT) principle, patient data were analysed according to the treatment to which the patient was assigned at randomisation. Efficacy variables were analysed based on the FAS as the primary population.

The **safety population (SAF)** consisted of all randomised patients who received at least one dose of study drug. Patient data were analysed according to the treatment actually received. The safety population was used for the analyses of safety variables.

The **per-protocol (PP) population** was a subset of the FAS that consisted of the patients who do not have major deviations from the protocol procedures in the double-blind study stage. Major protocol deviations were pre-specified prior to unblinding treatment codes for analyses. This supplementary efficacy population was used to support the primary analysis results.

Table 12: Summary of statistical analyses in PARADIGM-HF

Hypothesis objective	H_{10}:$\lambda_2/\lambda_1 \geq 1$ vs. H_{1a}:$\lambda_2/\lambda_1 < 1$[†]
Statistical analysis	Cox's proportional hazards model with treatment and region as fixed-effect factors
Sample size, power calculation	2,410 patients, providing a power of 97% to detect a 15% risk of outcome
Data management, patient withdrawals	The primary efficacy variable was considered as censored at each analysis time point for patients who withdrew, died from non-CV causes or were lost to follow-up
Stopping rule	Both the primary endpoint (CV death or HF hospitalisation) and CV death alone required a one-sided p-value <0.001 favouring sacubitril valsartan over enalapril at the final interim analysis to recommend stopping the study for established efficacy. The study was stopped early, having fulfilled these conditions, on March 28, 2014.

[†] λ_1 and λ_2 are hazards for enalapril treatment and sacubitril valsartan treatment
Abbreviations: HF, heart failure; CV, cardiovascular.

Primary efficacy outcome

Population included in primary analysis of primary outcome and methods for handling missing data

The FAS was used for the primary analysis. The primary efficacy variable, the time to the first occurrence of either CV death or HF hospitalisation, was considered as censored at each analysis time point (for the final analysis) for patients who had no event and at least one of the following applied at or prior to the analysis time point:

- Withdrawal of informed consent,
- Loss to follow-up, or

- Death from non-CV causes.

For those patients without events prior to the analysis time point, the censoring date was be defined as the following (whichever occurred first):

- Date when the patient withdrew informed consent.
- Date of the patient's last visit before analysis cut-off date.
- Date of death from non-CV causes.

Statistical test in primary analysis of primary outcome

The primary efficacy variable was analysed using Cox's proportional hazards model with treatment and region as fixed-effect factors. The estimated hazard ratio and the corresponding two-sided confidence interval are provided. The FAS was used for the primary analysis. The overall type I error was controlled at 2.5% (one-sided). The one-sided significance level of α used for the final analysis was adjusted for the interim efficacy analyses according to an interim analyses plan.

Primary hypothesis under investigation and power calculation

The primary hypothesis to be tested was H_{10}:$\lambda_2/\lambda_1 \geq 1$ vs. H_{1a}:$\lambda_2/\lambda_1 < 1$, where λ_1 and λ_2 are hazards for enalapril treatment and sacubitril valsartan treatment, respectively.

The annual rate of the primary endpoint in the enalapril group was estimated at 14.5% and the rate of death from CV causes at 7.0%. Calculation of the sample size was based on mortality from CV causes. Approximately 8,000 patients would have to be followed for 34 months, with 1,229 deaths from CV causes, to provide the study with a power of 80% to detect a relative reduction of 15% in the risk of death from CV causes in the sacubitril valsartan group, at an overall two-sided alpha level of 0.05. It was therefore estimated that the primary end point would occur in 2,410 patients, providing a power of 97% to detect a 15% reduction in the risk of this outcome.

Secondary analyses of the primary efficacy outcome

Sensitivity analyses of the primary efficacy outcome were performed using the same statistical test as for the primary efficacy outcome. The following analyses were performed:

- First composite endpoint of CV/unknown death or HF hospitalisation and its components (FAS)
- First primary endpoint (CV death or HF hospitalisation) and its components (PP set)
- On-treatment analysis of first primary endpoint (CV death or HF hospitalisation) and its components (FAS)

Secondary efficacy outcomes

Analysis of time to all-cause mortality

The time to all-cause mortality was analysed using the Cox proportional hazards model with treatment and region as fixed-effect factors. The estimated hazard ratio and the corresponding two-sided 95% CI were provided for the FAS.

The Kaplan-Meier curves by treatment group are presented. Additionally, the frequency and percentage of all-cause mortality are provided by treatment group.

Analysis of KCCQ CSS as a continuous variable

- The KCCQ is a valid and reliable self-administered questionnaire that contains 23 items covering physical function, clinical symptoms, social function, self-efficacy and knowledge, and QoL assessed by Likert scaling (181).
- Higher scores (on the scale of 0 to 100) indicate better HRQoL/ less symptoms
- The HF symptoms and physical limitation domains scores are the most highly correlated with improvement following a CHF exacerbation (181).

The KCCQ domains that address HF symptoms and physical limitations were analysed separately as a secondary endpoint. The clinical summary score (CSS) of KCCQ was computed as the mean of the physical limitation and total HF symptom scores. Changes in HRQoL assessed by total score and individual scores of the subdomains from the KCCQ were determined and analysed as exploratory outcomes (See Table 11).

Change from baseline in the clinical summary score of KCCQ was analysed based on a repeated measures analysis of covariance (ANCOVA) model in which treatment, region, visit, and treatment-by-visit interaction were included as fixed-effect factors and baseline value as a covariate, with a common unstructured covariance matrix among visits for each treatment group.

The analysis was based on the FAS and on the likelihood method with an assumption of missing at random for missing data. Patients from countries whose language did not have a validated translation of the KCCQ were excluded from the analysis.

Analysis of time to new onset of atrial fibrillation (AF)

The time to new onset AF was analysed using the Cox proportional hazards model with treatment and region as fixed-effect factors. The estimated hazard ratio and the corresponding two-sided 95% CI were provided for the FAS (subset of patients without AF history).

The Kaplan-Meier curves by treatment group were presented for the FAS. Additionally, the frequency and percentage of new onset AF were provided by treatment group.

Analysis of time to composite renal endpoint

Decline in renal function was defined as:

a) Reaching end stage renal disease (ESRD) or

b) A decrease in the eGFR of at least 50% or

c) A decrease of more than 30 mL/min per 1.73 m^2 from randomisation to <60 mL/min per 1.73 m^2

The time to this composite renal endpoint and its three components were analysed using the Cox proportional hazards model with treatment and region as fixed-effect factors. The estimated hazard ratio and the corresponding two-sided 95% CI were provided for the FAS.

The Kaplan-Meier curves by treatment group were presented for the FAS. Additionally, the frequency and percentage of composite renal endpoint were provided by treatment group.

The composite renal endpoint is not a conventional renal endpoint. The conventional renal endpoint is defined as first occurrence of a 50% decline in eGFR relative to baseline, or reaching ESRD. This conventional renal endpoint was also analysed using the Cox proportional hazard model with treatment and region as fixed effect, as a post-hoc analysis.

Changes to planned analyses

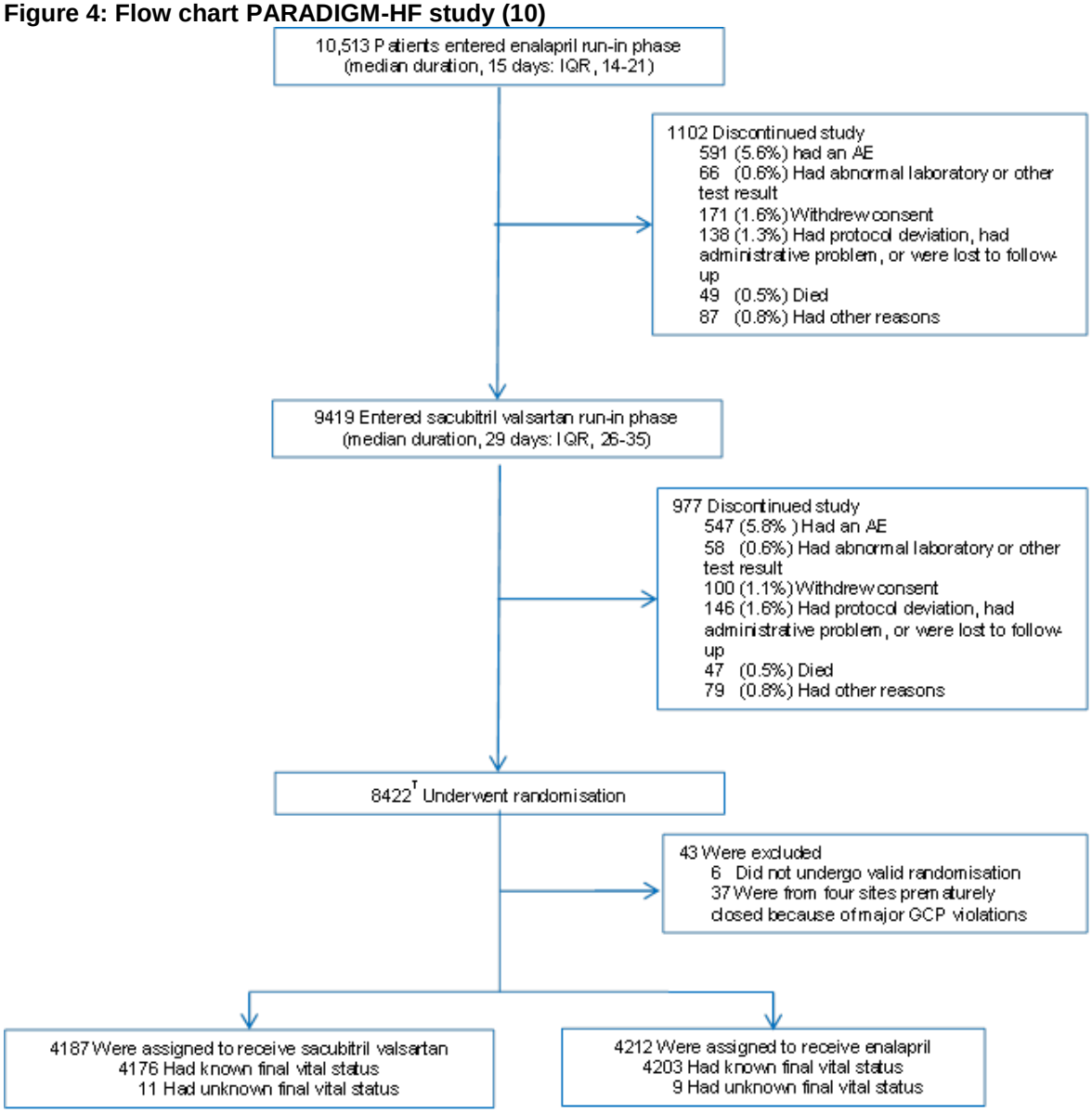
Alpha levels for the primary and secondary endpoints were planned to be adjusted in a manner to ensure strong control of the family-wise error rate across all primary and secondary endpoints and across all interim analyses and the final analysis. As per protocol, since the trial was stopped at the 3rd interim analysis, the 0.001 alpha level used for the primary endpoint boundary at that analysis was also to be used as the basis for testing the secondary endpoints. This approach is highly conservative for the secondary endpoints. The secondary endpoints did not influence the decision of early stopping, determine the success of the study and were only planned to be tested once during the course of the study. Therefore, in addition to applying the planned conservative method of strong control of the family-wise error rate (strict multiple testing procedure [MTP]), the results of the secondary endpoints may also be interpreted based on the commonly used approach of assigning the remaining alpha for the final analysis of 0.025−0.0001−2×0.001=0.0229 to the set of secondary endpoints and applying the pre-specified sequentially rejective MTP to control for multiplicity across the four secondary endpoints (alternative MTP).

4.5 *Participant flow in the relevant randomised controlled trials*

4.5.1 *Provide details of the numbers of participants who were eligible to enter the trials. Include the number of participants randomised and allocated to each treatment. Provide details of and the rationale for participants who crossed over treatment groups, were lost to follow-up or withdrew from the RCT. Provide a CONSORT diagram showing the flow of participants through each stage of each of the trials.*

The CONSORT flow chart showing the numbers of patients who were eligible to enter the PARADIGM-HF study, and who were randomised and allocated to each treatment are presented in Figure 4.

Figure 4: Flow chart PARADIGM-HF study (10)



Abbreviations: AE, adverse events; GCP, good clinical practice.
†Note that 6 patients which failed the sacubitril valsartan run-in phase were randomised to treatment, and 1 patient who completed the run-phase was not randomised.

4.5.2 *In a table describe the characteristics of the participants at baseline for each of the trials. Provide details of baseline demographics, including age, gender and relevant variables describing disease severity and duration and if appropriate previous treatments and concomitant treatment. Highlight any differences between trial groups. A suggested table format is presented below.*

Patient characteristics at baseline are summarised in Table 13. There were no significant differences between groups regarding any of the demographic or baseline characteristics. However, some differences were observed between the English population with HF and the study population (6).

The treatment effect of sacubitril valsartan has been explored in subgroup analysis (see Section 4.8.4, Figure 9 and the appendices Section 8.4). The subgroup analyses show

no differences in treatment effects of sacubitril valsartan versus enalapril in any subgroups with the exception of NYHA class for HF hospitalisation (See Section 4.8).

Standard care and background therapies used in combination with sacubitril valsartan or enalapril in PARADIGM-HF are comparable to standard therapies used in England (7, 16). In the PARADIGM-HF trial, at baseline 93% and 56% of patients were receiving treatment with beta blockers and aldosterone antagonists respectively (10).

Age and gender distribution: Compared with the English HFrEF population, subjects in PARADIGM-HF were younger and, more likely to be male. A lower average age is seen in HF trials as a result of clinical trials requiring clear pre-determined eligibility criteria and rigorous follow-up making recruitment of significant numbers of older patients difficult. However, in PARADIGM-HF, 49% of patients were ≥65 years of age (n=4120) and 19% of patients were ≥75 years of age (n=1563) with the oldest patient aged 96 at randomisation, and 22% (n=1,832) were female (10, 11).

NYHA: At randomisation patients in PARADIGM-HF were distributed into milder NYHA classes than the English general population (English HF population at admission - NYHA class I/II 21%, NYHA class III 44% NYHA class IV 35% (6); PARADIGM-HF see Table 13). At the run-in phase patients were comparably distributed to the SOLVD trial which is the key pivotal trial for enalapril.

Table 13: Characteristics of participants in PARADIGM HF across randomised groups

PARADIGM HF Baseline characteristics		**Sacubitril valsartan (n=4,187)**	**Enalapril (n=4,212)**
Age,	Mean ±SD Range, years	63.8±11.5 18-96	63.8±11.3 21-96
	<65 years, n (%) ≥65 years, n (%)	2011 (50.4) 2076 (49.6)	2168 (51.5) 2044 (48.5)
	<75 years, n (%) ≥75 years, n (%)	3403 (81.3) 784 (18.7)	3433 (81.5) 779 (18.5)
Females, n (%)		879 (21.0)	953 (22.6)
Race/ ethnicity, n (%)	White	2,763 (66.0)	2,781 (66.0)
	Black	213 (5.1)	215 (5.1)
	Asian	759 (18.1)	750 (17.8)
	Other	452 (10.8)	466 (11.1)
Region, n (%)	North America	310 (7.4)	292 (6.9)
	Latin America	713 (17.0)	720 (17.1)
	Western Europe, South Africa, Israel	1,026 (24.5)	1,025 (24.3)
	Central Europe	1,393 (33.3)	1,433 (34.0)
	Asia-Pacific	745 (17.8)	742 (17.6)
SBP, mmHg, mean ±SD		122±15	121±15
Heart rate, beats/min, mean ±SD		72±12	73±12
BMI, mean ±SD		28.1±5.5	28.2±5.5
Serum creatinine, mg/dL, mean ±SD		1.13±0.3	1.12±0.3

PARADIGM HF Baseline characteristics		Sacubitril valsartan (n=4,187)	Enalapril (n=4,212)
Clinical features of HF	IC, n (%)	2,506 (59.9)	2,530 (60.1)
	LVEF, %, mean ±SD	29.6±6.1	29.4±6.3
	Median BNP (IQR), pg/mL	255 (155–474)	251 (153–465)
	Median NT-proBNP (IQR), pg/mL	1,631 (885–3154)	1,594 (886–3305)
NYHA class, n (%)	I	180 (4.3)	209 (5.0)
	II	2,998 (71.6)	2,921 (69.3)
	III	969 (23.1)	1,049 (24.9)
	IV	33 (0.8)	27 (0.6)
	Missing data	7 (0.2)	6 (0.1)
Treatments at randomisation (standard care/ background therapies), n (%)	Diuretic	3,363 (80.3)	3,375 (80.1)
	Digitalis	1,223 (29.2)	1,316 (31.2)
	BB	3,899 (93.1)	3,912 (92.9)
	AA	2,271 (54.2)	2,400 (57.0)
Medical history, n (%)	Hypertension	2,969 (70.9)	2,971 (70.5)
	Diabetes	1,451 (34.7)	1,456 (34.6)
	AF	1,517 (36.2)	1,574 (37.4)
	Hospitalisation for HF	2,607 (62.3)	2,667 (63.3)
	MI	1,818 (43.4)	1,816 (43.1)
	Stroke	355 (8.5)	370 (8.8)
	Pre-trial use of ACEi	3,266 (78.0)	3,266 (77.5)
	Pre-trial use of ARB	929 (22.2)	963 (22.9)

Abbreviations: AA, aldosterone antagonists; ACEi, angiotensin converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin II receptor blocker; BB, beta blocker; BNP, B-type natriuretic peptide; BMI, body mass index; HF, heart failure; IC, ischaemic cardiomyopathy; IQR, interquartile range; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NT-proBNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association; SBP, systolic blood pressure; SD, standard deviation.

4.6 *Quality assessment of the relevant randomised controlled trials*

4.6.1 *Describe the methods used for assessing risk of bias and generalisability of individual RCTs (including whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.*

PARADIGM-HF enrolled patients currently receiving a stable dose of an ACEi or ARB. Patients had to continue their HF background treatment, but discontinue the ACEi or ARB, which was replaced with study treatment. Patients must have been treated with a beta blocker, unless contraindicated or not tolerated, at a stable dose for at least four weeks prior to Visit 1. An aldosterone antagonist should also have been considered in all patients. This treatment regimen is in line with current NICE recommendations (see Section 3.4).

4.6.2 *The complete quality assessment for each RCT should be included in an appendix.*

A complete quality assessment for PARADIGM-HF and TITRATION is provided in the Appendix, Section 8.3.

4.7 *Clinical effectiveness results of the relevant randomised controlled trials*

The outcomes specified in the scope and presented in this section are listed below (see Table 1, Section 1.2 and Section 4.7.1):

- Mortality as measured by time to death from any cause (Time to death from any cause)
- CV mortality as measured by time to CV death (Primary Efficacy Results – composite of CV death or HF hospitalisation)
- Hospitalisation for HF as measured by time to first hospitalisation for heart failure, number of patients hospitalised and number of hospital admissions (Primary Efficacy Results – composite of CV death or HF hospitalisation)
- All-cause hospitalisation as measured by time to first hospitalisation ([Number of patients hospitalised and number of hospital admissions (all-cause and cause-specific)]
- Symptoms of HF as measured by KCCQ (Secondary Efficacy Results) and shift in NHYA class (Change in NYHA class from randomisation)
- Health-related quality of life as measured by KCCQ total summary score and EQ-5D [Health-related quality of life (assessed by total score and individual scores of the sub-domains from the KCCQ and total score of the EQ-5D for health status)]
- Additionally, all remaining secondary endpoints have been presented; time to new onset of AF, time to first occurrence of a decline in renal function (Secondary Efficacy Results)

4.7.1 *Study PARADIGM-HF*

Datasets analysed

The presented results were based on the FAS population (following an intention to treat [ITT] approach); data from all patients who had undergone a valid randomisation were used in the analyses of the primary and secondary outcomes.

Primary Efficacy Results – composite of CV death or HF hospitalisation

Sacubitril valsartan was superior to enalapril in reducing the risk of the primary composite outcome of CV death or HF hospitalisation, CV death alone, and HF hospitalisation alone (Table 14). The magnitude of the advantages of the composite primary endpoint for sacubitril valsartan over enalapril was 20%; highly statistically significant and clinically meaningful, particularly since the drug was compared with a dose of enalapril that has been shown to reduce mortality, as compared with placebo (8, 9). For both individual items separately, CV death and HF hospitalisation, the results also significantly favour sacubitril valsartan.

Figure 5 shows the Kaplan-Meier curve for the primary composite outcome over time, demonstrating that the difference between sacubitril valsartan and enalapril became apparent early in the trial. Corresponding Kaplan-Meier curves for the individual components of the primary composite outcome are presented in Figure 6 and Figure 7.

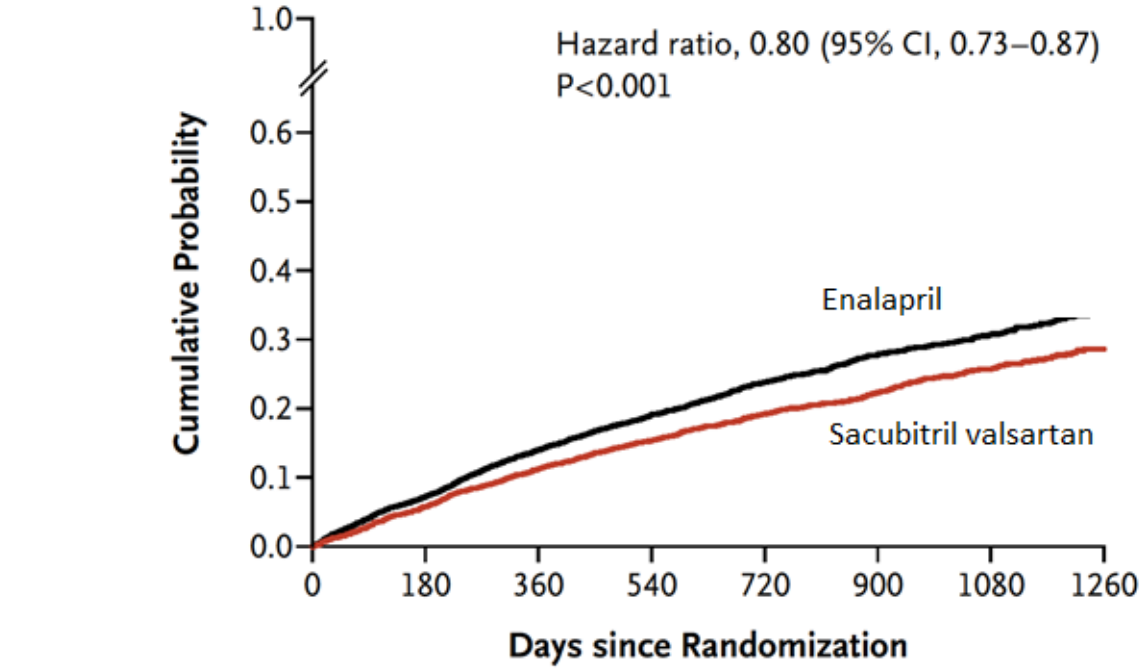
The numbers of patients needed to treat with sacubitril valsartan instead of enalapril to prevent one primary event and one death from CV causes over the trial period were 21 and 32, respectively (10).

Table 14: Primary composite outcome and component outcomes of PARADIGM-HF (FAS)

	Sacubitril valsartan n=4,187 n, %	**Enalapril n=4,212 n, %**	**HR (95% CI)**	**p-value†**
Death from CV causes or first hospitalisation for worsening HF	914 (21.8)	1117 (26.5)	0.80 (0.73–0.87)	<0.001
Death from CV causes	558 (13.3)	693 (16.5)	0.80 (0.71–0.89)	<0.001
First hospitalisation for worsening HF	537 (12.8)	658 (15.6)	0.79 (0.71–0.89)	<0.001

† p values are two-sided and were calculated by means of a stratified log-rank test without adjustment for multiple comparisons.
Events which occurred in the double-blind period up to 31 Mar 2014 are included in the analysis.
Abbreviations: CI, confidence interval; CV, cardiovascular; FAS, full analysis set; HF, heart failure; HR, hazard ratio.

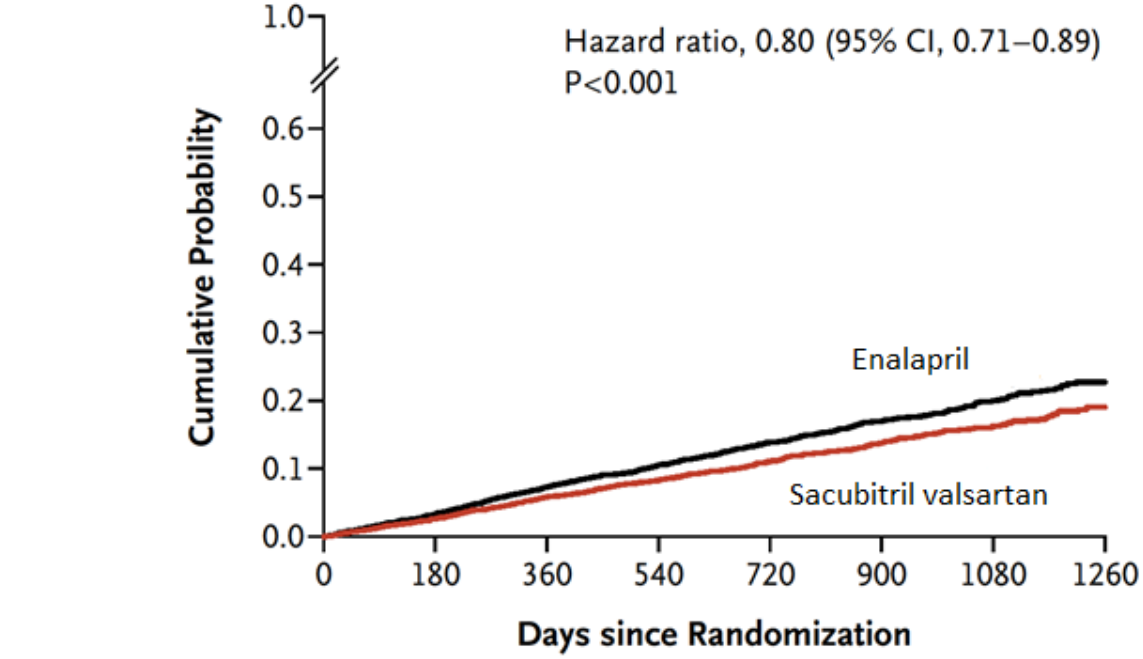
Figure 5: Study PARADIGM-HF, primary composite outcome of death from CV causes or first hospitalisation for worsening heart failure, Kaplan-Meier curve



No. at Risk

Sacubitril valsartan	4187	3922	3663	3018	2257	1544	896	249
Enalapril	4212	3883	3579	2922	2123	1488	853	236

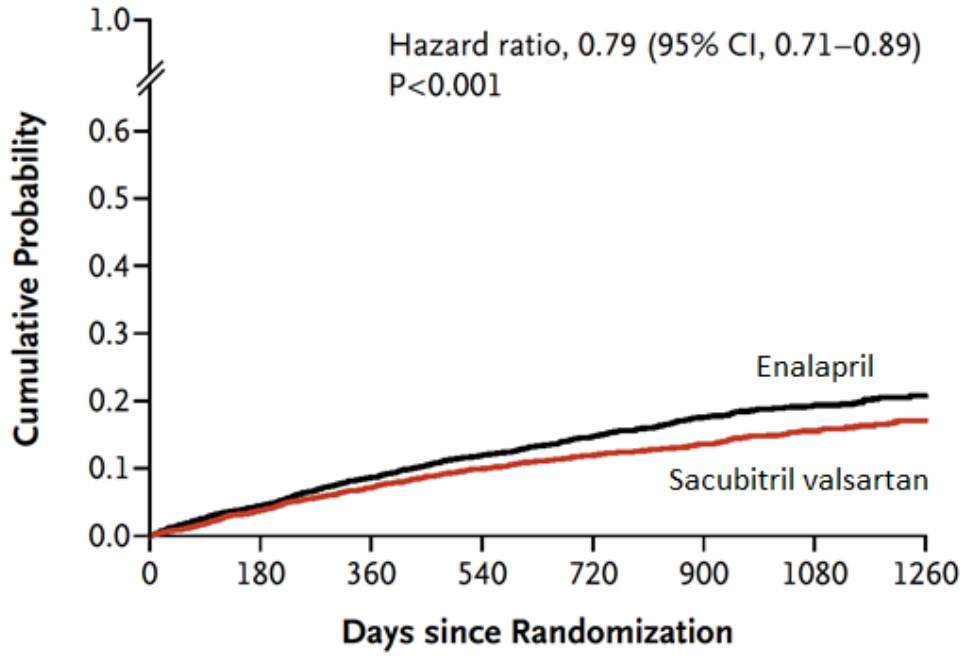
Figure 6: Study PARADIGM-HF, primary outcome component of death from CV causes, Kaplan-Meier curve



No. at Risk

Sacubitril valsartan	4187	4056	3891	3282	2478	1716	1005	280
Enalapril	4212	4051	3860	3231	2410	1726	994	279

Figure 7: Study PARADIGM-HF, primary outcome component of first hospitalisation for worsening HF, Kaplan-Meier curve



No. at Risk

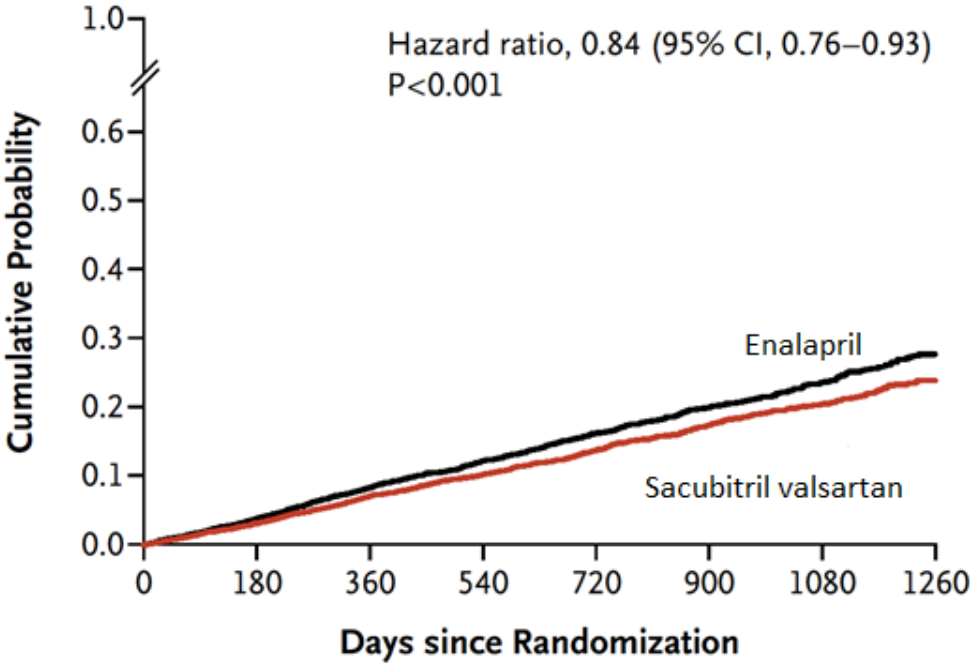
Sacubitril valsartan	4187	3922	3663	3018	2257	1544	896	249
Enalapril	4212	3883	3579	2922	2123	1488	853	236

Secondary Efficacy Results

Time to death from any cause

Sacubitril valsartan significantly reduced all-cause mortality compared with enalapril, by 16%. A total of 711 patients (17.0%) in the sacubitril valsartan group and 835 patients (19.8%) in the enalapril group died (HR 0.84 (0.76-0.93), p<0.001). The Kaplan-Meier curve representing the data for the time to death from any cause is shown in Figure 8.

Figure 8: Study PARADIGM-HF, time to death from any cause, Kaplan-Meier curve



No. at Risk

Sacubitril valsartan	4187	4056	3891	3282	2478	1716	1005	280
Enalapril	4212	4051	3860	3231	2410	1726	994	279

HF symptoms and physical limitation clinical summary score on the Kansas City Cardiomyopathy Questionnaire

- The KCCQ covers physical function, clinical symptoms, social function, self-efficacy and knowledge, and QoL Higher scores (on the scale of 0 to 100) indicate better HRQoL/ reduced HF symptoms. KCCQ scores were assessed at baseline, 4, 8, 12, 24 and 36 months as well as at the end of study visit.

- The HF symptoms and physical limitation domains scores are the most highly correlated with improvement following a HF exacerbation (181) and are computed into the KCCQ CSS.

- The KCCQ CSS was reduced for both sacubitril valsartan and enalapril; however, this reduction was less with sacubitril valsartan (by 2.99±0.36 points) than with enalapril (by 4.63±0.36 points). Detailed sub-score results for the KCCQ clinical summary score are shown in Table 15.

- The overall score and the remaining subdomains of the KCCQ were exploratory outcomes (see Section 4.7.1, Exploratory outcomes of interest).

Overall, patients experienced increased HF symptoms and physical limitation (based on a reduced KCCQ CSS); however, with sacubitril valsartan this increase in symptoms was significantly less than with enalapril.

Table 15: Between-treatment analysis for change from baseline to Month 8 for the KCCQ clinical summary score and KCCQ subdomain scores (FAS)

	n, LSM of CFB (SE)		LSM of difference (95% CI)	p-value†
	Sacubitril valsartan n=3,833	Enalapril n=3,873		
CSS	3,643, -2.99 (0.364)	3,638, -4.63 (0.364)	1.64, (0.63, 2.65)	0.001*
Physical limitation	3,588, -2.59 (0.390)	3,589, -4.13 (0.389)	1.54, (0.46, 2.62)	0.0052*
Symptom stability	3,631, -6.10 (0.401)	3,632, -7.92 (0.401)	1.82, (0.71, 2.93)	0.0014*
Symptom frequency	3,637, -3.00 (0.402)	3,632, -5.22 (0.402)	2.22, (1.10, 3.33)	0.0001*
Symptom burden	3,640, -3.59 (0.400)	3,635, -5.29 (0.400)	1.70, (0.59, 2.81)	0.0027*
Total symptom score	3,640, -3.32 (0.390)	3,635, -5.23 (0.390)	1.91, (0.83, 2.99)	0.0005*

For patients who died the worst score 0 was imputed for the CSS at all subsequent scheduled visits.
† p-values are two-sided * Indicates significant at alpha=0.05.
Abbreviations: CI, confidence interval; CFB, change from baseline; CSS, clinical summary score; FAS, full analysis set; KCCQ, Kansas City Cardiomyopathy Questionnaire; LSM, least squares mean; SE, standard error.

Time to a new onset of AF

New-onset AF developed in 84 patients in the sacubitril valsartan group and 83 patients in the enalapril group and there was no difference between the groups (HR, 0.97, 95% CI 0.72 to 1.31, two-sided p=0.83).

Time to first occurrence of a decline in renal function

Risk reduction of the composite renal endpoint (defined as ESRD or as a decrease in the eGFR of at least 50% or a decrease of more than 30 mL/min per 1.73 m^2 from randomisation to <60 mL/min per 1.73 m^2) was not statistically different between sacubitril valsartan and enalapril (Table 16).

Table 16: Between-treatment comparison of first confirmed renal dysfunction event (FAS)

Response variable	Sacubitril valsartan, n/N (%)	Enalapril, n/N (%)	HR (95% CI)	p-value†
Composite renal endpoint	94/ 4,187 (2.2)	108/ 4,212 (2.6)	0.86 (0.65,1.13)	0.28

† p-values are two-sided. Statistical significance was not reached according to MTP at overall alpha level of 0.001.
Abbreviations: CI, confidence interval; FAS, full analysis set; HR, hazard ratio.

Exploratory outcomes of interest

The exploratory endpoints presented in this submission are considered the most relevant with regard to the experience of patients (including endpoints regarding HF symptoms, NYHA shift, HRQoL, hospitalisations) aligned with the decision problem (see Section 1.2) and/or relevant as inputs in the pharmaco-economic evaluation (HRQoL, healthcare resource use and hospitalisations). These exploratory endpoints of interest include:

- Number of patients hospitalised and number of hospital admissions (all-cause and cause-specific)
- Health-related quality of life (assessed by total score and individual scores of the sub-domains from the KCCQ and total score of the EQ-5D for health status)
- Healthcare resource utilisation, e.g., number of days/stays in and ICU, number of rehospitalisations, and number of A&E visits for HF
- Change in NYHA class from randomisation

Additional exploratory endpoints were analysed in the PARADIGM-HF trial (see Table 11) and can be found in the Clinical Study Report (CSR) (11).

Number of patients hospitalised and number of hospital admissions (all-cause and cause-specific)

Compared with enalapril, sacubitril valsartan significantly reduced the risk of hospitalisation (whether all-cause or cause-specific). The risks of hospitalisation for CV causes and non-CV causes were reduced with sacubitril valsartan relative to enalapril by 12% (p=0.0008) and 13% (p=0.0047), respectively (Table 17) (129).

Table 17: All-cause and cause-specific hospital admissions (FAS)

Response variable	Sacubitril valsartan n/N (%)	Enalapril n/N (%)	HR (95% CI)	p-value
First all-cause hospitalisation	1,660/4,187 (39.65)	1,827/4,212 (43.38)	0.88 (0.82,0.94)	0.0001*
First CV hospitalisation	1,210/4,187 (28.90)	1,344/4,212 (31.91)	0.88 (0.81,0.95)	0.0008*
First non-CV hospitalisation	833/4,187 (19.89)	931/4,212 (22.10)	0.87 (0.80,0.96)	0.0047*

Events which occurred in the double-blind period up to 31 Mar 2014 are included in the analysis. The analysis is performed using a Cox-regression model with treatment and region as fixed factors. P-value is from a 2-sided test and is based on this model. A HR <1 favours sacubitril valsartan.
* Indicates statistical significance (2-sided) with an alpha level of 0.05.
Abbreviations: CI, confidence interval; CV, cardiovascular; FAS, full analysis set; HR, hazard ratio.

Compared with enalapril, sacubitril valsartan significantly reduced the number of patients experiencing multiple hospital admissions for HF (p=0.0001) (Table 18). The number (and percentage) of patients experiencing one or more hospitalisation for HF is also part of the primary composite outcome (Section 4.7.1) (129). The annual rate of HF hospitalisations was reduced by 23% in the sacubitril valsartan group vs. the enalapril group (rate ratio 0.77; 95% CI, 0.67 to 0.89; p=0.0004) (Table 18) (11).

Table 18: Hospital admission-related outcomes by treatment group (FAS)

	Sacubitril valsartan n=4,187	Enalapril n=4,212	p-value
Patients hospitalised, classified by number of hospital admissions for HF, n (%)			0.0001*‡
0	3,650 (87.2)	3,554 (84.4)	
1	367 (8.8)	418 (9.9)	
2	110 (2.6)	143 (3.4)	
3	33 (0.8)	53 (1.3)	
≥4	27 (0.6)	44 (1.0)	
≥1	537 (12.8)	658 (15.6)	
Number of hospital admission per patient for HF			
Mean (SD), median	0.20 (0.72), 0	0.26 (0.75), 0	
Min, max	0, 18	0, 11	
Total number of hospital admissions			
HF	851	1,079	<0.001
All-cause	3,564	4,053	<0.001
CV	2,216	2,537	<0.001

* Indicates statistical significance (2-sided) with an alpha level of 0.05.
Abbreviations: CI, confidence interval; FAS, full analysis set; HF, heart failure; SD, standard deviation.

Health-related quality of life (assessed by total score and individual scores of the sub-domains from the KCCQ and total score of the EQ-5D for health status)

Sacubitril valsartan has a favourable HRQoL and HF symptoms profile versus enalapril as shown by KCCQ overall and domain scores (Table 19) (11).

The EQ-5D self-reported questionnaire includes a visual analogue scale (VAS), which records the respondent's self-rated health status on a graduated (0–100) scale, with higher scores for higher HRQoL. The results of the EQ-5D VAS analysis also suggest that sacubitril valsartan has a favourable HRQoL profile compared with enalapril (Table 20) (11).

EQ-5D also includes a descriptive system, which comprises 5 dimensions of health: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. The VAS provides a direct valuation of the respondent's current state of health, whereas the descriptive system can be used as a health profile or converted into an index score representing a utility value for current health (183). Post-hoc analysis analysed the EQ-5D index score based on the UK population and used in the economic evaluation (See Section 5.4.2, Figure 28). These analysis shows that the HRQoL as measured by EQ-5D is significantly better for sacubitril valsartan versus enalapril over time.

Table 19: Between-treatment analysis for change from baseline to Month 8 for the KCCQ overall summary score and KCCQ subdomain scores (FAS)

	n, LSM of CFB (SE)		LSM of difference (95% CI)	p-value
	Sacubitril valsartan n=3,833	Enalapril n=3,873		
Self-efficacy	3,638, -1.70 (0.404)	3,632, -3.11 (0.404)	1.41, (0.29, 2.53)	0.0138*
Quality of life	3,635, -1.11 (0.390)	3,632, -3.23 (0.390)	2.11, (1.03, 3.20)	0.0001*
Social limitation	3,448, -2.06 (0.434)	3,454, -4.62 (0.433)	2.56, (1.36, 3.76)	0.0000*
Overall summary score	3,643, -2.35 (0.358)	3,638, -4.27 (0.357)	1.91, (0.92, 2.91)	0.0002*

For patients who died the worst score 0 was imputed for the clinical summary score at all subsequent scheduled visits.
* Indicates statistical significance (2-sided) with an alpha level of 0.05.
Abbreviations: CI, confidence interval; CFB, change from baseline; FAS, full analysis set; KCCQ, Kansas City Cardiomyopathy Questionnaire; LSM, least squares mean; SE, standard error.

Table 20: Between-treatment analysis of the change from baseline in EQ-5D VAS by treatment group (FAS)

	Sacubitril valsartan n=4,187	Enalapril n=4,212	Sacubitril valsartan vs. enalapril	
Visit	**n, LSM of CFB (SE)**	**n, LSM of CFB (SE)**	**LSM of Δ (95% CI)**	**p-value**
Month 4	[redacted]	[redacted]	[redacted]	[redacted]
Month 8	[redacted]	[redacted]	[redacted]	[redacted]
Year 1	[redacted]	[redacted]	[redacted]	[redacted]
Year 2	[redacted]	[redacted]	[redacted]	[redacted]
Year 3	[redacted]	[redacted]	[redacted]	[redacted]
Overall	[redacted]	[redacted]	[redacted]	[redacted]

LSM of difference = LSM of [CFB (sacubitril valsartan) - CFB (enalapril)].
The analysis is performed with a repeated measures ANCOVA model including treatment, region, visit, and treatment-by-visit interaction as fixed effect factors and baseline EQ-5D value as a covariate, with a common unstructured covariance for each treatment group.
* Indicates statistical significance (2-sided) with an alpha level of 0.05. Abbreviations: CFB, change from baseline; CI, confidence interval; FAS, full analysis set; LSM, least square of mean; SE, standard error; VAS, visual analogue scale.

Healthcare resource utilisation

Patients treated with sacubitril valsartan required fewer A&E visits for HF (129), spent fewer days in ICU and had reduced all-cause re-hospitalisation than in the enalapril group (11). The rate of A&E visits for HF per year in sacubitril valsartan patients was lower than in enalapril patients (Table 21). This is in line with the efficacy outcome of hospitalisations (Section 4.7.1, “Primary Efficacy Results – composite of CV death or HF hospitalisation” and “Exploratory outcomes of interest”). In addition, days spent in the hospital per patient per year for any cause and re-hospitalisation for HF favoured sacubitril valsartan over enalapril, but this did not reach statistical significance (Table 21).

Table 21: Healthcare resource utilisation (FAS)

Per patient per year	Sacubitril valsartan vs. enalapril, rate ratio (95% CI)	p-value
Total number of A&E visits for HF	0.70 (0.52, 0.94)	0.017
Days spent in the hospital per patient per year	0.916 (0.810, 1.036)	0.1616
Days spent in the ICU per patient per year	0.791 (0.629, 0.993)	0.0434
All-cause re-hospitalisation	0.845 (0.781, 0.913)	<0.0001
Re-hospitalisation for HF within 30 days	0.83 (0.52, 1.34).	0.4524

Abbreviations: CI, confidence interval; A&E, accidents and emergency; FAS, full analysis set; HF, heart failure; ICU, intensive care unit.

Change in NYHA class from randomisation

Patients treated with sacubitril valsartan were more likely to have an improved NYHA class from baseline compared with the enalapril group. When NYHA class after death was considered missing at random, the subject-specific odds of a favourable change in NYHA class (adjusted for region and NYHA class at baseline) was 30-39% higher in the sacubitril valsartan group than the enalapril group while if death was considered as worsening of NYHA class, favourable change in NYHA class was 26-51% higher (Table 21) indicating that sacubitril valsartan is more likely to improve HF symptoms (11).

Table 22: Between-treatment analysis of NYHA class change from randomisation (FAS)

Visit	Death considered as worsening		Death considered missing at random	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Month 4	1.26 (1.07, 1.49)	0.0057*	1.30 (1.08, 1.56)	0.0047*
Month 8	1.34 (1.13, 1.58)	0.0006*	1.39 (1.15, 1.67)	0.0005*
Year 1	1.38 (1.17, 1.63)	0.0002*	1.38 (1.14, 1.67)	0.0008*
Year 2	1.47 (1.23, 1.76)	<0.0001*	1.33 (1.07, 1.64)	0.0097*
Year 3	1.51 (1.22, 1.87)	0.0002*	1.31 (0.98, 1.75)	0.0696

Repeated measurement proportional odds model is used for analysing NYHA class change (ordinal class: improved, unchanged, worsened) from baseline to selected time points, which included patient as a random effect, and NYHA class at randomisation, region, treatment, visit (selected available post-randomisation visits) and treatment-by-visit interaction as fixed effect factors. The analysis is based on likelihood method.
* Indicates statistical significance (2-sided) with an alpha level of 0.05.
Abbreviations: CI, confidence interval; FAS, full analysis set; NYHA, New York Heart Association; OR, odds ratio.

A post-hoc analysis of change from randomisation for NYHA was performed in which patients who died were assigned worse rank (categorised as Class V). At eight months, NYHA functional class was improved for more patients in the sacubitril valsartan group than in the enalapril group and NYHA functional class worsened for fewer patients in the sacubitril valsartan group than in the enalapril group.

Table 23: Between-treatment analysis of change from randomisation for NYHA at Month 8 (FAS)

Measurement	Category	Sacubitril valsartan n (%)	Enalapril n (%)	p-value
Between-treatment analysis of change from randomisation for NYHA†	Patients with data	4,041 (100.00)	4,072 (100.00)	0.0002*
	Improved	639 (15.81)	569 (13.97)	
	Unchanged	2,989 (73.97)	2,990 (73.43)	
	Worsened	413 (10.22)	513 (12.60)	

†Post-hoc analysis of change from randomisation for NYHA was performed in which patients who died were assigned worse rank (categorised as Class V)
* Indicates statistical significance (2-sided) with an alpha level of 0.05.
Abbreviations: FAS, full analysis set; NYHA, New York Heart Association.

4.8 *Subgroup analysis*

4.8.1 *Provide details of any subgroup analyses carried out. Specify the rationale and whether they were pre-planned or post-hoc.*

The consistency of the treatment effect was assessed in a number of pre-specified subgroups. In PARADIGM-HF patients were stratified by age, gender, race, region, NYHA class, eGFR, diabetes, SBP, LVEF, AF, NT-proBNP, hypertension, prior ACEi, prior ARB, prior aldosterone antagonist, prior hospitalisation for HF, time since diagnosis of HF and use of beta blocker, diuretic or digoxin use. Subgroup analyses were performed for the FAS only and for both the primary and secondary outcomes.

Subgroup analyses were pre-planned, with the exception of a post-hoc analysis to assess the treatment effect in the subgroup of patients in Western Europe (excluding Israeli and South African patients) (For operational reasons, patients from Israel and South Africa were pooled with Western European patients in the primary subgroup analyses).

4.8.2 *Clearly specify the characteristics of the participants in the subgroups and explain the appropriateness of the analysis to the decision problem.*

Patients were stratified by age, gender, race, region, NYHA class, eGFR, diabetes, SBP, LVEF, AF, NT-proBNP, hypertension, prior ACEi, prior ARB, prior aldosterone antagonist, prior hospitalisation for HF, time since diagnosis of HF and use of beta blocker, diuretic or digoxin use.

Apart from general subgroups (like age, gender, race and region), subgroups were chosen to reflect disease characteristics (e.g. time since diagnosis or history of AF) and previous and concurrent medications of the eligible HF population.

4.8.3 *Provide details of the statistical tests used in the primary analysis of the subgroups, including any tests for interaction.*

To explore the beneficial effects in subgroups, the estimated hazard ratio, two-sided 95% CI, and p-value were provided for each of the subgroups based on the Cox proportional hazards model, in which treatment and region were included as fixed-effect factors. Interaction between the subgroup and treatment was evaluated using the above model plus additional terms for subgroup and the interaction between subgroup and treatment. Interaction p-value was provided based on this model. No adjustment for

multiple comparisons was made. Additionally, the frequency and percentage of patients reaching the primary composite endpoint were presented by treatment group for each of the subgroups.

4.8.4 *Provide a summary of the results for the subgroups, with full details provided in an appendix.*

Populations of interest we would like to highlight specifically are:

- ***Age, gender, and NYHA class*** due to baseline characteristics being different from the English population (See Section 4.5.2)
- ***SBP***: due to a greater vasodilator effect, treatment with sacubitril valsartan was associated with a higher rate of hypotension. However, there was no increase in the rate of discontinuation because of possible hypotension-related adverse effects (See Section 4.12).
- ***Ejection fraction (EF) and NT-proBNP*** as they might affect trial outcomes as inclusion criteria have specified these (See Section 4.3.1 'Eligibility criteria')

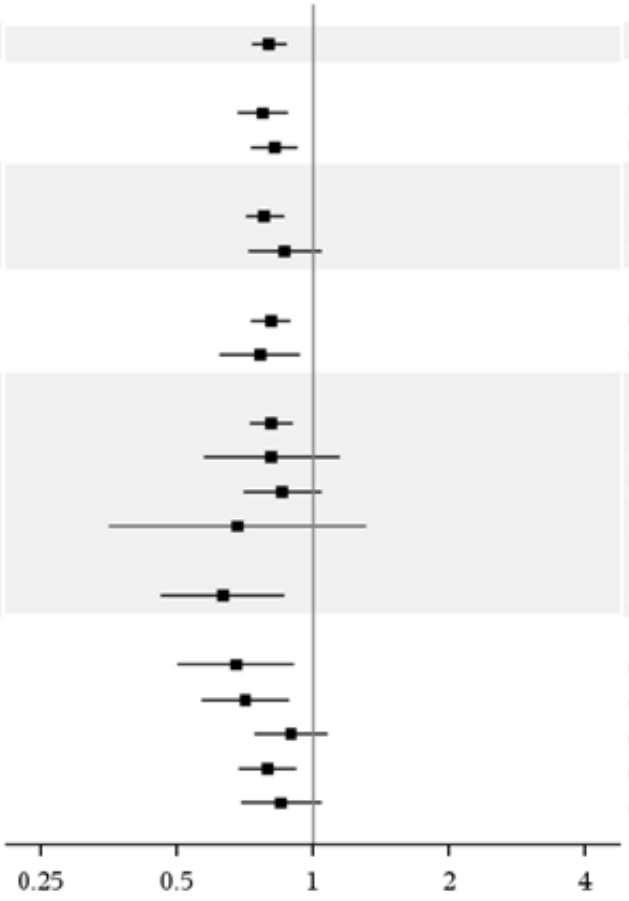
Sacubitril valsartan treatment reduced the risk of the primary composite endpoint of CV death or HF hospitalisation when compared with the active comparator enalapril, independent of all pre-defined subgroups including the subgroups of special interest, with the exception of NYHA (Figure 9). Some subgroup analysis did show results where the confidence interval crossed unity; however, these subgroups were not powered to detect differences between arms. Given the large number of subgroup classifications assessed, there is a high likelihood of chance findings in terms of subgroups with notable ($p<0.05$) treatment by subgroup interactions and subgroups with neutral or reverse treatment effect estimates.

There was a small, but statistically significant interaction between NYHA class at randomisation and the effect of treatment on the primary endpoint ($p=0.03$), which appears to be driven by the HF hospitalisation component only ($p=0.0007$). Subgroup analysis of CV death did not indicate a statistically significant interaction between NYHA class at randomisation and treatment group ($p=0.76$) (Appendix, Section 8.4).).

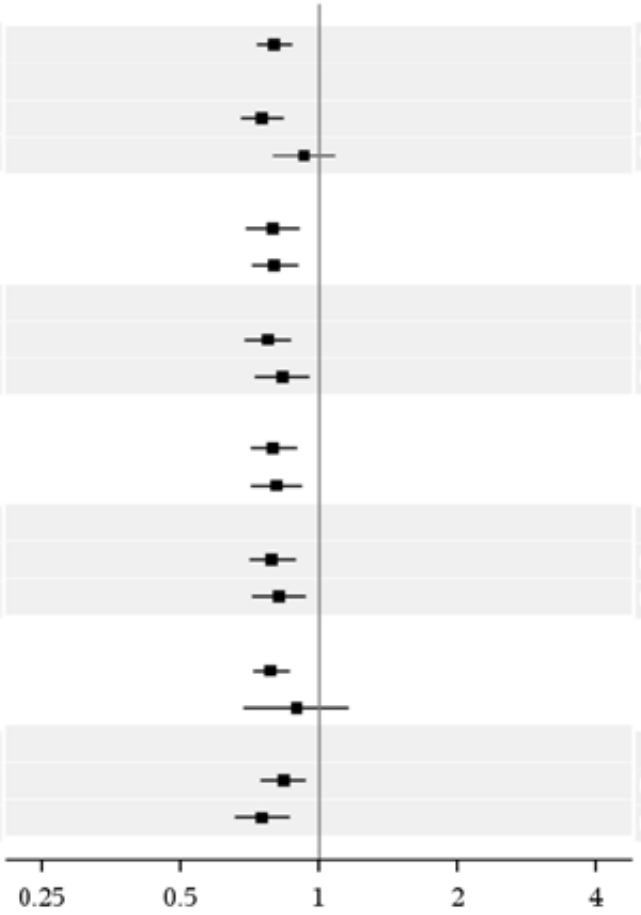
Sacubitril valsartan reduced the risk of the individual items of the primary composite endpoint as well as all-cause mortality. This observation was consistent across subgroups (Appendix, Section 8.4).

Figure 9: Study PARADIGM-HF, Forest plot for the first confirmed primary endpoint (CV death or hospitalisation for HF) comparing sacubitril valsartan with enalapril from pre-specified subgroups (FAS)

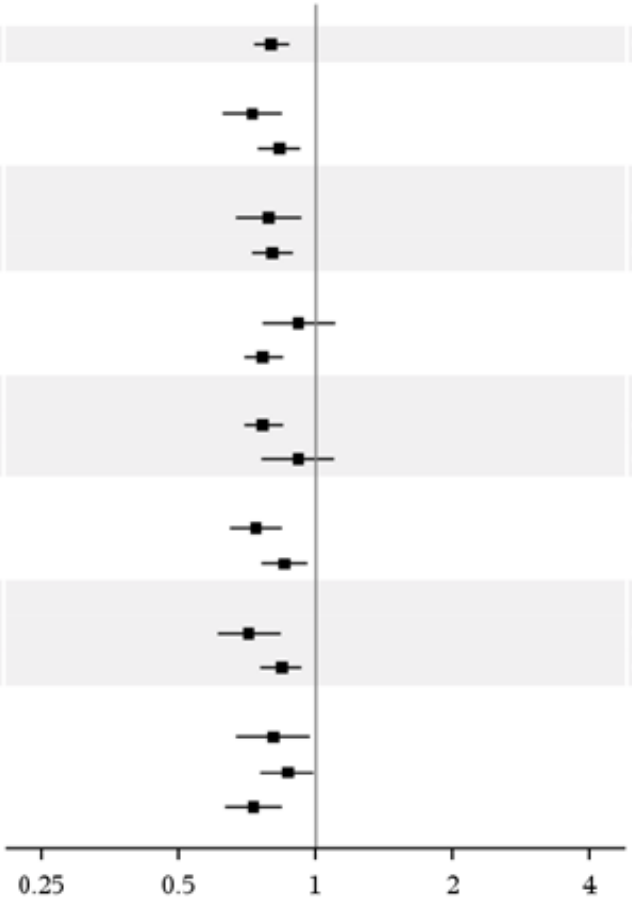
Subgroup	Sacubitril valsartan n / N (%)	Enalapril n / N (%)	Hazard Ratio Estimate (95% CI)	Interaction P-value
Overall	914/4187 (21.8)	1117/4212 (26.5)	0.80 (0.73, 0.87)	
Age (<65 >=65)				0.4715
<65	431/2111 (20.4)	556/2168 (25.6)	0.77 (0.68, 0.87)	
>=65	483/2076 (23.3)	561/2044 (27.4)	0.82 (0.73, 0.93)	
Age (<75 >=75)				0.3248
<75	706/3403 (20.7)	885/3433 (25.8)	0.78 (0.71, 0.86)	
>=75	208/ 784 (26.5)	232/ 779 (29.8)	0.86 (0.72, 1.04)	
Gender				0.6261
Male	756/3308 (22.9)	902/3259 (27.7)	0.80 (0.73, 0.89)	
Female	158/ 879 (18.0)	215/ 953 (22.6)	0.76 (0.62, 0.94)	
Race				0.5809
Caucasian	598/2763 (21.6)	717/2781 (25.8)	0.81 (0.72, 0.90)	
Black	58/ 213 (27.2)	72/ 215 (33.5)	0.81 (0.57, 1.14)	
Asian	179/ 759 (23.6)	204/ 750 (27.2)	0.85 (0.70, 1.04)	
Native American	15/ 84 (17.9)	22/ 88 (25.0)	0.68 (0.35, 1.31)	
Pacific Islander		1/ 1 (100.0)		
Other	64/ 368 (17.4)	101/ 377 (26.8)	0.63 (0.46, 0.86)	
Region				0.3737
North American	77/ 310 (24.8)	103/ 292 (35.3)	0.67 (0.50, 0.90)	
Latin America	131/ 713 (18.4)	183/ 720 (25.4)	0.71 (0.56, 0.88)	
Western Europe	217/1026 (21.2)	239/1025 (23.3)	0.89 (0.74, 1.07)	
Central Europe	318/1393 (22.8)	394/1433 (27.5)	0.79 (0.68, 0.92)	
Asia/Pacific and Other	171/ 745 (23.0)	198/ 742 (26.7)	0.85 (0.69, 1.04)	



Subgroup	Sacubitril valsartan n / N (%)	Enalapril n / N (%)	favours sacubitril valsartan favours enalapril	Hazard Ratio Estimate (95% CI)	Interaction P-value
Overall	914/4187 (21.8)	1117/4212 (26.5)		0.80 (0.73, 0.87)	
NYHA Class					0.0335
NYHA class I/II	611/3178 (19.2)	777/3130 (24.8)		0.75 (0.68, 0.84)	
NYHA class III/IV	302/1002 (30.1)	340/1076 (31.6)		0.92 (0.79, 1.08)	
eGFR (<60 >=60)					0.9065
<60 ml/min/1 73m^2	397/1541 (25.8)	479/1520 (31.5)		0.79 (0.69, 0.90)	
>=60 ml/min/1 73m^2	517/2646 (19.5)	638/2692 (23.7)		0.80 (0.71, 0.90)	
Diabetes at BL					0.4046
No	519/2736 (19.0)	661/2756 (24.0)		0.77 (0.69, 0.87)	
Yes	395/1451 (27.2)	456/1456 (31.3)		0.83 (0.73, 0.95)	
SBP at BL					0.8709
<=Median	516/2298 (22.5)	627/2299 (27.3)		0.79 (0.71, 0.89)	
> Median	398/1889 (21.1)	490/1913 (25.6)		0.81 (0.71, 0.92)	
EF at BL					0.7130
<=Median	524/2239 (23.4)	660/2275 (29.0)		0.79 (0.70, 0.89)	
> Median	390/1948 (20.0)	457/1936 (23.6)		0.82 (0.71, 0.93)	
EF at BL (<=35% >35%)					0.3599
<=35%	811/3715 (21.8)	999/3722 (26.8)		0.78 (0.72, 0.86)	
>35%	103/ 472 (21.8)	118/ 489 (24.1)		0.89 (0.68, 1.16)	
Atrial Fibrillation history					0.2524
No	552/2670 (20.7)	637/2638 (24.1)		0.83 (0.74, 0.93)	
Yes	362/1517 (23.9)	480/1574 (30.5)		0.75 (0.66, 0.86)	



Subgroup	Sacubitril valsartan n / N (%)	Enalapril n / N (%)	favours sacubitril valsartan favours enalapril	Hazard Ratio Estimate (95% CI)	Interaction P-value
Overall	914/4187 (21.8)	1117/4212 (26.5)		0.80 (0.73, 0.87)	
NT-proBNP at BL					0.1648
<=Median	299/2079 (14.4)	403/2116 (19.0)		0.73 (0.63, 0.84)	
> Median	614/2103 (29.2)	711/2087 (34.1)		0.83 (0.75, 0.93)	
Hypertension at BL					0.8712
No	245/1218 (20.1)	303/1241 (24.4)		0.79 (0.67, 0.93)	
Yes	669/2969 (22.5)	814/2971 (27.4)		0.80 (0.72, 0.89)	
Prior use of ACE					0.0913
No	221/ 921 (24.0)	246/ 946 (26.0)		0.92 (0.76, 1.10)	
Yes	693/3266 (21.2)	871/3266 (26.7)		0.77 (0.69, 0.85)	
Prior use of ARB					0.0928
No	691/3258 (21.2)	866/3249 (26.7)		0.77 (0.69, 0.85)	
Yes	223/ 929 (24.0)	251/ 963 (26.1)		0.91 (0.76, 1.09)	
Use of ALD at BL					0.1045
No	399/1916 (20.8)	494/1812 (27.3)		0.74 (0.65, 0.84)	
Yes	515/2271 (22.7)	623/2400 (26.0)		0.85 (0.76, 0.96)	
Prior HF hospitalization					0.0963
No	262/1580 (16.6)	348/1545 (22.5)		0.71 (0.61, 0.84)	
Yes	652/2607 (25.0)	769/2667 (28.8)		0.84 (0.76, 0.93)	
Time since diagnosis of HF					0.2677
<=1 year	202/1275 (15.8)	240/1248 (19.2)		0.80 (0.67, 0.97)	
1-5 years	392/1621 (24.2)	447/1611 (27.7)		0.86 (0.75, 0.99)	
> 5 years	320/1291 (24.8)	430/1353 (31.8)		0.73 (0.63, 0.84)	



Abbreviations: ACE, angiotensin converting enzyme; ALD, aldosterone antagonist (AA); ARB; Angiotensin II receptor blocker; BL, baseline; CI, confidence interval; CV, cardiovascular; EF, ejection fraction; eGFR, estimated glomerular filtration rate; FAS, full analysis set; HF, heart failure; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; SBP, systolic blood pressure.

4.9 *Meta-analysis*

A meta-analysis was not undertaken.

4.10 *Indirect and mixed treatment comparisons*

Search strategy

4.10.1 *Provide details of the search strategies used to identify trials included in the indirect comparison and network meta-analyses.*

Please see Section 4.1 for the search strategy used to identify evidence on the efficacy of comparator treatments of relevance to the decision problem.

In the systematic review 108 studies were identified that matched the inclusion and exclusion criteria, of these studies 64 were identified that were eligible for the NMA. (See Section 4.10.3 for reasons for inclusion and exclusion in the NMA).

Study selection

4.10.2 *Provide details of the treatments to be compared. This should include all treatments identified in the final NICE scope. If additional treatments have been included, the rationale should be provided. For example, additional treatments may be added in order to make a connected network.*

Objective of mixed treatment comparison

The NMA was not used to inform the ACEi comparison as a head-to-head trial exists for the sacubitril valsartan versus ACEi (PARADIGM-HF, Section 4.4.1) and the results of one of the NMA scenarios aligned closely with the results of PARADIGM-HF (for further detail see Section 4.10.18 below).

Although direct evidence for sacubitril valsartan was available to inform a primary comparison against first-line therapy, ACEi, no head-to-head trials compared to ARBs have been conducted in a population with HFrEF. As ARBs have been outlined as a secondary comparator within the decision problem (for patients intolerant to ACEi), it was essential to investigate possible analyses and data sources to inform this indirect comparison.

Recently, a Cochrane SR and meta-analysis assessing the relative effect of ARBs compared with ACEis in HF with regard to morbidity and mortality was conducted by Heran et al, 2012 (184). In addition to the available published evidence, a SR and NMA was conducted and presented in this submission to incorporate the latest evidence in HF, including the PARADIGM-HF study, to provide evidence for a comparison of current treatments against sacubitril valsartan (12). In contrast to the Cochrane meta-analysis which considers both HFrEF and HFpEF study populations, the NMA presented in this section reflects the population considered in this submission, by analysing study populations with HFrEF only.

Therefore, the main objective of this NMA was to estimate the effectiveness of sacubitril valsartan compared with ARBs, as well as the effectiveness of ARBs compared with ACEi to inform the economic model inputs.

Interventions of interest

Treatments of interest were classified as single treatment classes (ACEi, ARB, and ARNI [sacubitril valsartan]) or combinations of treatment classes (including standard care therapies like beta blockers (BB) and aldosterone antagonists (AA), e.g. ACEi + BB) depending on the NMA scenario. Based on the clinical trials identified in the systematic review the individual interventions of interest included in the NMA (categorised as investigational or standard care therapies) are presented in Table 24.

Table 24: Interventions of interest for NMA

Class	Drug
Investigational therapies	
ARNI	sacubitril valsartan
ACEi	alacepril, benazepril, captopril, cilazapril, delapril, enalapril, fosinopril, imidapril, lisinopril, moexipril, perindopril, quinapril, ramipril, spirapril, trandolapril, zofenopril
ARB	azilsartan, candesartan, eprosartan, irbesartan, losartan, olmesartan, telmisartan, valsartan
Standard care therapies	
BB	acebutolol, atenolol, betaxolol, bisoprolol, bucindolol, carvedilol, celiprolol, labetalol, metoprolol, nadolol, nebivolol, penbutolol, pindolol, propranolol, sotalol, timolol
AA	eplerenone, spironolactone, canrenone

Abbreviations: AA, aldosterone antagonists; ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; ARNI, angiotensin receptor neprilysin inhibitor; BB, beta blockers; NMA, Network meta-analysis.

Treatment classes: The categorisation of treatments at the class level assumed equal efficacy across all molecules within a class. This assumption has been tested for ACEis in a SR and NMA by Chatterjee et al, 2013 (185). The findings show that “benefits of ACEi in patients with heart failure appear to be due to a class effect” and note that “there is currently no statistical evidence in support of the superiority of any single agent over the others” (185). No similar SR has been conducted to assess the class effect of ARBs, however, the aforementioned Cochrane meta-analysis (184) has assumed a class effect for ARBs. Furthermore, since guideline recommendations are made at the class level, it was of interest to compare the efficacy of treatments at the class level (rather than the molecule level).

Analysis

The core NMA presented in this submission includes data from 28 RCTs. These studies were included out of a total of 108 RCTs identified in the SR (see Figure 2) and out of 64 RCTs eligible for the NMA (See Section 4.10.3 for further detail on inclusion/exclusion criteria). Trials of 7 different ACEis and 4 ARBs were included in the core NMA.

The core NMA presented in this submission considers a simple network focusing on the comparison of investigational therapies ARNI versus ARB through an indirect comparison to ACEi independent of concomitant standard care therapies. This scenario reflects the approach taken by the Cochrane meta-analysis which assessed ACEis versus ARBs with regard to morbidity and mortality irrespective of concomitant treatment with standard care therapies (184).

The following treatments and combinations of treatments could be compared in this NMA scenario: Placebo (PLBO); ACEi; ARB; and ARNI. ARNI is the main intervention of interest and is linked to the other treatments in the network through ACEi based on data from PARADIGM-HF.

Sensitivity analyses were conducted to (1) adjust for baseline characteristics identified as potential treatment modifiers using meta-regression (See Section 4.10.15) and (2) categorise treatments based on investigational therapies in addition to concomitant standard care therapies (beta blockers and aldosterone antagonists) (See Section 4.10.17).

4.10.3 ***In a table, describe the inclusion and exclusion selection criteria, language restrictions and the study selection process. Justification should be provided to ensure that the rationale for study selection is transparent. A suggested table format is provided below.***

Please see Section 4.1.3, Table 7 for inclusion and exclusion criteria applied in the SR which led to 108 RCTs. The primary exclusion criteria for the core NMA were as follows:

- Intra-class studies (e.g. enalapril versus ramipril) that did not report relative treatment effects between different classes of drug and therefore could not inform the NMA
- Studies reporting zero events in all arms for a given outcome as this data could not inform the NMA and would only lead to greater uncertainty. This was of particular importance when a study reported safety data simply as “no deaths”, or when studies report no deaths as a reason for withdrawal
- Studies that did not report data on the outcomes of interest (See Section 4.10.6 below for further detail on selection of outcomes). Outcomes included in the NMA:
    - Deaths due to any cause
    - Deaths due to CV events (or cardiac events)
    - Hospitalisations due to all causes
- Studies reporting outcomes from drug classes that were not included in the NICE scope as the SR had a broader scope (i.e., ivabradine)

Table 25 below lists the 44 studies that were excluded from the NMA categorised by the reason for exclusion. As a result, 64 studies out of a total of 108 studies identified in the SR were eligible in the NMA.

Table 25: Studies identified in SR that were not eligible for the NMA (primary exclusion)

Reason for exclusion from NMA	Study, year	
Intraclass study n=26	Acanfora 1997 (37) Azevedo 2001 (40) Bach 1992 (41) BETACAR 2006 (77) Beynon 1997 (44) Cinquegrana 2005 (55) COMET 2003 (56, 139, 152) Dalla-Volta 1995 (64) Dirksen 1991 (69) Fosinopril in Heart Failure 1998 (167) Fuchs 1995 (80) Karabacak 2014 (71, 91, 92) Kaya 2014 (93)	Kubo 2001 (106) Kukin 1999 (107) Lainscak 2011 (108) Lombardo 2006 (114) Metra 2000 (118) Metra 2002 (119) Morisco 1997 (121) Multicentre Lisinopril-Captopril Congestive Heart Failure 1989 (82, 141) Patrianakos 2005 (132) Rengo 1995 (145) van den Broek 1997 (155) Zannad 1992 (169) ZEBRAH 1993 (38)
All-cause mortality zero events in all arms, reported only as an AE or reason for withdrawal (n=3)	Brehm 2002 (46) Crozier 1995 (63) RALES dose-finding study 1996 (142)	
No outcomes of interest (n=14)	ADEPT 2001 (123) Barr 1995 (42) Cohen-Solal 2005 (58) de Tommasi 2003 (67) Khattar 2001 (94) Krum 1996 (102) Leonetti 2000 (112)	Olsen 1995 (124) Refsgaard 2002 (143) TITRATION 2015, (170, 171) Udelson 2010 (153) Uhlir 1997 (154) Vizzardi 2010 (157) White 2007 (160)
Not a comparison of interest (n=1)	SHIFT 2010 (151)	

Abbreviation: AE, adverse event; NMA, network meta-analysis; SR, systematic review

For the core NMA, only studies that informed a comparison between investigational therapies including, ACEi versus ARB, ARB versus PLBO, ACEi versus PLBO and ARNI versus ACEi were included. This resulted in secondary exclusion of a further 36 trials, as shown in Table 26 below.

Table 26: Studies identified in SR that were not eligible for the core NMA (secondary exclusion)

Reason for exclusion from NMA	Study, year	
No comparison between investigational therapies: • ACEi vs ARB • ARB vs PLBO • ACEi vs PLBO • ARNI vs ACEi (n=36)	Colucci 1996 (62) CIBIS III 2005 (70, 105, 164) RALES 1999 (138) Val-HeFT 2001 (49, 60) BEST 2001 (75) CIBIS I 1994 (110) CIBIS II 1999 (111) COPERNICUS 2001 (79, 103, 126, 128) MERIT-HF 1999 (83, 88-90) Packer 1996 (127) Sturm 2000 (149) CHARM-added 2003 (117) EMPHASIS-HF 2011 (147, 168) Vizzardi 2014 (158) Cice 2010 (51) SENIORS 2005 (78, 122) EPHESUS 2003 (135, 137) Cice 2001 (52)	Cice 2000 (53) CARMEN 2004 (100, 144) CELICARD 2000 (130) ENECA 2005 (74) MIC 2000 (81) MOCHA 1996 (47) PRECISE 1996 (125) SYMPOXYDEX 2004 (57) Cohn 1997 (59) de Milliano 2002 (66) Krum 1995 (104) MERIT-HF (pilot study) 1999 Hamroff 1999 (87) AREA-IN CHF 2009 Cicoira 2002 (54) Dubach 2002 (72) Palazzuoli 2005a (130) Palazzuoli 2005b (131)

Abbreviations: ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; ARNI, angiotensin receptor neprilysin inhibitor; NMA, network meta-analysis; PLBO, placebo; SR, systematic review

Following primary and secondary exclusion criteria, the total number of studies eligible/non-eligible for the NMA and the core NMA are shown in Table 27 below.

Table 27: Overview of identified trials for NMA

	Total	Sacubitril valsartan	Comparators	NMA		Core NMA	
				Eligible for NMA	Not eligible for NMA	Eligible for core NMA	Not eligible for core NMA
Publications	138	4	134	88	50	39	49
RCTs	108	2	106	64	44	28	36

Abbreviation: NMA, network meta-analysis; RCT, randomised controlled trial.

4.10.4 *In a table provide a summary of the trials used to carry out the indirect comparison or mixed treatment comparison. A suggested table format is presented below. When there are more than 2 treatments in the comparator sets for synthesis, show a network diagram.*

As outlined in Section 4.10.3 above, 28 RCTs were included in the core NMA out of a total of 64 RCTs eligible for the NMA. NMA results were generated for three clinical endpoints: all-cause mortality, all-cause hospitalisation and CV mortality (see Section 4.10.6 for further detail regarding selection of outcomes).

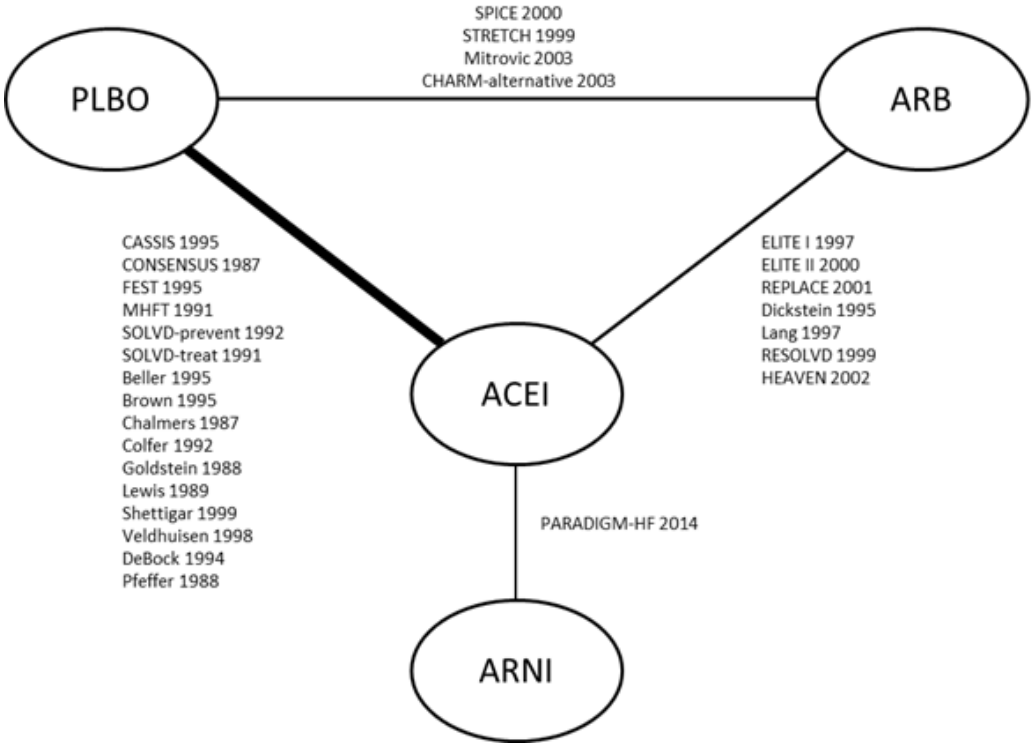
Network diagrams showing comparator sets for the following scenarios and outcomes are presented below:

- All-cause mortality (Figure 10)

- CV mortality (Figure 11)
- All-cause hospitalisation (Figure 12)

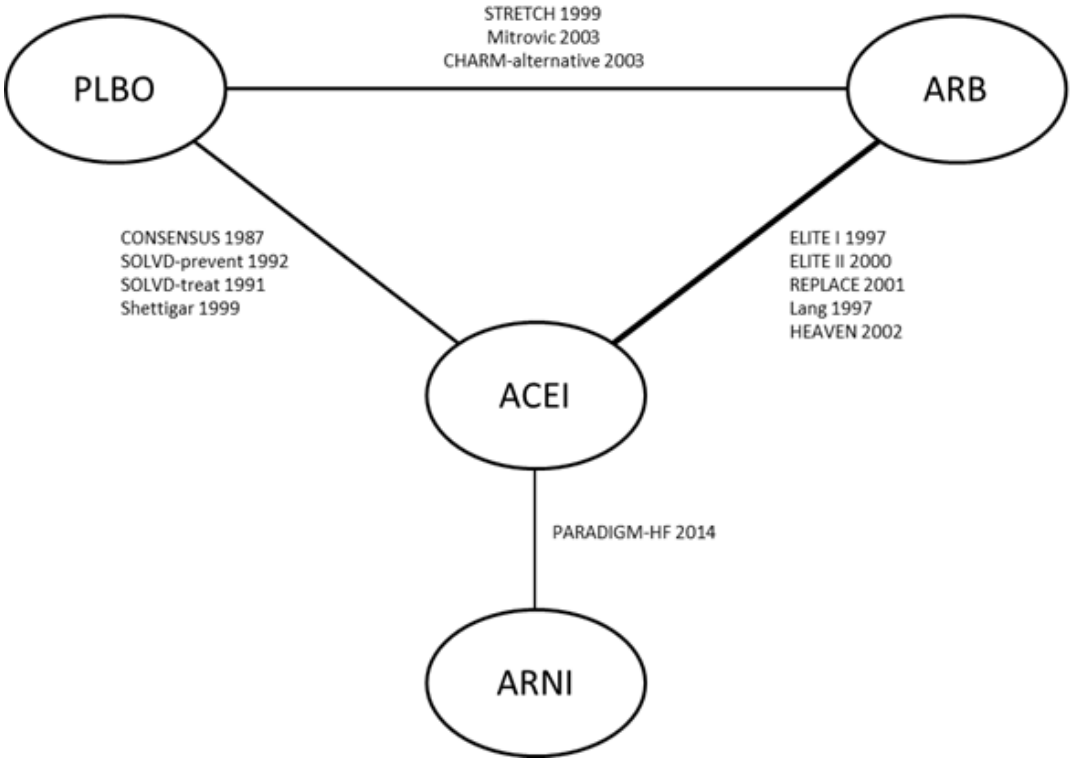
Additionally, please see Table 28 below for a tabular representation of the 28 studies included in the core NMA, indicating the treatment comparison and outcomes contributed by each study.

Figure 10: Core NMA, Network of all included studies – All cause mortality (28 RCTs, 4 treatment comparisons)



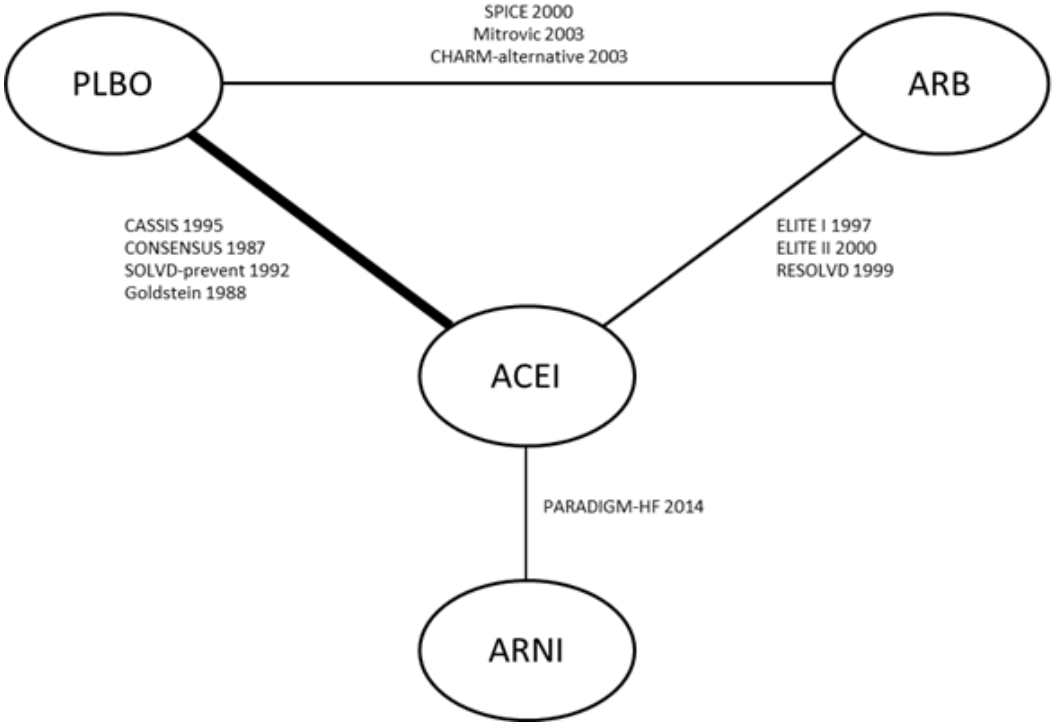
Abbreviations: ACEi; Angiotensin-converting enzyme inhibitor; ARB: Angiotensin receptor blocker; ARNI: angiotensin receptor neprilysin inhibitor; NMA, network meta-analysis; PLBO: Placebo; RCT, randomised controlled trial.

Figure 11: Core NMA, Network of all included studies – CV mortality (13 RCTs, 4 treatment comparisons)



Abbreviations: ACEi; Angiotensin-converting enzyme inhibitor; ARB: Angiotensin receptor blocker; ARNI: angiotensin receptor neprilysin inhibitor; CV, cardiovascular; NMA, network meta-analysis; PLBO: Placebo; RCT, randomised controlled trial.

Figure 12: Core NMA, Network of all included studies – All-cause hospitalisation (11 RCTs, 4 treatment comparisons)



Abbreviations: ACEi; Angiotensin-converting enzyme inhibitor; ARB: Angiotensin receptor blocker; ARNI: angiotensin receptor neprilysin inhibitor; NMA, network meta-analysis; PLBO: Placebo; RCT, randomised controlled trial.

Table 28: Treatment comparison and outcomes contributing to 28 RCTs included in core NMA

Studies in core NMA	ARNI	ACEi	ARB	PLBO	All-cause mortality	CV mortality	All-cause hospitalisation
PARADIGM-HF 2014 (10) (129)	✓	✓			✓	✓	✓
CASSIS 1995 (161, 162)		✓		✓	✓		✓
CONSENSUS 1987 (8, 95, 96, 150)		✓		✓	✓	✓	✓
FEST 1995 (76)		✓		✓	✓		
MHFT (97-99)		✓		✓	✓		
SOLVD prevention (166)		✓		✓	✓	✓	✓
SOLVD treatment (9, 140)		✓		✓	✓	✓	
Beller 1995 (43)		✓		✓	✓		
Brown 1995 (48)		✓		✓	✓		
Chalmers 1987 (50)		✓		✓	✓		
Colfer, 1992 (61)		✓		✓	✓		
Captopril-Digoxin Multicenter Research Group 1988 (39)		✓		✓	✓		✓
Lewis 1989 (113)		✓		✓	✓		
Shettigar 1999 (148)		✓		✓	✓	✓	
Veldhuisen 1998 (156)		✓		✓	✓		
DeBock 1994 (65)		✓		✓	✓		
Pfeffer 1988 (133)		✓		✓	✓		
SPICE 2000 (85)			✓	✓	✓		✓
STRETCH 1999 (146)			✓	✓	✓	✓	
Mitrovic 2003 (120)			✓	✓	✓	✓	✓
CHARM-alternative 2003 (86)			✓	✓	✓	✓	✓
ELITE I 1997 (136)	✓	✓			✓	✓	✓
ELITE II 2000 (101, 134)	✓	✓			✓	✓	✓
REPLACE 2001 (73)	✓	✓			✓	✓	
Dickstein 1995 (68)	✓	✓			✓		
Lang 1997 (109)	✓	✓			✓	✓	
RESOLVD 1999 (163)	✓	✓			✓		✓
HEAVEN 2002 (163)	✓	✓			✓	✓	

Abbreviations: ACEi; Angiotensin-converting enzyme inhibitor; ARB: Angiotensin receptor blocker; ARNI: angiotensin receptor neprilysin inhibitor; CV, cardiovascular; NMA, network meta-analysis; PLBO: Placebo; RCT, randomised controlled trial.

4.10.5 ***If the table or network diagram provided in response to section 4.10.4 does not include all the trials that were identified in the search strategy, the rationale for exclusion should be provided.***

See Section 4.10.3 for explanation regarding the secondary exclusion criteria applied to the eligible NMA studies in order to inform the core NMA.

Methods and outcomes of included studies

4.10.6 ***Provide the rationale for the choice of outcome measure chosen, along with the rationale for the choice of outcome scale selected.***

The outcomes identified for inclusion were based on the key clinical outcomes for HF (i.e. mortality and hospitalisation) which also align with the clinical data inputs for the economic model, as well as the available data (i.e. primarily PARADIGM-HF). The outcomes included in the NMA are:

- All-cause mortality
- All-cause hospitalisation
- CV mortality

4.10.7 ***Discuss the populations in the included trials, especially if they are not the same as the populations specified in the NICE scope. If they are not the same:***

The patient population in the included trials was defined as adult patients with HFrEF (defined by LVEF below 40-45% or simply reported as “reduced”) and NYHA class II-IV which is aligned with the population in the PARADIGM-HF trial, the population defined in the NICE scope and the anticipated license for sacubitril valsartan.

4.10.8 ***Describe whether there are apparent or potential differences in patient populations between the trials. If this is the case, explain how this has been taken into account.***

Clinical heterogeneity in terms of treatment definitions, outcome definitions, study characteristics, and patient characteristics were assessed. An assessment of differences within and across treatment comparisons in terms of baseline risk and the observed treatment effects was also performed.

There was considerable variation observed in the baseline characteristics between studies overall, however the 28 RCTs in the core NMA were considered broadly comparable for the purpose of this analysis and provided data on the outcomes of interest for the NMA. To account for between-study heterogeneity, both fixed and random effects models were run with random effects providing the best model fit as assessed by the deviance information criterion (DIC) (See Section 4.10.16).

In PARADIGM-HF, tests of interaction identified no differences in treatment effect between subgroups for sacubitril valsartan and ACEi (enalapril), although a nominally significant interaction was observed between NYHA class at randomisation and the effect of treatment on the primary composite endpoint (p=0.03 [without adjustment for primary comparisons] See Section 4.8). Without evidence of heterogeneity between subgroups, it is appropriate to apply the overall result to each subgroup, supporting the conclusion that there is evidence of benefit overall but no evidence that the benefit does not apply to each

subgroup (186). However, as this may not necessarily apply to the treatment effect between subgroups for ACEi and ARB and the comparison between these interventions and placebo, the following factors were identified *a priori* as potential treatment effect modifiers and analysed for the NMA based on clinical and methodological expertise: HF severity based on NYHA class, LVEF and digoxin use as well as use of concomitant standard care treatments including beta blockers and aldosterone antagonists.

Although age and gender in PARADIGM-HF vary compared to the English HFrEF population, a similar lower average age and differential gender distribution is observed in other HF trials (See Section 4.5.2) (173). Hence age and gender were not considered as a possible treatment effect modifier in the NMA.

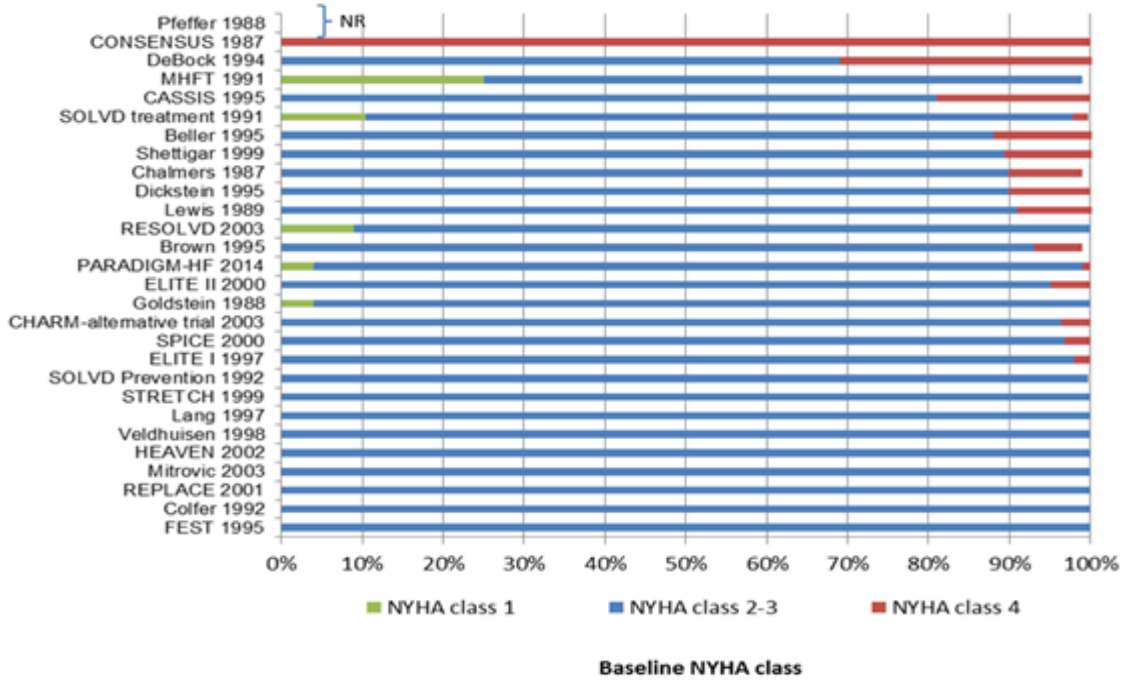
The below figures provide a summary of the distribution of values for the above patient and study characteristics across all studies identified by the systematic review.

- Figure 13 – Distribution plot of values for baseline NYHA class across studies
- Figure 14 – Distribution plot of values for baseline LVEF across studies
- Figure 15 – Distribution plot of values for baseline digoxin use across studies
- Figure 16 – Distribution plot of values for concomitant beta blocker use across studies
- Figure 17 – Distribution plot of values for concomitant aldosterone antagonist use across studies

The distribution plots for baseline characteristics indicating HF severity (NYHA class, LVEF and digoxin use) were generated for the 28 RCTs include in the core NMA to inform a sensitivity analysis where these characteristics are adjusted for using meta-regression (Section 4.10.15).

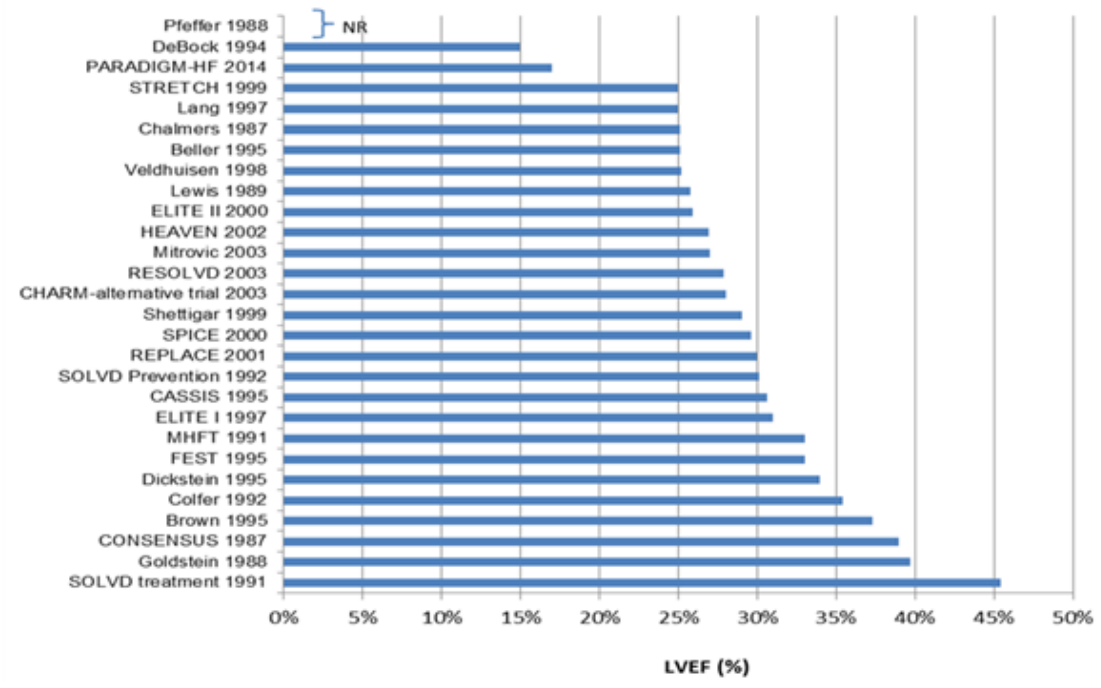
Separately, distribution plots for concomitant standard care therapies (beta blockers and aldosterone antagonists) were generated for all 64 RCTs eligible for the NMA. This informed an additional sensitivity analysis which categorised treatment nodes in the network by both investigational therapies (ARNI, ACEi and ARB) as well as any concomitant therapies (beta blockers and aldosterone antagonists). This expanded the number of RCTs in the network to 64 (Section 4.10.17).

Figure 13: Distribution plots for treatment effect modifiers –baseline NYHA class (28 RCTs)



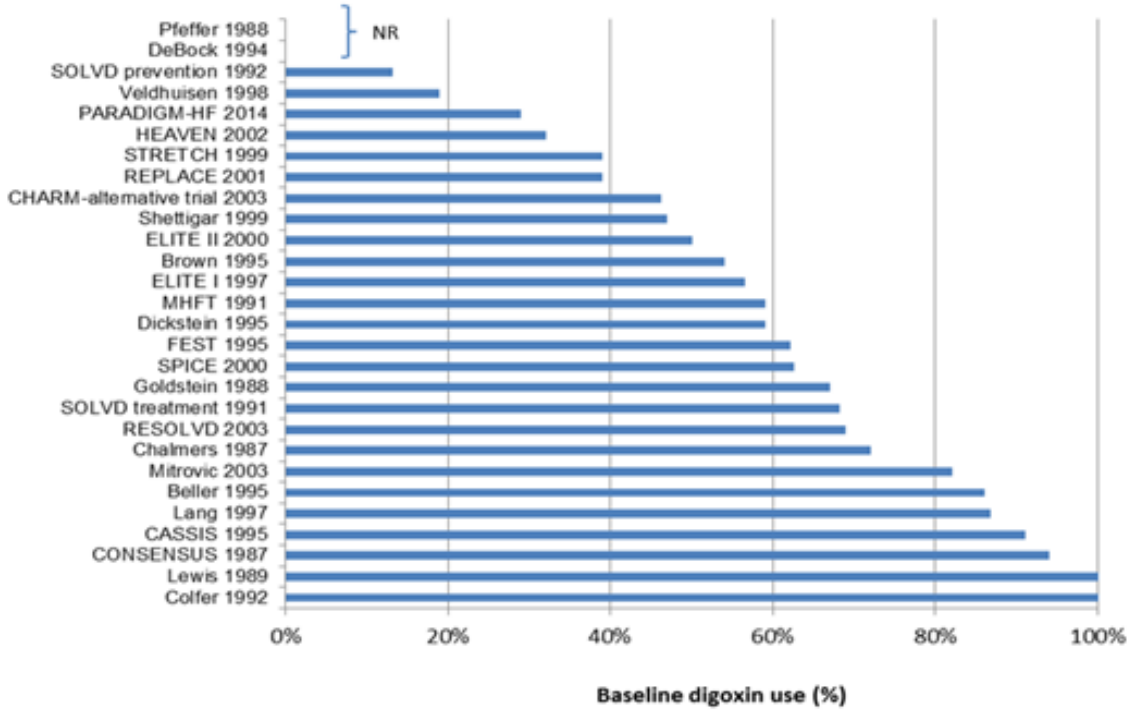
Abbreviations: NYHA, New York Heart Association; NR, not reported; RCT, randomised controlled trial.

Figure 14: Distribution plots for treatment effect modifiers – baseline LVEF (28 RCTs)



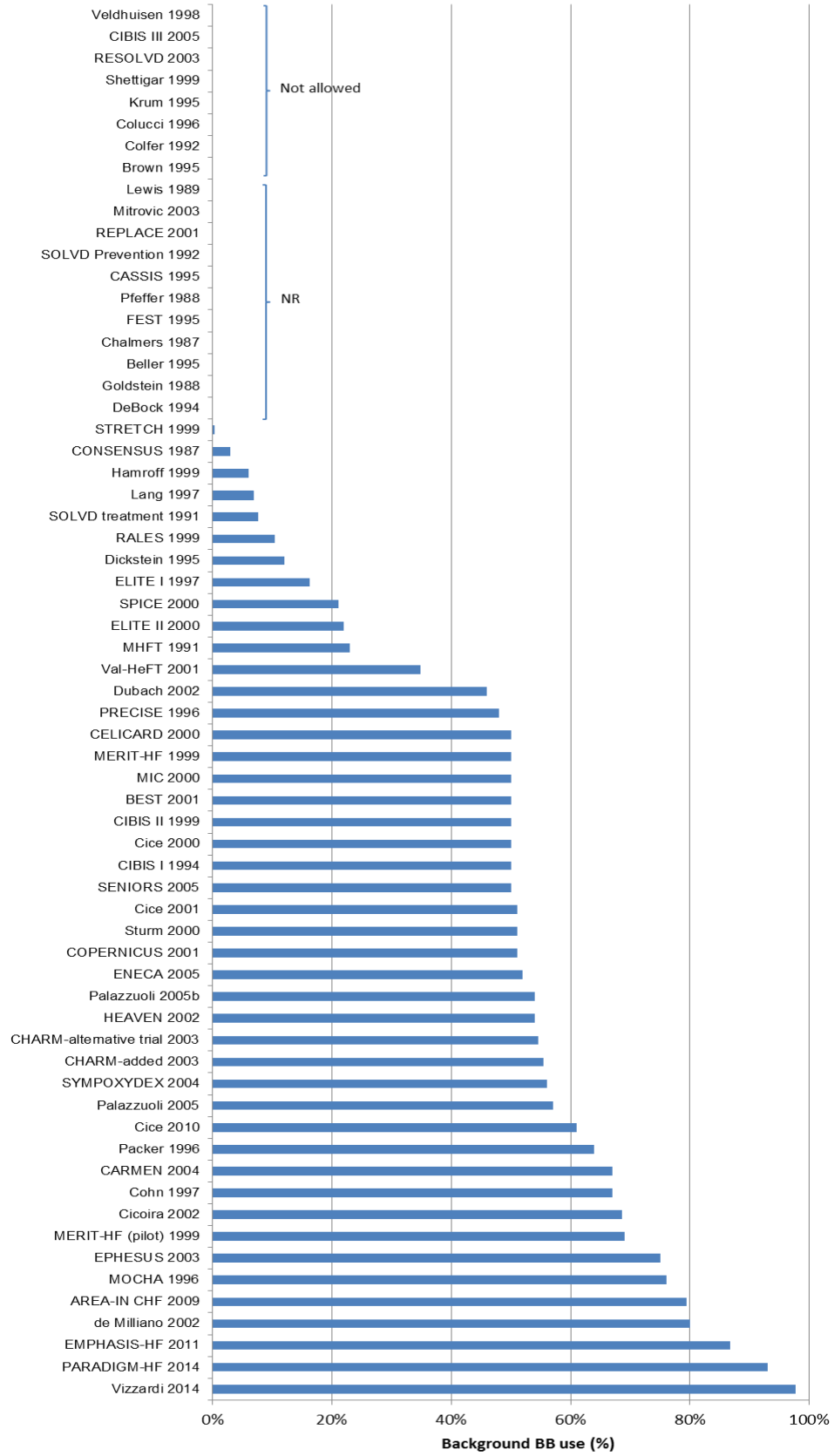
Abbreviations: LVEF, left ventricular ejection fraction; NR, not reported; RCT, randomised controlled trial.

Figure 15: Distribution plots for treatment effect modifiers – baseline digoxin use (28 RCTs)



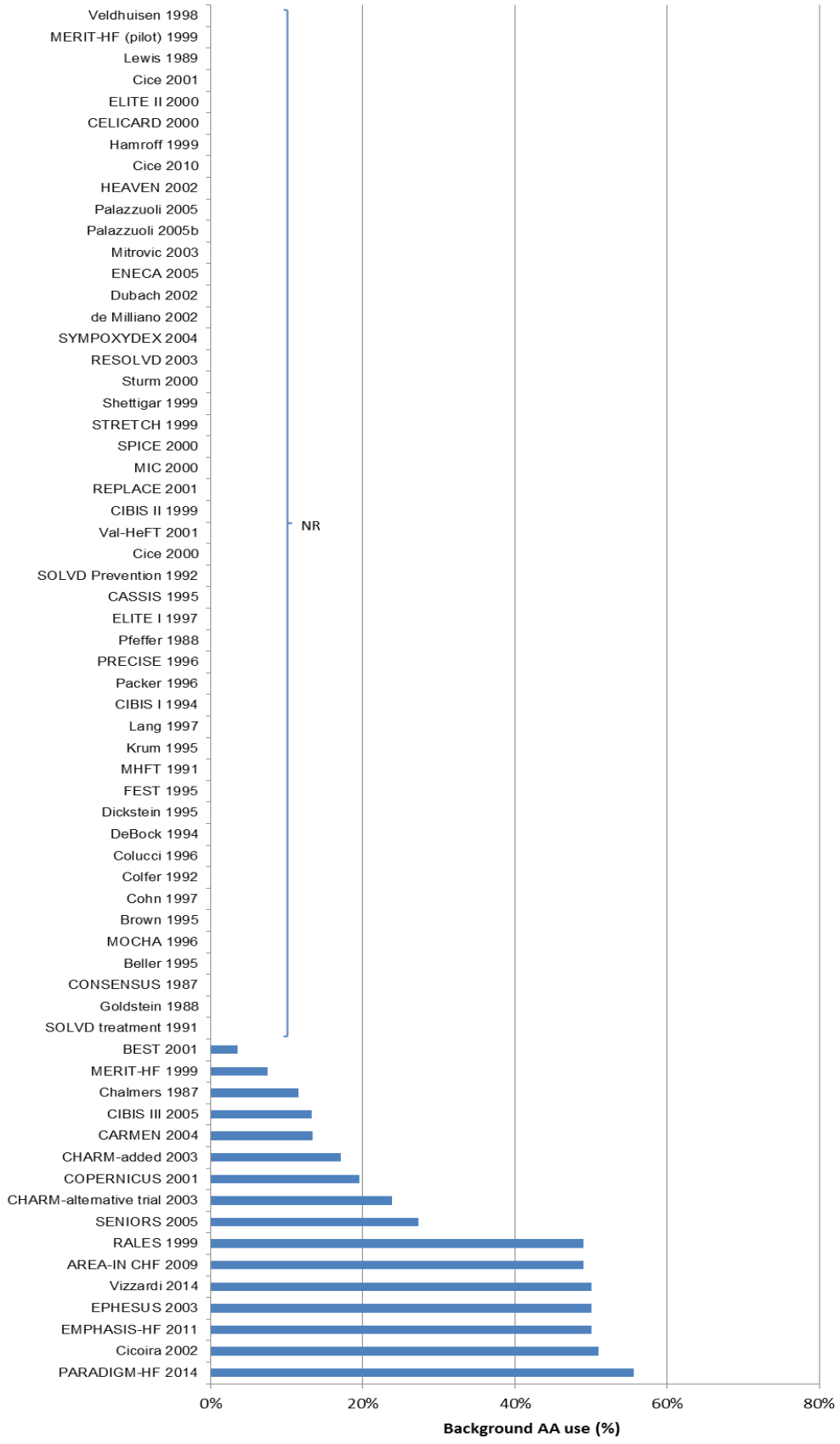
Abbreviations: NR, not reported; RCT, randomised controlled trial.

Figure 16: Distribution plots for treatment effect modifiers– baseline BB use (64 RCTs)



Abbreviations: BB, beta blocker; NR, not reported; RCT, randomised controlled trial.

Figure 17: Distribution plots for treatment effect modifiers– baseline AA use (64 RCTs)



Abbreviations: AA: Aldosterone antagonist; NR, not reported; RCT, randomised controlled trial.

4.10.9 ***In an appendix, provide the following for each trial included in response to section 4.10.4:***

Please see Appendix Section 8.5 for:

- The methods used for the trials included in the NMA (Section 8.5.1)
- The outcomes and the results for the trials included in the NMA (Section 8.5.2)
- Participants' baseline characteristics for the trials included in the NMA (Section 8.5.3)

Risk of bias

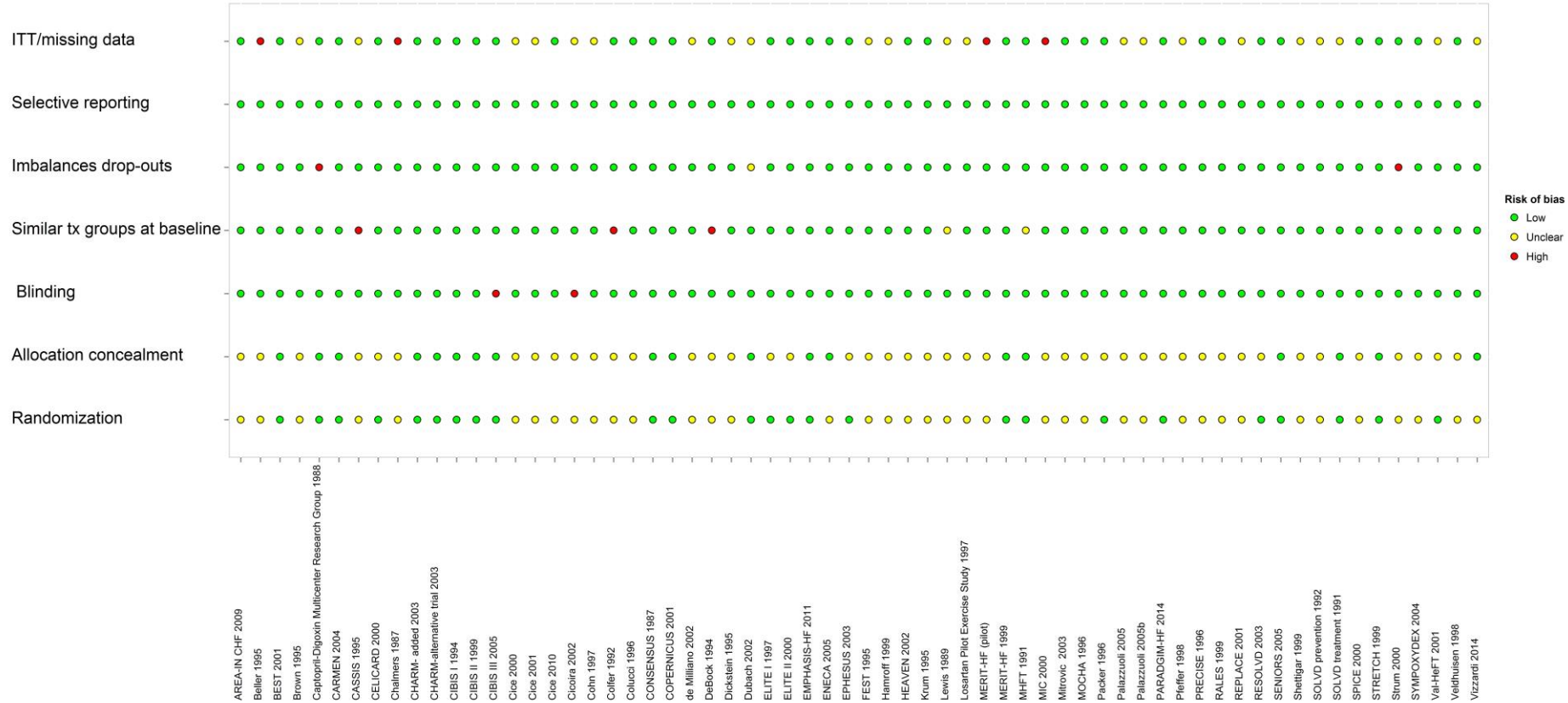
4.10.10 ***In an appendix, provide a complete quality assessment of each trial included in response to section 4.10.4.***

The validity of each trial identified in the systematic review was assessed using “Quality assessment of the study according to the Centre for Reviews and Dissemination of the University of York” (187). Please see Appendix Section 8.5.4 for a summarised quality assessment of each trial included in the NMA.

4.10.11 ***Identify any risk of bias within the trials identified, and describe any adjustments made to the analysis.***

Figure 18 provides a summary of the judgement of each risk of bias item for each trial included in the NMA. The risk of bias was categorised as low, unclear or high. Across the majority of items the risk of bias was low; however the risk of bias due to ITT missing data, allocation concealment and blinding was unclear for many studies included in the NMA. No adjustment was made to the analysis to address the potential risk of bias.

Figure 18: Summary of risk of bias assessment of all included NMA studies



Abbreviations: IIT, intention to treat; NMA, network meta-analysis

Methods of analysis and presentation of results

4.10.12 *Provide a clear description of the indirect or mixed treatment comparison methodology.*

Bayesian NMA models were used to analyse the created data set for the outcomes of interest in order to simultaneously synthesise the results of the included studies and to obtain treatment effects (188-191). NMA within the Bayesian framework involves data, a hierarchical model or likelihood function with parameters, and prior distributions (192). The model relates the data from the individual studies to basic parameters reflecting the (pooled) relative treatment effect of each intervention compared with an overall reference treatment, i.e. placebo. Based on these basic parameters, the relative efficacy between each of the competing interventions was obtained.

For the all-cause death outcome, a generalised linear model with a binary likelihood distribution and a complementary log-log (cloglog) link was used (189) where the tails of the distribution were truncated as suggested by Ntzoufras to prevent arithmetic overflow (193).

For each outcome, a fixed and a random effects approach were evaluated. The fixed effects model assumes that the differences in true relative treatment effects across studies in the network of evidence are only caused by the differences in treatment comparisons (i.e. that there is no variation in relative treatment effects for a particular pair wise comparison). The random effects model, on the other hand, assumes that differences in observed treatment effects across the studies in the network are not only caused by the different treatment comparisons, but that there is also heterogeneity in the relative effects for a particular type of comparison caused by factors that modify that relative treatment effect. With the NMA models used, the variance for trial specific relative effects is assumed constant for every treatment comparison. The random effects models are presented in the next section.

In order to identify the most appropriate model (i.e. fixed or random effects models) given the evidence base, the goodness-of-fit of model predictions to the observed data can be measured by calculating the posterior mean residual deviance, $\overline{D}$ (194). The deviance information criterion (DIC) was used to compare the fixed and random effects model and provides a measure of model fit that penalises model complexity according to $DIC = \overline{D} + pD, pD = \overline{D} - \widehat{D}\ pD$ (195) is the 'effective number of parameters' and $\widehat{D}$ is the deviance evaluated at the posterior mean of the model parameters. Given the dataset used, the random effect model was chosen over the fixed effects model unless there was enough evidence to suggest the fixed effects model was substantially different (i.e. the difference in DIC was at least 3 points lower for the fixed effects model).

In any networks where a 'closed loop' is present, unrelated means models were performed, which provide estimates of the relative treatment effects based on only the direct evidence (i.e. excluding the indirect evidence) for the treatment comparisons in which head-to-head RCTs are available. It is possible to identify inconsistencies in the closed loops by evaluating the differences between the estimates for the relative treatment effects based on the consistency NMA model and the independent means model (190). Plots of the residual deviance from the consistency model versus the

residual deviance from the unrelated means models were used to identify inconsistencies.

In order to avoid prior beliefs influencing the results of the model, non-informative prior distributions were used. Prior distributions of the relative treatment effects were normal distributions with mean 0 and a variance of 10^4. A uniform distribution with range of 0-5 was used for the prior distribution of the variance for trial specific relative effects for the random effects models.

4.10.13 *Supply any programming language in an appendix (for example the WinBUGS code).*

All analyses were performed in R using the R2OpenBUGS package to link with OpenBUGS version 3.3.2 software (see Appendix, Section 8.5 for the code).

4.10.14 *Provide the results of the analysis.*

A summary of the results from the core NMA is shown in Table 29 below for all outcomes. Outcomes presented are based on the random effects model (according to results of the DIC statistic, see Table 36 below).

The results of NMA demonstrated that ARBs and ACEis were broadly equivalent and ARNI (sacubitril valsartan) was superior to ARBs with regards to mortality and equivalent with regards to hospitalisation outcomes.

Table 29: Summary of random effects results from the core NMA

Scenario	All-cause mortality HR (95% CrI) P(better)	CV mortality HR (95% CrI) P(better)	All-cause hospitalisation HR (95% CrI) P(better)
ARB vs. ACEi			
ARNI vs. ARB			

Abbreviations: ;ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; ARNI, angiotensin receptor neprilysin inhibitor; BB, beta blockers; CrI, credible intervals; CV, cardiovascular; HR, hazard ratio; NMA, network meta-analysis; P, probability

Detailed contrast tables showing the core NMA results all treatment combinations across all scenarios and outcomes are presented below.

- All-cause mortality outcome (Table 30)
- CV mortality outcome (Table 31)
- All-cause mortality outcome, all-cause hospitalisation (Table 32)

Table 30: Core NMA, All-cause mortality (Hazard ratios, Random effects)

	Comparator				
Intervention		PLBO	ACEi	ARB	ARNI
PLBO	estimate HR (95% CrI)	1 (1,1)			
	P(better)	NA			
ACEi	estimate HR (95% CrI)		1 (1,1)		
	P(better)		NA		
ARB	estimate HR (95% CrI)			1 (1,1)	
	P(better)			NA	
ARNI	estimate HR (95% CrI)				1 (1,1)
	P(better)				NA

Abbreviations: ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; ARNI, angiotensin receptor neprilysin inhibitor; CrI, credible intervals; HR, hazard ratio; NMA, network meta-analysis; P, probability; PLBO, placebo;

Table 31: Core NMA, CV mortality (Hazard ratios, Random effects)

	Comparator				
Intervention		PLBO	ACEi	ARB	ARNI
PLBO	estimate HR (95% CrI)	1 (1,1)			
	P(better)	NA			
ACEi	estimate HR (95% CrI)		1 (1,1)		
	P(better)		NA		
ARB	estimate HR (95% CrI)			1 (1,1)	
	P(better)			NA	
ARNI	estimate HR (95% CrI)				1 (1,1)
	P(better)				NA

Abbreviations: ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; ARNI, angiotensin receptor neprilysin inhibitor; CV, cardiovascular; HR, hazard ratio; NMA, network meta-analysis; P, probability; PLBO, placebo; CrI, credible intervals

Table 32: Core NMA, All-cause hospitalisations (Hazard ratios, Random effects)

	Comparator				
Intervention		PLBO	ACEi	ARB	ARNI
PLBO	estimate HR (95% CrI)	1 (1,1)			
	P(better)	NA			
ACEi	estimate HR (95% CrI)		1 (1,1)		
	P(better)		NA		
ARB	estimate HR (95% CrI)			1 (1,1)	
	P(better)			NA	
ARNI	estimate HR (95% CrI)				1 (1,1)
	P(better)				NA

Abbreviations: ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; ARNI, angiotensin receptor neprilysin inhibitor; HR, hazard ratio; NMA, network meta-analysis; P, probability; PLBO, placebo; CrI, credible intervals

4.10.15 *Provide the results of the statistical assessment of heterogeneity. The degree of heterogeneity, and the reasons for it, should be explored as fully as possible.*

As discussed in Section 4.10.8 above, to account for between-study heterogeneity, random effects models were run, which provided the best model fit as assessed by the deviance information criterion (DIC) (see Section 4.10.16 and Table 36 below).

To further assess the degree of heterogeneity between studies, the impact of potential effect modifiers across studies on the NMA was assessed. The following baseline patient characteristics, identified *a priori* as potential treatment effect modifiers based on clinical and methodological expertise, were adjusted for by using meta-regression techniques.

- LVEF at baseline
- NYHA class at baseline
- Digoxin use at baseline

Figure 15, Figure 16 and Figure 17 present the distribution plots for these modifiers in the trials included in the core NMA. The results of the meta-regressions for the above characteristics for the core NMA are shown in Table 33 and Table 34 below for the ARB vs. ACEi and ARNI vs. ARB comparisons, respectively.

Results of these sensitivity analyses show that there is no statistical significant interaction of the covariates analysed from the beta parameter (LVEF, NYHA class, and digoxin use, see Table 33). The results were mostly consistent with the core NMA, however, ACEis are more likely to reduce hospitalisations versus ARBs and the benefit of ARNI versus ARBs are larger than in the core NMA (see Table 34 and Table 35).

Table 33: Beta parameter (β [95% CI]) for meta-regression

Outcome	Covariate		
	LVEF	NYHA class	Digoxin use
All-cause mortality	[redacted]	[redacted]	[redacted]
CV mortality	[redacted]	[redacted]	[redacted]
All cause hospitalisation	[redacted]	[redacted]	[redacted]

Abbreviations: CI, confidence internal; CV, cardiovascular; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association.

Table 34: Meta-regression results of adjustment of baseline characteristics on ARB vs. ACEi in core NMA

	All-cause mortality HR (95% CrI) P (better)	CV mortality HR (95% CrI) P (better)	All-cause hospitalisation HR (95% CrI) P (better)
Adjust for baseline LVEF	[redacted]	[redacted]	[redacted]
Adjust for baseline NYHA Class	[redacted]	[redacted]	[redacted]
Adjust for baseline digoxin use	[redacted]	[redacted]	[redacted]

Abbreviations: ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CrI, credible intervals; CV, cardiovascular; HR, hazard ratio; LVEF, left ventricular ejection fraction; NMA, network meta-analysis; NYHA, New York Heart Association; P, probability;

Table 35: Meta-regression results of adjustment of baseline characteristics on ARNI vs. ARB in core NMA

	All-cause mortality HR (95% CrI) P (better)	CV mortality HR (95% CrI) P (better)	All-cause hospitalisation HR (95% CrI) P (better)
Adjust for baseline LVEF	[redacted]	[redacted]	[redacted]
Adjust for baseline NYHA Class	[redacted]	[redacted]	[redacted]
Adjust for baseline digoxin use	[redacted]	[redacted]	[redacted]

Abbreviations: ARB, angiotensin II receptor blocker; ARNI, angiotensin receptor neprilysin inhibitor; HR, hazard ratio; LVEF, left ventricular ejection fraction; NMA, network meta-analysis; NYHA, New York Heart Association; P, probability; CrI, credible intervals

4.10.16 *Justify the choice of random or fixed effects model.*

Where model likelihoods and data were consistent (i.e. fixed and random effects models with and without covariates), the DIC was used to compare the fixed and random effects model and provides a measure of model fit that penalizes model complexity according to

$DIC = \overline{D} + pD, pD = \overline{D} - \hat{D}$. pD is the 'effective number of parameters' and $\hat{D}$ is the deviance evaluated at the posterior mean of the model parameters. Where it can be compared, the model with the lowest DIC, and therefore the most parsimonious model was considered the base case model given the dataset used. If the DIC was comparable (i.e. within 3-5 points), the more conservative model was preferred (i.e. if results of fixed and random effect models result in comparable DIC value, the random effects model was preferred). Due to the known heterogeneity in the evidence base, the random effects model was the more appropriate method. Table 36 provides the summary of DIC scores and the between-study heterogeneity parameter (SD) per outcome measure.

Table 36: Summary of model fit (DIC) scores for core NMA

Outcome measure	Fixed effects	Random effects	SD (95% CI)†	Model presented
All-cause mortality	[redacted]	[redacted]	[redacted]	Random effects
All-cause hospitalisation	[redacted]	[redacted]	[redacted]	Random effects
CV mortality	[redacted]	[redacted]	[redacted]	Random effects

Abbreviations: CI, confidence interval; CV, cardiovascular; DIC, deviance information criterion; NMA, network meta-analysis; SD, standard deviation
† SD represents the between study heterogeneity
Note, if the DIC suggested a comparable fit for FE and RE models (i.e. within 3-5 points) , the RE model was preferred. Lower absolute DIC suggests a better fit.

Random effects models were determined to be the model with the best fit for the data presented based on the DIC. This model accounts for between-study heterogeneity from these influential studies contributing points outside the DIC parabola in the NMA as shown in leverage plots. The between-study heterogeneity parameters for the random effects model is provided in Table 36 for all three outcomes of the core NMA.

4.10.17 *If there is doubt about the relevance of particular trials, present separate sensitivity analyses in which these trials are excluded.*

Further to the sensitivity analyses (meta-regressions for treatment effect modifiers) described in Section 4.10.15, sensitivity analyses were conducted to assess the impact on results of modifying categorisation of treatments based on consideration of concomitant standard care therapies.

In this scenario, treatments or treatment combinations included in the network were defined by both investigational therapies (ARNI, ACEi or ARB) and any concomitant standard care therapies (BB or AA). In this scenario, when ≥50% patients in the included studies were reported to receive a concomitant class of interest at the beginning of the trial, the treatment categorisation in the NMA network was based on the investigational intervention in combination with the concomitant class (e.g. ACEi + BB versus BB). As a result, all the 64 RCTs eligible for inclusion in the NMA were considered in this scenario.

The ≥50% threshold was developed based on feedback from clinical experts and the evaluation of a range of cut-points (50%-75%). The 50% threshold yielded clinically meaningful results in previous analyses (196), showing monotherapies to be less effective than combination therapies and regimens including three or more treatment

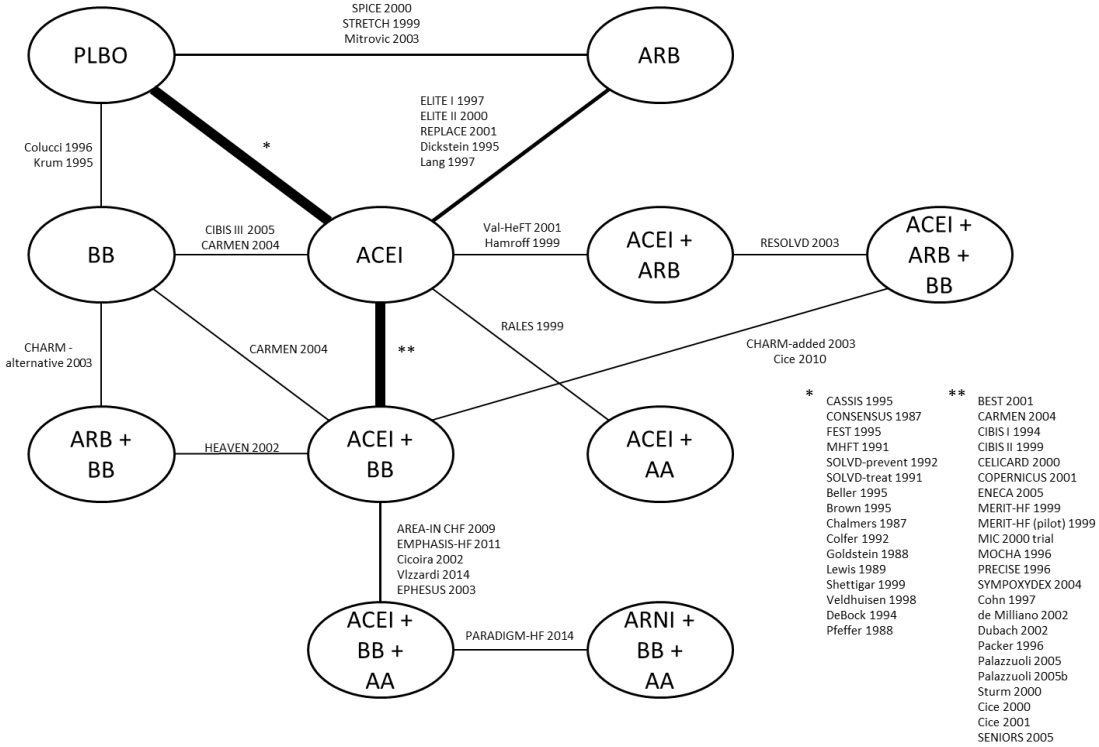
classes likely to be most efficacious. Where BB or AA use was not reported in a study, no treatment was assumed with the particular medication.

Based on the evidence base identified in the systematic review, the following treatments and combinations of treatments could be compared in this NMA scenario: PLBO; ACEi; ARB; BB; ACEi + BB; ARB + BB; ACEi + ARB; ACEi + AA; ACEi + ARB + BB; ACEi + BB + AA and ARNI + BB + AA. In this scenario, ARNI + BB + AA is the main intervention of interest for these analyses and linked to the other treatments in the network through ACEi + BB + AA based on data from PARADIGM-HF.

The categorisation of treatments from PARADIGM-HF as triple-therapies is a result of the fact that ≥50% patients in the RCT were receiving background BB and AA therapy (93% and 54%, respectively). None of the identified RCTs reported data for the treatment combination ARB + BB + AA (given the ≥50% concomitant treatment threshold), therefore ARNI + BB + AA and ACEi + BB + AA were compared against ARB + BB in this scenario.

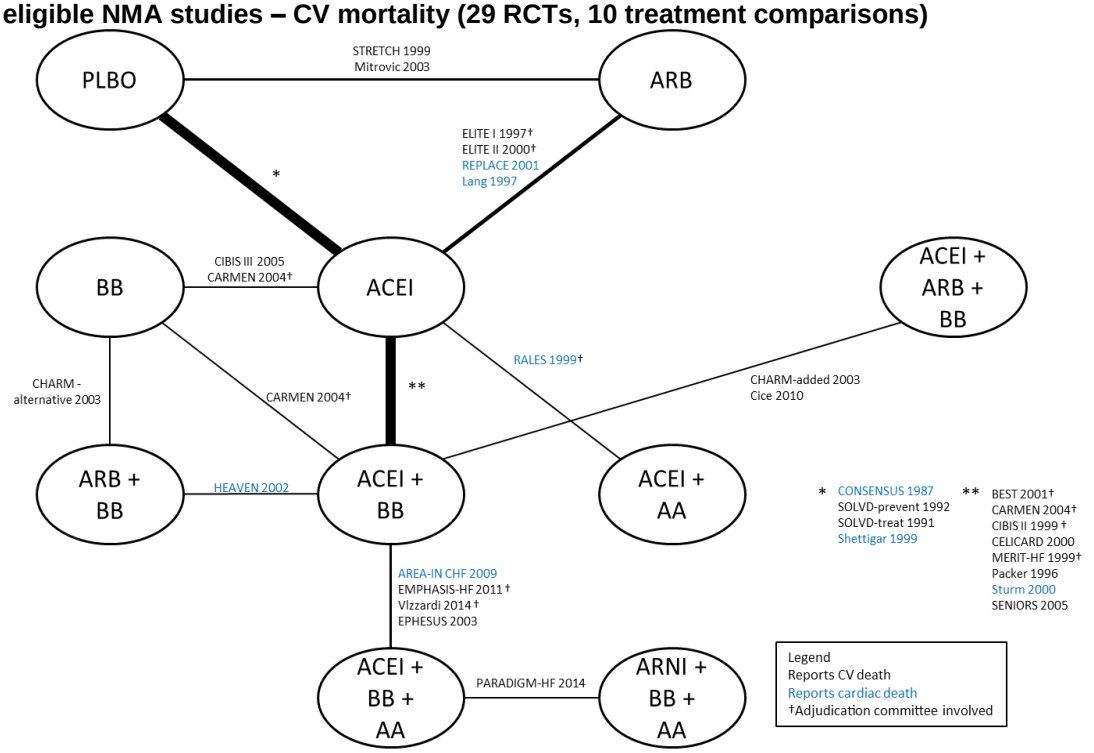
Figure 19, Figure 20 and Figure 21 show the network diagrams for the all-cause mortality, CV mortality and all-hospitalisation outcomes in this scenario respectively. Random effects models were chosen as the best fit for this data based on the DIC. Table 37 below provides a summary of the results of this scenario. The contrast tables for these results are presented in the appendices (see Section 8.7).

Figure 19: NMA scenario considering concomitant standard care therapies, Network of all eligible NMA studies – All-cause mortality (64 RCTs, 11 treatment comparisons)



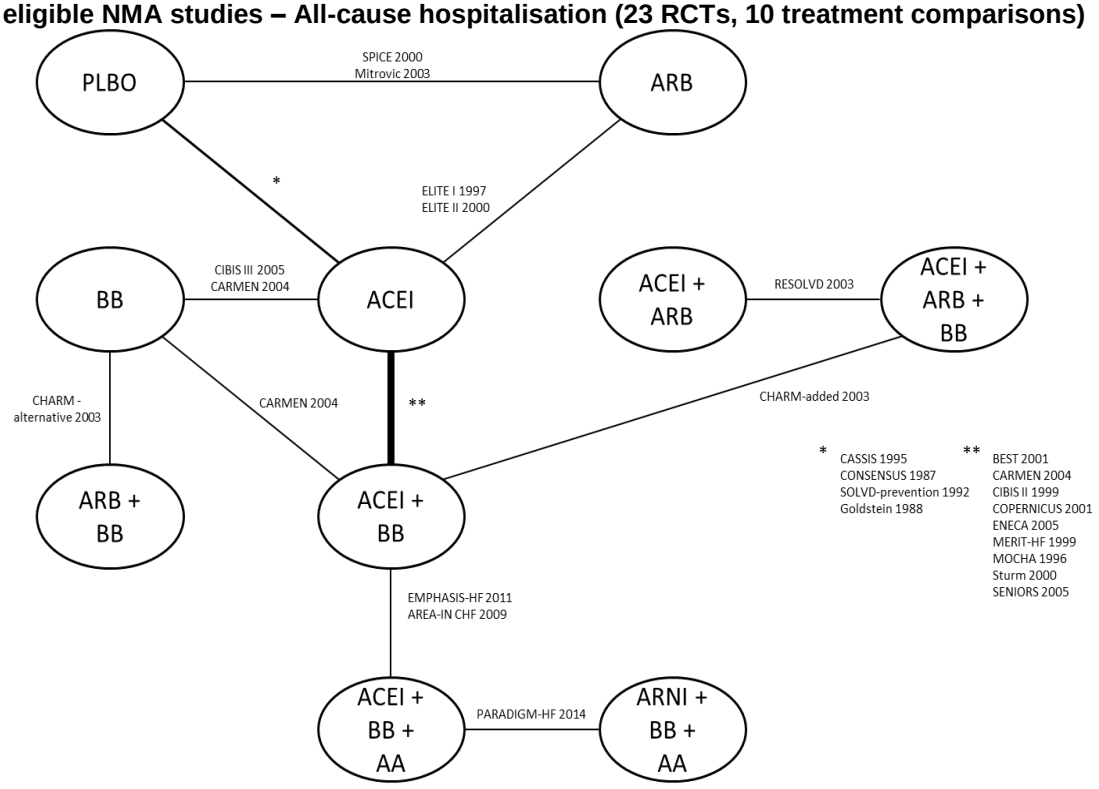
Abbreviations: AA, Aldosterone antagonist; ACEi; Angiotensin-converting enzyme inhibitor; ARB: Angiotensin receptor blocker; ARNI: angiotensin receptor neprilysin inhibitor; BB: Beta blocker; NMA, network meta-analysis; PLBO: Placebo; RCT, randomised controlled trial.

Figure 20: NMA scenario considering concomitant standard care therapies, Network of all eligible NMA studies – CV mortality (29 RCTs, 10 treatment comparisons)



AA: Aldosterone antagonist; ACEi; Angiotensin-converting enzyme inhibitor; ARB: Angiotensin receptor blocker; ARNI: angiotensin receptor neprilysin inhibitor; BB: Beta blocker; NMA, network meta-analysis; PLBO: Placebo; RCT, randomised controlled trial.

Figure 21: NMA scenario considering concomitant standard care therapies, Network of all eligible NMA studies – All-cause hospitalisation (23 RCTs, 10 treatment comparisons)



AA: Aldosterone antagonist; ACEi; Angiotensin-converting enzyme inhibitor; ARB: Angiotensin receptor blocker; ARNI: angiotensin receptor neprilysin inhibitor; BB: Beta blocker; PLBO: Placebo

Table 37: Summary of results from the standard care therapy NMA scenario

Comparison	All-cause mortality HR (95% CrI) P(better)	CV mortality HR (95% CrI) P(better)	All-cause hospitalisation HR (95% CrI) P(better)
ARB+BB vs. ACEi+BB+AA	[redacted]	[redacted]	[redacted]
ARNI+BB+AA vs. ARB+BB	[redacted]	[redacted]	[redacted]

Abbreviations: AA, aldosterone antagonist; ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; ARNI, angiotensin receptor neprilysin inhibitor; BB, beta blocker; CrI, credible intervals; CV, cardiovascular; HR, hazard ratio; NMA, network meta-analysis; P, probability

4.10.18 *Discuss any heterogeneity between results of pairwise comparisons and inconsistencies between the direct and indirect evidence on the technologies.*

No pairwise meta-analyses were conducted as a NMA was performed. However, Cochrane performed a recent pairwise meta-analysis in patients with HF (HFrEF and HFpEF) comparing ACEis vs ARBs (184). Most studies included in the comparisons were the same with the exception of the following:

- ***All-cause mortality:*** Mazayev et al, 1998 (197), did not specify whether the population was HFrEF or HFpEF and was therefore excluded from the NMA
- ***CV mortality:*** REPLACE 2001 (73) was not included in the Cochrane meta-analysis. In the NMA, CV death was derived from the description of cardiac deaths in the article [b], it is expected Cochrane excluded this as it doesn't specifically state CV death.
- ***All-cause hospitalisation:*** no differences

Table 38 presents the comparison of the results of the NMA and Cochrane meta-analysis; results of these two analyses were broadly consistent.

[b] There were six deaths: two on telmisartan 20 mg (ventricular fibrillation; sudden death); one on telmisartan 40 mg (sudden death); one on telmisartan 80 mg (sudden death), and two on enalapril 20 mg sudden death; myocardial infarction, dyspnoea, pulmonary oedema).

Table 38: Comparison of results from NMA and Cochrane meta-analysis (184)

Scenario	All-cause mortality HR (95% CrI) P(better)	CV mortality HR (95% CrI) P(better)	All-cause hospitalisation HR (95% CrI) P(better)
Core NMA			
ARB vs. ACEi	[redacted]	[redacted]	[redacted]
Cochrane meta-analysis			
ARB vs. ACEi	1.05 (0.91, 1.22)	1.08 (0.91, 1.28)	1.00 (0.92, 1.08)

Abbreviations: ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CrI, credible intervals; CV, cardiovascular; HR, hazard ratio; NMA, network meta-analysis; P, probability

Although the comparison between ACEi and ARNI in the NMA was not part of a closed loop, the outcomes were compared to the outcomes from PARADIGM-HF (see Table 39). The results of the NMA were consistent with the results from PARADIGM-HF.

Table 39: Results of ACEi comparison from NMA versus PARADIGM-HF

Outcome measure	ARNI vs. ACEi	
	Core NMA HR (95% CrI)	PARADIGM-HF trial HR (95% CI)
All-cause mortality	[redacted]	0.84 (0.76,0.93)
CV mortality	[redacted]	0.80 (0.71, 0.89)
All-cause hospitalisation	[redacted]	0.88 (0.82, 0.94)

Abbreviations: ACEi, angiotensin converting enzyme inhibitor; ARNI, angiotensin receptor neprilysin inhibitor; CV, cardiovascular; CI, confidence interval; CrI, credible intervals; HR, hazard ratio; NMA, network meta-analysis

No significant inconsistencies were identified in the NMA. The posterior mean deviance contribution figures do not show any difference between the consistency and unrelated means models. Table 40 below compares the DICs between the inconsistency and consistency models and shows that the consistency model is the better fit (i.e. lower value).

Table 40: DICs between consistency and inconsistency models for core NMA

Scenario	Outcome	DIC	
		Inconsistency model	Consistency model
Core	All-cause mortality	[redacted]	[redacted]
	CV mortality	[redacted]	[redacted]
	All cause hospitalisation	[redacted]	[redacted]
Additional	All-cause mortality	[redacted]	[redacted]
	CV mortality	[redacted]	[redacted]
	All cause hospitalisation	[redacted]	[redacted]

Abbreviations: CV, cardiovascular; DIC, deviance information criterion; NMA, network meta-analysis.

4.11 *Non-randomised and non-controlled evidence*

A non-RCT search was not conducted, as all clinical data on sacubitril valsartan is in the possession of Novartis. Novartis confirm that no other additional relevant studies have been performed outside their organisation.

4.12 *Adverse reactions*

The identification of clinical evidence is described in Section 4.1. All trials relevant to this submission are listed in Table 8 in Section 4.2.1. Safety results from studies primarily designed to assess efficacy (PARADIGM-HF) are described in Section 4.12.1. The methodology and results of the relevant trial designed primarily to assess safety outcomes (TITRATION) are presented in Section 4.12.2.

4.12.1 *In a table, summarise adverse reactions reported in the studies listed in section 4.2.*

PARADIGM-HF

Run-in period

The run-in design allowed a careful assessment of the patients' tolerability to the target doses of enalapril (10 mg bid) and sacubitril valsartan (200 mg bid) prior to randomisation. During the run-in period, 6.05% and 5.51% of patients discontinued study medication due to adverse events during the enalapril and the sacubitril valsartan run-in periods, respectively.

Interpretation of the safety data from the run-in period is limited by the sequential design, which meant that patients entering the sacubitril valsartan run-in had been exposed to enalapril, but when entering the enalapril run-in, patients had not been exposed to sacubitril valsartan. Furthermore, patients were exposed to enalapril for a substantially shorter time than to sacubitril valsartan (median exposure to enalapril was 15 days versus 29 days to sacubitril valsartan).

In the run-in period, 22.48% and 28.65% of patients experienced one or more adverse event in the enalapril and the sacubitril valsartan phase, respectively. The most frequent adverse events during the run-in phase were hyperkalaemia, hypotension and renal impairment for both treatment groups in addition to cough for enalapril only (with no event occurring in more than approximately 3% of patients). One or more serious

adverse events occurred in 2.61% and 3.45% of patients in the enalapril and sacubitril valsartan run-in periods, respectively. One or more treatment related adverse events (cough, hyperkalaemia, renal impairment or hypotension) were reported by 6.28% and 7.26% of patients in the enalapril and sacubitril valsartan run-in periods, respectively.

Double-blind trial period

The overall adverse event profile was comparable between sacubitril valsartan and enalapril. The mean duration of treatment was similar between the two treatment groups (24.66 months in the sacubitril valsartan group and 23.91 months in the enalapril group). Table 41 presents a summary of adverse events in the double-blind trial period.

Table 41: Summary of adverse events in the double-blind trial period of PARADIGM-HF

Adverse events (SAF)	**Sacubitril valsartan n=4,203 n (%)**	**Enalapril n=4,229 n (%)**
≥1 adverse event	3,419 (81.35)	3,503 (82.83)
≥1 treatment related adverse event	910 (21.65)	976 (23.08)
Hypotension	430 (10.23)	293 (6.93)
Hyperkalaemia	193 (4.59)	237 (5.60)
Renal impairment	117 (2.78)	179 (4.23)
Cough	64 (1.52)	161 (3.81)
≥1 serious adverse event	1,937 (46.09)	2,142 (50.65)
Cardiac failure	588 (13.99)	649 (15.35)
Pneumonia	155 (3.69)	181 (4.28)
Cardiac failure chronic	112 (2.66)	135 (3.19)
Cardiac failure congestive	112 (2.66)	140 (3.31)
AF	108 (2.57)	113 (2.67)
Cardiac death	85 (2.02)	114 (2.70)
≥1 treatment related serious adverse event	111 (2.64)	174 (4.11)
Cardiac disorders	58 (1.37)	38 (0.90)
Cardiac failure	26 (0.61)	19 (0.45)
Discontinuation due to adverse events	450 (10.7)	516 (12.2)
Cardiac failure leading to discontinuation	63 (1.50)	65 (1.54)
Deaths	729 (17.3)	848 (20.1)
Deaths (Randomised set)	**Sacubitril valsartan n=4,209 n (%)**	**Enalapril n=4,233 n (%)**
Deaths	714 (16.96)	837 (19.77)
CV death	560 (13.30)	694 (16. 39)
Sudden death	251 (5.96)	311 (7.35)
Pump failure	147 (3.49)	185 (4.37)
Presumed CV death	67 (1.59)	95 (2.24)

Abbreviations: AF, atrial fibrillation; CV, cardiovascular; SAF, safety population

The most common adverse events (≥2% of patients in any group) are presented in Table 42.

- Due to greater vasodilator effect, treatment with sacubitril valsartan was associated with a higher rate of hypotension. However there was no increase in the rate of discontinuation because of possible hypotension-related adverse effects. In addition, the incidence of dizziness was also higher in the sacubitril valsartan group compared with the enalapril group.
- Fewer patients receiving sacubitril valsartan experienced renal adverse events compared with those receiving enalapril. This difference was driven by a lower incidence of renal impairment and renal failure on sacubitril valsartan (10.14% and 2.66%, respectively) compared with enalapril (11.52% and 3.41%, respectively). The rate of acute renal failure was similar between the treatment groups (2.26% and 2.20%, respectively).
- Other adverse events that were more frequent in the enalapril group vs. the sacubitril valsartan group included hyperkalaemia, cardiac failure, cough, dyspnoea, hypertension, hyperuricemia, and constipation.

The adverse events of special interest included hypotension, angioedema, and cognitive impairment. These adverse events were identified as possibly associated with mechanism of action of treatment and hence identified as special interest. These adverse events are determined in categories associated with this adverse event, which is different from the determination of the adverse events summarised in Table 42 (See Table 9-6 of the CSR (11)).

- Hypotension was reported more frequently in the sacubitril valsartan group (24.43% vs. 18.59%).
- The treatment groups were comparable in the incidence of adverse events in both narrow (approximately 0.3%) and broad (approximately 2%) dementia SMQs.
- There was also no difference between the two treatment groups with regard to angioedema (approximately 7.25%) (per broad and narrow SMQs) and other safety topics.

For a detailed summary of all adverse events of special interest, please see Table 12-16 in the CSR (11).

Table 42: Most common adverse events (≥2% of patients in any group) during the double-blind period by preferred term and treatment group (Safety set)

Adverse events	Sacubitril valsartan, N=4,203 n (%)	Enalapril, N=4,229 n (%)
Hypotension	740 (17.61)[†]	506 (11.97)
Cardiac failure	730 (17.37)	832 (19.67)
Hyperkalaemia	488 (11.61)	592 (14.00)
Renal impairment	426 (10.14)	487 (11.52)
Cough	369 (8.78)	533 (12.60)
Dizziness	266 (6.33)	206 (4.87)
Atrial fibrillation	251 (5.97)	236 (5.58)
Pneumonia	227 (5.40)	237 (5.60)
Oedema peripheral	215 (5.12)	213 (5.04)
Dyspnoea	213 (5.07)	306 (7.24)
Nasopharyngitis	204 (4.85)	175 (4.14)
Upper respiratory tract infection	203 (4.83)	201 (4.75)
Urinary tract infection	199 (4.73)	195 (4.61)
Diarrhoea	194 (4.62)	189 (4.47)
Bronchitis	183 (4.35)	224 (5.30)
Angina pectoris	172 (4.09)	170 (4.02)
Anaemia	168 (4.00)	201 (4.75)
Back pain	164 (3.90)	138 (3.26)
Influenza	159 (3.78)	132 (3.12)
Hypokalaemia	139 (3.31)	107 (2.53)
Cardiac failure chronic	135 (3.21)	155 (3.67)
Cardiac failure congestive	133 (3.16)	167 (3.95)
Arthralgia	126 (3.00)	119 (2.81)
Hypertension	126 (3.00)	193 (4.56)
Fatigue	125 (2.97)	129 (3.05)
Diabetes mellitus	123 (2.93)	134 (3.17)
Gout	121 (2.88)	120 (2.84)
Renal failure	112 (2.66)	144 (3.41)
Hyperuricaemia	108 (2.57)	151 (3.57)
Ventricular tachycardia	108 (2.57)	137 (3.24)
Non cardiac chest pain	106 (2.52)	122 (2.88)
Headache	103 (2.45)	106 (2.51)
Renal failure acute	95 (2.26)[‡]	93 (2.20)[‡]
Syncope	94 (2.24)[§]	114 (2.70)
COPD	93 (2.21)	106 (2.51)

Adverse events	Sacubitril valsartan, N=4,203 n (%)	Enalapril, N=4,229 n (%)
Insomnia	92 (2.19)	92 (2.18)
Pain in extremity	92 (2.19)	100 (2.36)
Asthenia	88 (2.09)	78 (1.84)
Nausea	88 (2.09)	100 (2.36)
Cardiac death	86 (2.05)	114 (2.70)
Constipation	86 (2.05)	124 (2.93)
Pyrexia	78 (1.86)	85 (2.01)
Cardiac failure acute	72 (1.71)	100 (2.36)
Vomiting	71 (1.69)	85 (2.01)

Abbreviations: COPD, chronic obstructive pulmonary disease
[†]One additional patient in the sacubitril valsartan group had a hypotension event that was recorded in the safety database, but not in the clinical database for an overall total of 741 (17.63%).
[‡]One additional patient in each group had a renal failure acute event that was recorded in the safety database, but not in the clinical database for an overall total of 96 (2.28%) and 94 (2.22%) in the sacubitril valsartan and enalapril groups, respectively.
[§]One additional patient in the sacubitril valsartan group had a syncope event that was recorded in the safety database, but not in the clinical database for an overall total of 95 (2.26%).

4.12.2 *Provide details of any studies that report additional adverse reactions to those reported in section 4.2.*

Search strategy to identify trials designed to primarily assess safety

Please see Section 4.1. The TITRATION study was identified during hand searching, as part of the clinical systematic review.

TITRATION

TITRATION was a Phase II, multicentre, randomised, double-blind study designed to assess the safety and tolerability of initiating sacubitril valsartan in HF patients, naïve to or receiving varying doses or ACEi/ARB, comparing two titration regimens to achieve a target dose of sacubitril valsartan 200 mg bid (twice daily) (176).

Summary of methodology of trials designed to primarily assess safety

Study objective

Primary: To characterise the safety and tolerability of initiating sacubitril valsartan in patients with HFrEF with 3-week and 6-week up-titration regimens over 12 weeks based on reported adverse events and laboratory assessments.

Secondary: To evaluate the proportion of patients who:

- achieved treatment success in the two treatment groups, defined as those achieving and maintaining sacubitril valsartan 200 mg bid without any dose interruption or down-titration over 12 weeks
- tolerated a regimen of sacubitril valsartan 200 mg bid for at least 2 weeks leading to study completion, regardless of previous dose interruption or down-titration

Study design

TITRATION was a multicentre, randomised, double-blind, parallel-group study conducted to evaluate the safety and tolerability of sacubitril valsartan comparing two up-titration regimens in both outpatients and hospitalised patients with HFrEF. Randomisation was stratified based on patient levels of RAAS inhibition as follows:

- **High RAAS stratum:** patients receiving >160 mg of valsartan or >10 mg total daily dose of enalapril, or equivalent doses of other angiotensin II receptor blockers (ARBs)/angiotensin converting enzyme inhibitors (ACEis), respectively, at screening
- **Low RAAS stratum:** patients receiving ≤160 mg of valsartan or >10 mg total daily dose of enalapril, or equivalent doses of other ACEis/ARBs, respectively, at screening. This included patients who were not receiving an ACEi or an ARB 4 weeks prior to screening (ACEi/ARB naive patients)

At least 25% (but not more than 50%) of randomised patients were planned to be in the low RAAS inhibition stratum.

The study comprised three phases (see Figure 22):

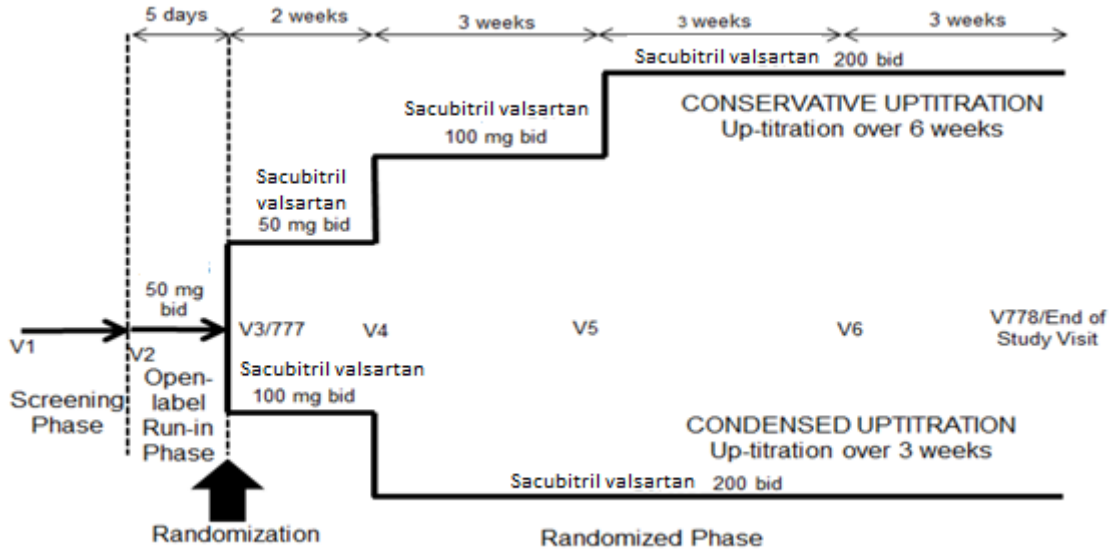
a) Screening (for inclusion and exclusion criteria)

b) Open-label sacubitril valsartan run-in phase: 1-week duration. Patients who met entry criteria and completed the ACEi-free washout period (if required) attended Visit 2 within approximately 1 week after Visit 1 and began taking open-label sacubitril valsartan 50 mg bid. Eligible hospitalised patients also took study medication while in hospital and before discharge.

c) Randomised phase: 11-week duration. Patients who successfully completed the open-label run-in and tolerated sacubitril valsartan 50 mg bid were randomised to receive double blind sacubitril valsartan at one of two titration schemes in a 1:1 ratio.

All patients in the study received sacubitril valsartan with the intent to uptitrate them to the target dose of 200 mg bid.

Figure 22: TITRATION study design



Abbreviations: bid, twice daily; V, visit.

All patients in the study received sacubitril valsartan with the intent to uptitrate them to the target dose of 200 mg bid.

Key inclusion and exclusion criteria

Key eligibility criteria for TITRATION study are provided in Table 43. The patient population in TITRATION included patients who were treatment naïve prior to enrolment, patients with different prior exposures to RAAS, as well as outpatients and inpatients.

Table 43: Eligibility criteria for TITRATION

Key inclusion criteria	Key exclusion criteria
• ≥18 years old • Diagnosis of CHF, NYHA class II–IV • LVEF ≤35% at screening [redacted]	• Previous history of intolerance to recommended target doses of ACEi or ARB • Symptomatic hypotension and/or SBP <100 mmHg or SBP>180 mmHg at screening • eGFR <30 mL/min per 1.73 m^2 • Serum potassium >5.2 mmol/L at screening [redacted]

Abbreviations: ACEi, angiotensin converting enzyme inhibitor; ACS, acute coronary syndrome; ARB, angiotensin II receptor blocker; CHF, chronic heart failure; CRT, cardiac resynchronisation therapy; CRT-D, cardiac resynchronisation therapy-defibrillator; CRT-P, cardiac resynchronisation therapy pacemaker; CV, cardiovascular; eGFR, estimated glomerular filtration rate; HF, heart failure; ICD, implantable cardioverter defibrillator; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; SBP, systolic blood pressure; TIA, transient ischaemic attack

Study drugs

Patients were assigned to one of the following treatment arms in a ratio of 1:1:

- Condensed up-titration: up-titration of sacubitril valsartan from 50 mg bid to 200 mg bid over 3 weeks (including the run-in phase)
- Conservative up-titration: up-titration of sacubitril valsartan 50 mg bid to 200 mg over 6 weeks (including the run-in phase)

Patients were required to take study medication in addition to their background HF therapy (except for ACEi or ARB, which was replaced with study drug). Placebo treatments to match sacubitril valsartan 50 mg, 100 mg, and 200 mg tablets were also used during the study for blinding purposes.

Permitted and disallowed concomitant medications

Patients were to be on an optimal medical regimen of background HF medications, including (if appropriate) an individually optimised dose of a β-blocker, aldosterone antagonist, isosorbide dinitrate/hydralazine hydrochloride (for black patients). If possible, HF medications were stable throughout the study. If a patient's change in condition

warranted a change of medication, it was allowed at the discretion of the investigator. Diuretics were also permitted and could be adjusted throughout the study at the discretion of the investigator. Prohibited concomitant medications were ACEis and ARBs, bile acid sequestering agents and renin inhibitors (e.g. aliskiren).

Populations analysed

Analyses were conducted using the following populations:

- Full analysis set (FAS): all randomised patients with the exception of mis-randomised patients who had not received the study drug but had been inadvertently randomised into the study. Patients were analysed according to the treatment to which they were assigned at randomisation
- Per protocol set (PP): all randomised patients in the FAS who received at least one dose of study medication during the double-blind phase of the study and had no major protocol deviations
- Safety set (SAF): all randomised patients who received at least one dose of study medication. Patients were analysed according to the treatment they actually received

Primary variables

The primary variables assessed were based on adverse events and laboratory assessments.

The number and proportion of patients experiencing the following specified adverse events after Visit 3 were analysed:

- Hypotension
- Hyperkalaemia
- Renal dysfunction
- Angioedema at any time while taking active study medication

The number and proportion of patients experiencing the following specified laboratory assessment outcomes after Visit 3 were analysed:

- SBP <95 mmHg
- Serum potassium >5.5 mmol/L and ≥6.0 mmol/L
- Serum creatinine >3.0 mg/dL (267 µmol/L)
- Doubling of serum creatinine

Population included in primary analysis of primary variables and methods for handling missing data

The primary analysis was conducted in the FAS, within each randomisation stratum (low or high RAAS) due to the forced stratification ratio in randomisation. Missing data caused by early discontinuation, such as withdrawal of informed consent, loss to follow-up, death, or other reasons, were considered as censored. The censoring between treatment groups are assumed to be balanced and independent of the event generating process. The proposed estimation methods are unbiased under this assumption.

Statistical test in primary analysis of primary outcome

The primary analysis was conducted by summarising descriptive statistics of the count and percentage, as well as the annualised percentage of the primary variables (four types of pre-specified adverse events and four types of laboratory assessment outcomes) throughout the double-blind treatment phase, within each stratum (low or high RAAS) and by treatment group. The annualised percentage was used instead of the ordinary percentage to overcome the effects of premature study discontinuation caused by withdrawal of informed consent, loss to follow-up, death, or other reasons.

Power calculation

The primary objective of the TITRATION study was to characterise the safety and tolerability of initiating sacubitril valsartan in HFrEF patients with 3-week and 6-week up-titration regimens, in a descriptive manner. Assuming the stratification ratio as 1:1 between the pre-study anti-RAAS inhibition levels (high/low), the sample size used in this study, 120 per stratum (480 in total for both treatment arms), was considered sufficient to provide useful estimates of the event rates in each stratum, also based on experience from other safety studies. Given this sample size, the approximate event rates of 1.7%, 1.2%, 1.6%, and 0.1% for hypotension, hyperkalaemia, renal dysfunction, and angioedema, respectively (based on the information available from the LCZ696B2314 at that time), the precision of the estimates (length of the 95% CI) were 0.045, 0.038, 0.044, and 0.011, respectively.

Secondary variables

Secondary variables included:

- **Treatment success:** the number and percentage of patients who achieved and maintained the target dose of sacubitril valsartan (200 mg bid) without any dose interruption or down-titration over 12 weeks.
- **Tolerability:** the number and percentage of patients who tolerated the regimen of sacubitril valsartan 200 mg bid for at least 2 weeks leading to study completion, regardless of dose interruption or down-titration.

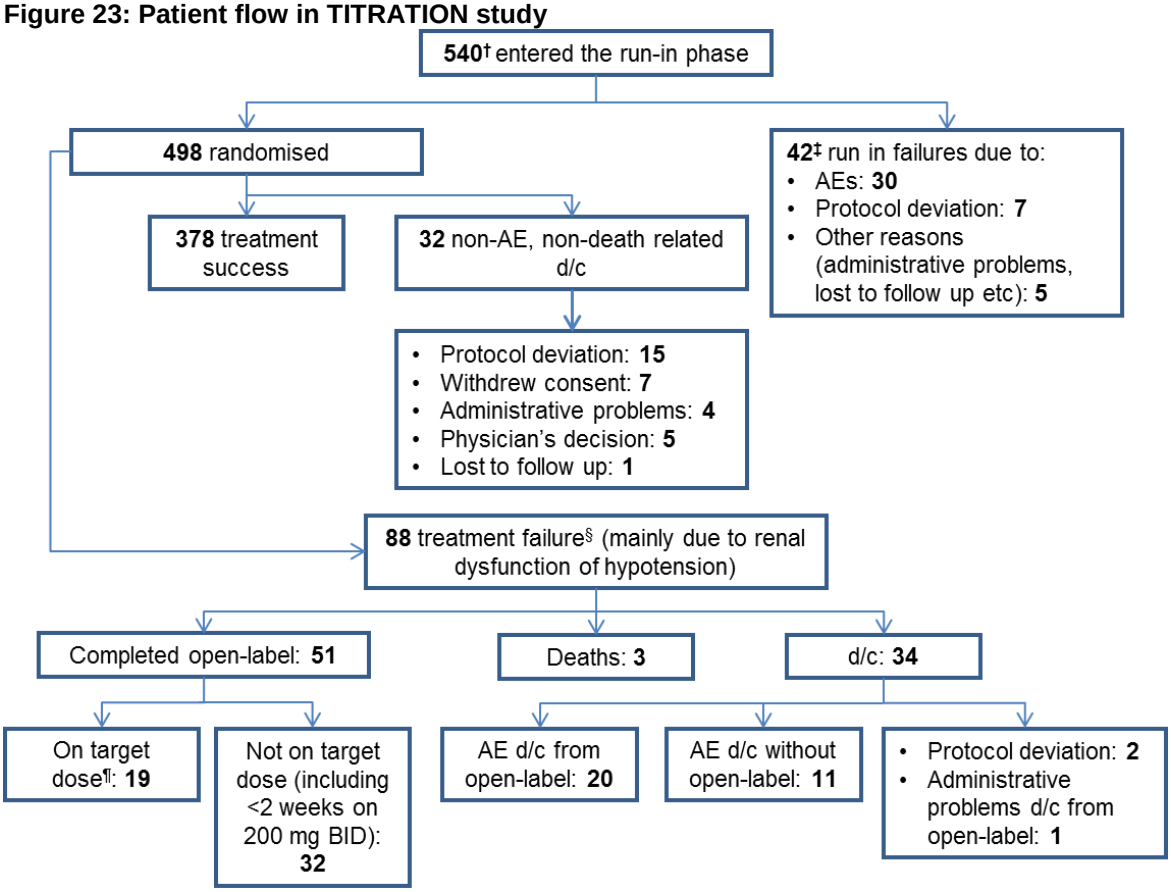
Secondary variables were analysed using a logistic regression model with treatment group, the pre-study RAAS treatment level stratum (high/low), and the geographic region as fixed factors. Statistical testing was performed at the two-sided significance level of 0.05 and the estimated odds ratio (OR) and 95%CI were provided based on the model for the overall population. For stratum specific estimates, separate logistic regression models were fitted with treatment group and region as the fixed factors, within each stratum. The analysis was based on the FAS.

Patient population

Patient flow

Patient flow in the TITRATION study is summarised in Figure 23.

Figure 23: Patient flow in TITRATION study



Abbreviations: AE, adverse event; BID, twice daily; d/c, discontinued.
†540 patients in the run-phase included 2 patients who discontinued the run-in period due to a protocol deviation without taking any run-in medication.
‡42 run-in failure patients included 2 patients who discontinued the run-in period due to a protocol deviation without taking any run-in medication.
§Included 3 patients who died.
¶19 patients achieved the target dose of LCZ696 200 mg BID and maintained it for at least 2 weeks leading to study completion.

Patient demographics and baseline characteristics

Patient demographics, baseline disease characteristics, HF and CV disease history, and relevant medical history were comparable between treatment regimens (Table 44). Patients were stratified by pre-study level of RAAS therapy, and demographics and baseline characteristics generally similar between strata. However, the low RAAS stratum differed from the high RAAS stratum in the following aspects:

- More patients with LVEF <30% (39.0% low RAAS vs. 27.9% high RAAS)
- Higher proportion of NYHA class III patients (35.1% low RAAS vs. 22.7% high RAAS)
- Higher proportion of patients with eGFR <60 mL/min/1.73^2 (37.8% low RAAS vs. 29.6% high RAAS)
- Lower mean SBP (129.0 mmHg for low RAAS vs. 132.7 mmHg for high RAAS)
- Higher proportion of inpatients (15.5% for low RAAS vs. 6.9% for high RAAS)

251 (50.4%) patients were in the low RAAS stratum, including 33 patients (6.6%) who were ACEi/ARB-naïve, and 247 patients (49.6%) were in the high RAAS stratum.

Table 44: Characteristics of participants in TITRATION across randomised groups (FAS)

Baseline characteristics	Condensed sacubitril valsartan up-titration (n=247)	Conservative sacubitril valsartan up-titration (n=251)
Age		
Mean ±SD	64.2±11.9	63.8±10.9
Gender, n (%)		
Male	191 (77.3)	201 (80.1)
Female	56 (22.7)	50 (19.9)
Predominant race, n (%)		
Caucasian	228 (92.3)	234 (93.2)
Black	12 (4.9)	11 (4.4)
Asian	0 (0.0)	1 (0.4)
Other	7 (2.8)	5 (2.0)
Region		
North America	34 (13.8)	33 (13.1)
Western Europe	117 (47.4)	118 (47.0)
Central Europe	96 (38.9)	100 (39.8)
NYHA class at Visit 1, n (%)		
II	175 (70.9)	178 (70.9)
III	72 (29.1)	72 (28.7)
IV	0 (0.0)	1 (0.4)
SBP (mmHg) at Visit 2		
Mean ±SD	130.8±16.6	130.8±16.0
Treated with ACEi, n (%)	170 (68.8)	161 (64.1)
Treated with ARB, n (%)	60 (24.3)	74 (29.5)
Treated with diuretic, n (%)	205 (83.0)	195 (77.7)
Treated with AA, n (%)	147 (59.5)	152 (60.6)
Treated with BB, n (%)	235 (95.1)	238 (94.8)
High RAAS	120 (48.6%)	127 (50.6%)
Low RAAS	127 (51.4%)	124 (49.4%)
Low RAAS – Treated with ARB or ACEi	110 (44.5%)	108 (43.0%)
Low RAAS- naïve *	17 (6.9%)	16 (6.4%)

Abbreviations: AA, aldosterone antagonist; ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BB, beta blocker; BMI, body mass index; CHF, chronic heart failure; NYHA, New York Heart Association; SBP, systolic blood pressure; SD, standard deviation; RAAS, renin angiotensin aldosterone system.

*Patients not on ARB or ACEi for 4 weeks prior to screening

Patient exposure to study medication

The median duration of exposure to the sacubitril valsartan 200 mg bid target dose was 62 days for the condensed regimen and 42 days for the conservative regimen. A similar pattern of exposure was observed in inpatients and outpatients, with no differences between treatment regimens in either hospitalisation status subgroup.

Results

The primary safety endpoint and secondary endpoints is presented. Additional exploratory endpoints result can be found in the CSR (11).

4.12.2.1 Primary variables: pre-specified adverse events and abnormal laboratory and vital signs outcomes

Primary analysis

In the overall population, the sacubitril valsartan condensed (3-week up-titration) and conservative (6-week up-titration) treatment regimens showed comparable incidence of adverse events (Table 45). Rates of hypotension, renal dysfunction, and hyperkalaemia adverse events were higher in the low RAAS stratum compared with the high RAAS stratum, irrespective of the up-titration regimen. Angioedema was rare, with two non-severe cases in the randomised phase that did not involve airway compromise. Similar results were observed for primary variables based on pre-specified laboratory measurements (Table 45).

Table 45: Number (%) of patients pre-specified adverse events and abnormal laboratory and vital signs during randomised phase (FAS)

Variable/ Stratum	Condensed sacubitril valsartan up-titration (n=247)		Conservative sacubitril valsartan up-titration (n=251)	
	Patients included in analysis (n)	Patients with specified AEs, n (%)	Patients included in analysis (n)	Patients with specified AEs, n (%)
Pre-specified AEs				
Hypotension				
All	247	24 (9.7)	251	21 (8.4)
High RAAS	120	5 (4.2)	127	7 (5.5)
Low RAAS	127	19 (15.0)	124	14 (11.3)
Renal dysfunction				
All	247	18 (7.3)	251	19 (7.6)
High RAAS	120	5 (4.2)	127	9 (7.1)
Low RAAS	127	13 (10.2)	124	10 (8.1)
Hyperkalaemia				
All	247	19 (7.7)	251	11 (4.4)
High RAAS	120	8 (6.7)	127	5 (3.9)
Low RAAS	127	11 (8.7)	124	6 (4.8)
Angioedema				

Variable/ Stratum	Condensed sacubitril valsartan up-titration (n=247)		Conservative sacubitril valsartan up-titration (n=251)	
	Patients included in analysis (n)	Patients with specified AEs, n (%)	Patients included in analysis (n)	Patients with specified AEs, n (%)
All	247	0 (0.0)	251	2 (0.8)
High RAAS	120	0 (0.0)	127	1 (0.8)
Low RAAS	127	0 (0.0)	124	1 (0.8)
Abnormal laboratory and vital signs outcomes				
SBP <95 mmHg				
All	246	22 (8.9)	249	13 (5.2)
High RAAS	120	4 (3.3)	126	7 (5.6)
Low RAAS	126	18 (14.3)	123	6 (4.9)
Serum potassium >5.5 mmol/L				
All	245	18 (7.3)	247	10 (4.0)
High RAAS	119	9 (7.6)	125	6 (4.8)
Low RAAS	126	9 (7.1)	122	4 (3.3)
Serum potassium ≥6.0 mmol/L				
All	245	3 (1.2)	247	1 (0.4)
High RAAS	119	2 (1.7)	125	0 (0.0)
Low RAAS	126	1 (0.8)	122	1 (0.8)
Serum creatinine >3.0 mg/dL (267 µmol/L)				
All	245	1 (0.4)	248	0 (0.0)
High RAAS	119	0 (0.0)	125	0 (0.0)
Low RAAS	126	1 (0.8)	123	0 (0.0)
Doubling of serum creatine (200% of baseline)				
All	245	2 (0.8)	248	1 (0.4)
High RAAS	119	0 (0.0)	125	0 (0.0)
Low RAAS	126	2 (1.6)	123	1 (0.8)

Abbreviations: AEs, adverse events; FAS, full analysis set; RAAS, renin angiotensin aldosterone system; SBP, systolic blood pressure.

4.12.2.2 Secondary analysis: treatment success and tolerability of sacubitril valsartan

Treatment success in the randomised population excluding non-adverse event related discontinuations was achieved by 81.1% of patients (Table 46). The rate of treatment success in the high RAAS stratum was similar regardless of titration regimen (82.6% condensed group, 83.8% conservative group p=0.783). The rate of success for the low RAAS stratum was higher in the conservative titration regimen group compared with the condensed titration regimen group (84.9%, 73.6% respectively, p=0.030) (Table 30). The rate of tolerability in the randomised population, excluding non-adverse event related

discontinuations, was 85.2% (Table 46). The rate of tolerability was independent of dosing regimen or RAAS stratum.

Table 46: Between-treatment analysis for treatment success and tolerability of sacubitril valsartan 200 mg bid for at least 2 weeks leading to study completion (FAS)

Variable/ Stratum	Total, n/N (%)	Condensed sacubitril valsartan up-titration, n/N (%)	Conservative sacubitril valsartan up-titration, n/N (%)	OR (95% CI)	p-value
Treatment success					
All	378/466 (81.1)	179/230 (77.8)	199/236 (84.3)	0.65 (0.41, 1.05)	0.0781
High RAAS	188/226 (83.2)	90/109 (82.6)	98/117 (83.8)	0.50 (0.26, 0.94)	0.7827
Low RAAS	190/240 (79.2)	89/121 (73.6)	101/119 (84.9)	0.91 (0.45, 1.83)	0.0302
Tolerability					
All	397/466 (85.2)	191/230 (83.0)	206/236 (87.3)	0.72 (0.43, 1.20)	0.2072
High RAAS	197/226 (87.2)	94/109 (86.2)	103/117 (88.0)	0.84 (0.38, 1.84)	0.6569
Low RAAS	200/240 (83.3)	97/121 (80.2)	103/119 (86.6)	0.63 (0.32, 1.26)	0.1894

Abbreviations: bid, twice daily; CI, confidence interval; FAS, full analysis set; n, total number of successes included in the analysis; N, total number of patients included in the analysis; OR, odds ratio; RAAS, renin angiotensin aldosterone system.

There were no major differences between the up-titration regimens in the rates of treatment success and tolerability among the ACEi/ARB-naïve patients, although the number of ACEi/ARB-naïve patients (16-17 per treatment arm) is too low to draw reliable conclusions. The profile of the AEs in the ACEi/ARB-naïve patients was consistent with that in the other low RAAS patients. Most AEs in the ACEi/ARB-naïve patients were not serious and did not result in discontinuation.

4.12.2.3 Secondary analysis: reasons for dose adjustment/interruption or discontinuation

The most common reasons for patients requiring dose adjustment/interruption or permanent discontinuation were adverse events related to hypotension (6.6%), renal dysfunction (4.8%) and hyperkalaemia (4.6%).

4.12.3 *Provide a brief overview of the safety of the technology in relation to the decision problem.*

PARADIGM-HF demonstrated that sacubitril valsartan has a comparable safety profile to enalapril. Any differences between the safety profiles of sacubitril valsartan and ACEi were as expected, based on previously observed adverse events associated with the mechanism of action of ACEi and ARBs (valsartan in sacubitril valsartan) such as hypotension and cough. Discontinuations due to adverse events were slightly less frequent in the enalapril compared with the sacubitril valsartan run-in period (6.05% vs. 5.51%). In the double-blind period, discontinuations due to adverse events were less frequent in the sacubitril valsartan group compared with the enalapril group (10.7% vs. 12.2% (Table 42).

Among the adverse events of special interest, the risk of hypotension was significantly higher with sacubitril valsartan compared with enalapril (relative risk [RR] 1.386, 95% CI 1.263–1.521); whereas the risks of renal impairment, hyperkalaemia and hepatotoxicity were significantly lower with sacubitril valsartan compared with enalapril. The risks of the remaining adverse events of special interest were comparable between the treatment groups.

In TITRATION safety and tolerability of sacubitril valsartan was assessed based on dosing regimen and stratification of RAAS and included patients who were treatment-naïve. The majority of patients in the TITRATION study were able to achieve the sacubitril valsartan 200 mg bid target dose, regardless of treatment regimen, ACEi/ARB treatment-naïve status, or baseline RAAS exposure.

4.13 *Interpretation of clinical effectiveness and safety evidence*

4.13.1 *A statement of principal (interim) findings from the clinical evidence highlighting the clinical benefits and harms of the technology.*

The large multinational Phase III clinical trial PARADIGM-HF (Table 11) demonstrated that sacubitril valsartan was significantly superior to enalapril with regard to reducing mortality, hospitalisation and HRQoL decline for patients with HFrEF. The enalapril target dose of 10 mg bid in PARADIGM-HF was selected on the basis of evidence from the SOLVD-Treatment study, in which it was shown to reduce the risk of mortality in patients with HF versus placebo. The overwhelming benefit of sacubitril valsartan compared with ACEi (current first-line treatment) led to a premature termination of the trial.

Specifically, sacubitril valsartan reduced the risk of CV mortality, all-cause mortality, all-cause hospitalisation and HF hospitalisation in patients with HFrEF compared with enalapril, by 20%, 16%, 12%, 21% respectively over a mean study duration of 27 months (see Section 4.7.1, Table 14, Table 17 and Figure 8).

The superior outcomes associated with sacubitril valsartan were independent of any subgroup analyses that were performed (See Section 4.8.4: Figure 9 and Appendix, Section 8.4). This includes populations of interest e.g., 1) age, gender, and NYHA class due to baseline characteristics being different from the English population; 2) SBP: due to a greater vasodilator effect, treatment with sacubitril valsartan was associated with a higher rate of hypotension. However, there was no increase in the rate of discontinuation because of possible hypotension-related adverse effects, and 3) EF and NT-proBNP as they might affect trial outcomes as inclusion criteria have specified these.

With regard to HF symptoms and physical limitations, the reduction in KCCQ scores (higher scores indicate better health) was consistently numerically less with sacubitril valsartan than with enalapril (Section 4.7.1, Table 15) and improvement in NYHA class was more likely for patients treated with sacubitril valsartan compared with enalapril (Section 4.7.1: Table 22). Using the EQ-5D and KCCQ to measure HRQoL, the results significantly favoured sacubitril valsartan over enalapril (see Section 4.7.1: Table 19 and Table 20).

PARADIGM-HF demonstrated that sacubitril valsartan has a comparable safety profile to enalapril. Any differences between the safety profiles of sacubitril valsartan and ACEi were as expected, based on previously observed adverse events associated with the mechanism of action of ACEi and ARBs (valsartan in sacubitril valsartan) such as

hypotension (due to valsartan, See Section 4.12.1: Table 41 and Table 42), however this was not associated with increased treatment discontinuation related to hypotension. Discontinuations due to adverse events were less frequent in the sacubitril valsartan group compared with the enalapril group (10.7% vs. 12.3% (10))

In TITRATION, a Phase II, multicentre, randomised, double-blind study designed to assess the safety and tolerability of initiating sacubitril valsartan in HF patients, was assessed based on dosing regimen and stratification of RAAS. The majority of patients in the TITRATION study achieved treatment success based on achieving and maintaining the sacubitril valsartan 200 mg bid target dose, regardless of treatment regimen, ACEi/ARB treatment-naïve status, or baseline RAAS exposure (see Section 4.12.2, Table 46). The safety data from this patient population is consistent with the adverse event profile of sacubitril valsartan in the treatment-experienced patient population in the PARADIGM-HF study (see Section 4.12.2).

The NICE scope included ARBs as a secondary comparator to sacubitril valsartan, specifically for patients who are intolerant to ACEi. Due to the lack of head-to-head evidence, an indirect comparison was conducted to inform a comparison between sacubitril valsartan and ARBs (Section 4.10). The NMA was not used to inform the ACEi comparison as head-to-head trial exists for the sacubitril valsartan versus ACEi (PARADIGM-HF, Section 4.4.1) and the results of one of the NMA scenarios aligned closely with the results of PARADIGM-HF (See Section 4.10.18, Table 39).

A systematic review (SR) and network meta-analysis (NMA) was conducted to inform an indirect comparison versus ARBs, given the lack of head-to-head evidence between sacubitril valsartan and ARBs in the population of interest. The SR identified 108 studies that fitted the inclusion criteria and 64 of these studies were eligible for the NMA. The core NMA (based on data from 28 RCTs) provided comparative evidence on the outcomes of interest (all-cause mortality, CV mortality and all-cause hospitalisations) for input into the economic model. The NMA categorised treatment by class: angiotensin receptor neprilysin inhibitor [ARNI; sacubitril valsartan], ACEi, ARB, or placebo. Trials of 7 different ACEis and 4 different ARBs were included in the core NMA. There was uncertainty associated with the relative treatment effects obtained from the NMA as shown by wide credible intervals. The NMA demonstrated that:

- ARBs and ACEis were broadly equivalent.
- Sacubitril valsartan was superior to ARBs with regards to all-cause and CV mortality and broadly equivalent with regards to all-cause hospitalisation outcomes.
- Sacubitril valsartan was superior to ACEis with regards to all-cause and CV mortality and superior with regards to all-cause hospitalisation which is aligned with the results from PARADIGM-HF.

Overall, sacubitril valsartan, based on overwhelming mortality, hospitalisation, and HRQoL benefit and a comparable safety profile shown in a head-to-head comparison with the English first-line treatment for HF, ACEi (10), at a dose that has been shown to reduce mortality (9) (both in combination with standard care), will offer patients with HFrEF substantial improvements and represents a breakthrough in the treatment of HFrEF.

4.13.2 *A discussion of the strengths and limitations of the clinical evidence base for the technology.*

PARADIGM-HF is the key clinical trial presented in this submission (Section 4.7.1 and 4.12), for both efficacy and safety. PARADIGM-HF included 8,442 randomised patients (242 from England) was a Phase III, randomised, double-blind, parallel group, active controlled, head-to-head trial of good quality (Section 4.7.1).

In order to compensate for the lack of Phase II data in this patient population, an active sequential run-in phase was included in the trial design. The run-in design allowed a careful assessment of the patients' tolerability to the target doses of enalapril (10 mg bid) and sacubitril valsartan (200 mg bid) prior to randomisation. This maximised the number of randomised patients able to tolerate the dose of both sacubitril valsartan and enalapril during the long term follow-up period making it a true head to head comparison. The target dose of enalapril in PARADIGM-HF was 10 mg bid, which was the target dose used in the SOLVD-T trial (9). In PARADIGM-HF, nearly 75% of enalapril patients were on the target dose at the final visit and the mean dose among patients still taking the study medication was 18.9 mg per day. Thus, sacubitril valsartan at a target dose of 200 mg bid was superior to enalapril, given at the dose shown to reduce mortality, in reducing CV mortality, HF hospitalisation, and all-cause mortality. It is noted that PARADIGM-HF patients were titrated to a comparable level as patients enrolled in SOLVD (average daily enalapril doses in PARADIGM-HF and SOLVD were 18.9 mg (10) (9) and 16.6 mg (182), respectively).

Despite excluding patients intolerant of target doses of either enalapril or sacubitril valsartan using the run-in period, the PARADIGM-HF patients' characteristics were similar to those included in many previous studies that targeted the same patient population with some variations reflecting changes in clinical practice over time (173). Although patients' in PARADIGM-HF had similar characteristics to those in previous clinical trials, the PARADIGM-HF population was observed to be younger, with a higher proportion of males, and with, on average, milder NYHA class than the population covered by the National Heart Failure Audit (Section 5.2.4). A lower average age and NYHA class is seen in HF trials due to multiple reasons including clinical trials requiring clear pre-determined eligibility criteria and rigorous follow-up making recruitment of significant numbers of older patients difficult. This difference to clinical practice may affect the generalisability of the trial results to English clinical practice. However, in PARADIGM-HF 22% of patients were females (n=1832), 49% of patients were ≥65 years of age (n=4120) and 19% of patients were ≥75 years of age (n=1563) with the oldest patient aged 96 at randomisation (11). In the subgroup analysis based on age no statistically significant impact on treatment effect was observed.

The treatment regimens, including enalapril as active comparator, administered in PARADIGM-HF corresponded to the licensed indications and were in line with current NICE clinical guidelines and clinical practice in England (Section 3.4) (7, 16). Moreover, the PARADIGM-HF patients were well-treated with evidence-based HF therapy with nearly 100%, >93%, and >58% receiving an ACEi/ARB (before start of study medication), a beta blocker, and an aldosterone antagonist, respectively. The use of these 'standard care' therapies are reflective of clinical practice and NICE Clinical Guidelines in England (Section 3.4) (7, 16).

Patients in PARADIGM-HF must have been on an ACEi or an ARB at a stable dose for at least 4 weeks before Visit 1, hence, this study did not include patients who were treatment-naïve, while these patients would be eligible for sacubitril valsartan based on its anticipated licensed indication. The supportive TITRATION study presented in Section 4.12.2 which was designed to assess safety and tolerability of sacubitril valsartan included 498 patients of which 6.6% were treatment naïve. The safety data from this patient population is consistent with the adverse event profile of sacubitril valsartan in the treatment-experienced patient population in the PARADIGM-HF study. Treatment success (defined as the number and percentage of patients who achieved and maintained the target dose of sacubitril valsartan (200 mg bid) without any dose interruption or down-titration over 12 weeks.) was achieved by 73.6% and 84.9% depending on up-titration regimen of low RAAS patients which included the treatment-naïve patients (see Table 45 and Table 46).

The core NMA presented in the submission (Section 4.10.2) was based on a previously published Cochrane meta-analysis assessing ARBs versus ACEis and includes data from relevant ARB studies identified in the clinical SR. The SR and NMA demonstrated that ARBs are less studied than ACEi. It is expected that this is due to ACEi already being established as first-line treatment in HF when ARBs were studied. One of the key limitations of the NMA for the ARB comparison was that the results were associated with a large amount of uncertainty due to the heterogeneity of studies informing each node. Also the core NMA did not explicitly consider concomitant standard care therapies therefore it was not able to isolate the relative treatment effect in patient population treated with ARNI/ACEi/ARB in combination with BB and/or AA which is reflective of English clinical practice. To address the latter limitation, a sensitivity analysis was conducted to isolate the treatment effect of investigational therapies (ARNI/ACEi/ARB) in combination with standard care therapies (BB and AA) at a threshold ≥50%. Recent trials were identified that investigated the use of concomitant therapies in HF, however, many of these (>45%) considered ACEi as the investigational therapy (e.g. ACEi vs ACEi + BB, ACEI + BB vs ACEi + BB + AA) which again is likely due to ACEi already being established as standard of care and limited data being available on ARBs with concomitant standard therapies. As a result no studies of ARBs in combination with both BB and AA (≥50% threshold) were identified in this sensitivity analysis. This prevented a consistent comparison between any ARB studies and the treatment arms of PARADIGM-HF which reflect triple therapy of sacubitril valsartan or ACEi with beta blockers and aldosterone antagonists (i.e. ARNI+BB+AA). Also in this scenario, only one active-controlled ARB+BB trial was identified. This trial (HEAVEN 2002) has a small sample size (n=141), short duration of follow-up (12 weeks), and was not powered to detect mortality or morbidity differences (163). Therefore this study did not provide robust evidence to inform this network with regard to the impact of ARB (in combination with BB) on mortality and hospitalisations. Finally, the concomitant standard care scenario required subjective assumptions around the proportion of patients on background therapy (≥50% threshold) so the limitations of the core NMA remain, at least partially.

Results of all NMA sensitivity analyses (considering concomitant standard care therapies, meta-regressions adjusting for baseline characteristics) did not demonstrate a substantial difference in results compared to the core NMA.

Also, the results of the ARNI+BB+AA vs ACEi+BB+AA comparison from the concomitant standard care scenario closely replicated the results from PARADIGM-HF for the comparison of sacubitril valsartan versus ACEi (both in combination with beta blockers and aldosterone antagonists).

Overall the results of the NMA (Table 29) align with a recently published Cochrane meta-analysis, demonstrating that ARBs and ACEi are broadly equivalent across mortality and hospitalisation outcomes (184). However the Cochrane MA considered studies in both HFrEF and HFpEF patients while the NMA presented in this submission considered HFrEF studies only to align with the patient population considered in the decision problem. Furthermore, equivalent efficacy between ARBs and ACEi could be considered a conservative conclusion as clinical practice in England has established ACEi as the first-line therapy and ARBs as an alternative, which is reflected in the NICE clinical guidelines (7).

Sacubitril valsartan is not considered an end-of-life treatment.

Table 47: End-of-life criteria

Criterion	Data available
The treatment is indicated for patients with a short life expectancy, normally less than 24 months	No
There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment	No
The treatment is licensed or otherwise indicated for small patient populations	No

4.14 *Ongoing studies*

4.14.1 *Provide details of all completed and ongoing studies from which additional evidence is likely to be available in the next 12 months for the indication being appraised.*

In addition, further data analyses from the PARADIGM-HF trial (NCT01035255) will be published and made available in 2015, including: renal effects of sacubitril valsartan, neurohormonal effects of sacubitril valsartan, atrial fibrillation at baseline and new onset, QTc intervals, baseline effects of LVEF and BP (blood pressure).

An open-label follow-on study of PARADIGM-HF is currently recruiting patients (NCT02226120) and is estimated to be completed in April 2017.

5 Cost effectiveness

Methodology

- An economic evaluation was performed comparing sacubitril valsartan with ACEi (both in combination with standard care) in the treatment of HFrEF based on head-to-head PARADIGM-HF trial data (primary comparison).
- A secondary comparison was performed for sacubitril valsartan to ARBs, based on indirect evidence from a NMA.
- The economic evaluation is structured as a two-state Markov model (health states defined as alive and dead), with hospitalisation rates, EQ-5D and adverse event rates estimated within the alive health state.
- The base case analysis uses all-cause mortality data from PARADIGM-HF for the primary comparison against ACEis and data from the NMA for the secondary comparison against ARBs.
- An alternative mortality analysis exploring the impact of considering CV mortality from PARADIGM-HF instead of all-cause mortality is presented; non-CV mortality was informed using UK life table data in this alternative analysis.
- To extrapolate beyond the duration of PARADIGM-HF, statistical analysis was performed to generate multivariable models predicting events and outcomes over a lifetime time horizon.
- HRQoL was modelled directly from PARADIGM-HF data using a mixed model of EQ-5D including baseline characteristics, time, treatment, adverse events, and hospitalisation as explanatory variables. A small but highly significant HRQoL benefit was observed for sacubitril valsartan, even after controlling for these explanatory variables.
- Costs included were those for pharmacological therapies, hospitalisation, adverse events and background medical resource use.
- Relevant unit costs were taken from publicly available sources including the NHS National Schedule of Reference Costs and the British National Formulary (BNF).

Results

- The base case analysis is associated with an ICER below £20,000 per QALY, compared with the evidence-based dose of ACEis in combination with standard care (£18,187 per QALY gained). This is consistent with the alternative analysis in which only CV mortality is modelled from PARADIGM-HF, which is associated with an ICER of £16,894 per QALY gained.
- The secondary comparison of sacubitril valsartan versus ARBs results in an ICER of £16,753 per QALY gained.
- Cost-effectiveness findings were robust to changes in most structural assumptions.
- The only scenarios associated with ICERs over £30,000 per QALY gained were 1) sacubitril valsartan treatment effect assumed to persist for durations of <5 years,

which represents a conservative assumption, and 2) modelled time horizon reduced to <5 years, which is not an adequate time horizon to model the costs and benefits associated with a lifelong treatment for a chronic condition.

- Deterministic sensitivity analysis suggests that cost-effectiveness is driven principally by reductions in mortality associated with sacubitril valsartan, but also by superior HRQoL and reduction in hospitalisations.
- Probabilistic sensitivity analysis demonstrated that the probability of sacubitril valsartan being cost-effective versus ACEi at a £20,000 per QALY threshold is 61% increasing to 93% at £30,000 per QALY. The probabilistic ICER is £18,955 (95% CI: £8,599, £37,222).
- The probability that sacubitril valsartan is cost-effective versus ARB at a £20,000 per QALY threshold is 56% and 76% at £30,000 per QALY gained. The probabilistic ICER is £18,180 (the 95% CI was undefined). The higher level of uncertainty associated with the results of the ARB analysis is due to wide credible intervals of relative treatment effect results generated from the NMA compared to the relative treatment effect results from the head-to-head ACEi analysis from PARADIGM-HF.

5.1 *Published cost-effectiveness studies*

Identification of studies

5.1.1 *Describe the strategies used to retrieve cost-effectiveness studies relevant to decision-making in England from published NICE technology appraisals, the published literature and from unpublished data held by the company.*

A SR was conducted to identify cost-effectiveness studies from the published literature relevant to the decision problem.

The following databases were searched using OVID:

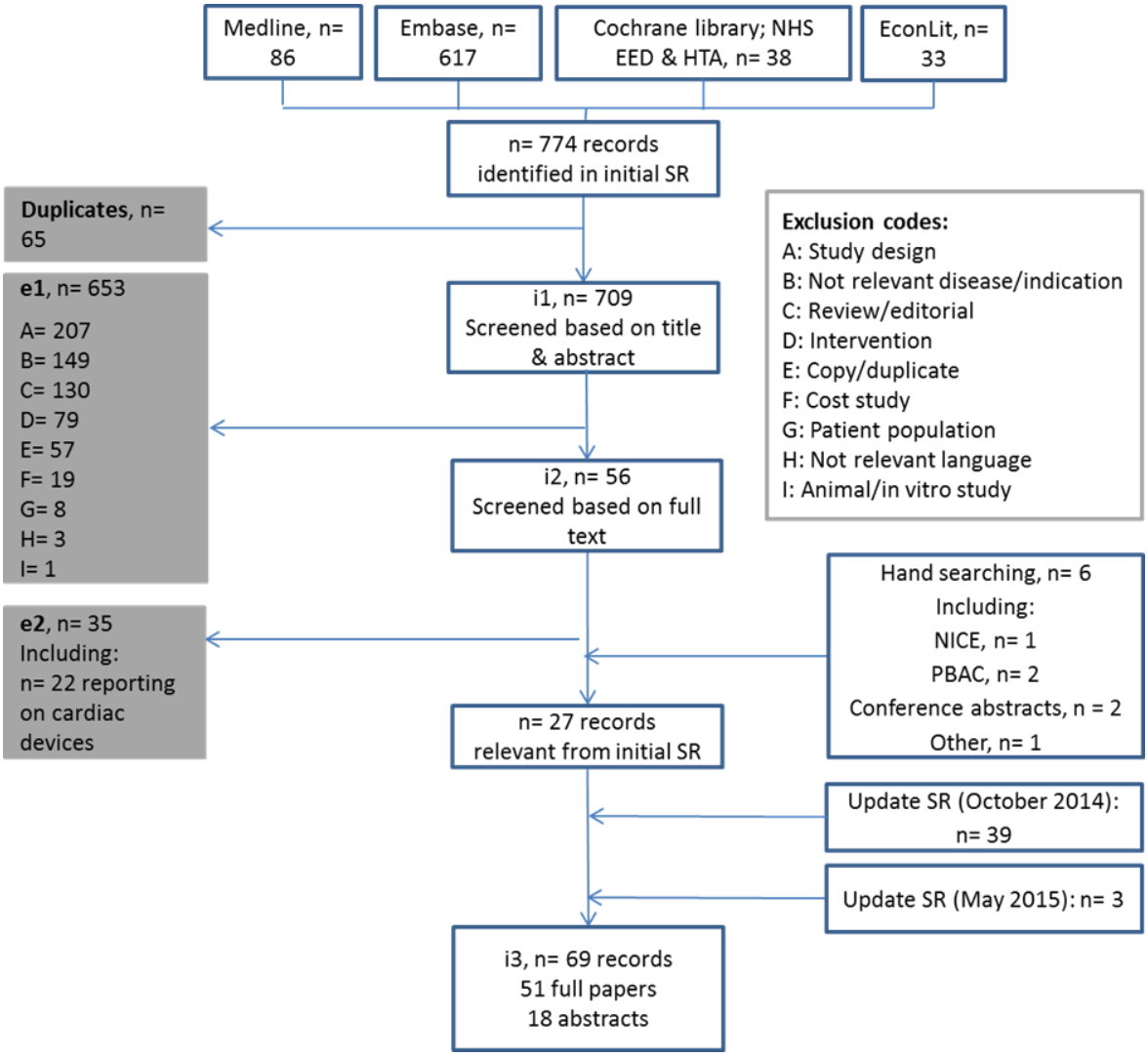
- MEDLINE(R) In-Process & Other Non-Indexed Citations and MEDLINE(R) 1976 to present
- Embase 1980 to 2015 week 20
- Cochrane Library: NHS Economic Evaluation Database (NHS-EED) 2nd Quarter 2015, Health Technology Assessment (HTA) Database 2nd Quarter 2015
- EconLit 1886 to April 2015
- Electronic searches were supplemented by hand searching of the Cost-Effectiveness Analysis (CEA) Registry, NICE HTA submissions, Pharmaceutical Benefits Advisory Committee (PBAC) submissions and Canadian Agency for Drugs and Technologies in Health (CADTH) submissions, and conference proceedings

The first search was performed in March 2014 to identify studies published from 2008 onwards. The second search was an update search conducted in October 2014 to identify any studies published before 2008 and after March 2014. The third search was

an update search performed in May 2015 to identify studies published between October 2014 and May 2015. Figure 24 presents the screening and inclusion of papers for all three searches.

Full details of the search strategy are provided in the Appendix, Section 8.8. Section 8.8.6 provides the detailed flow diagram of the second and third search.

Figure 24: Schematic for the systematic review of cost-effectiveness evidence



Abbreviations: e, excluded; EED, Economic Evaluation Database; HTA, health technology assessment; i, included; NHS, National Health Service; SR, systematic review.

This resulted in a total of 69 relevant publications for final inclusion, of which 51 were full papers and 18 were abstracts (Figure 24).

Four of the included 69 publications reported on the same cost-effectiveness model (198-201). As a result, the four publications were classified as two studies, using McKenna et al. 2010 (200) and Kourlaba et al. 2013 (198) as the parent studies. A further two publications, both PBAC submissions (original and re-submission), included the same model (202, 203). Study details of the 66 models from the included 69 publications are summarised in Section 5.1.2.

Description of identified studies

5.1.2 *Provide a brief overview of each cost-effectiveness study only if it is relevant to decision-making in England.*

There were no analyses of sacubitril valsartan. The recent literature in economic evaluations of HF treatment is dominated by evaluations of ivabradine, including several adaptations of the model submitted to NICE as part of TA267 (34). This model was found to capture the most important aspects of HF, and was therefore selected as the basis from which the *de novo* analysis would be developed. A proposed model based on the ivabradine model structure was presented at UK advisory board 1 (see Section 5.3.4), and was considered appropriate.

Study details of the 66 models from the included 69 publications are summarised in the Appendix, Section 8.8.8. Table 48 provides an overview of the structure and parameters used in the identified cost-effectiveness studies. Additional parameters, such as discounting and perspective, were also identified, but were deemed not relevant, as the NICE reference case (204) will be followed for this.

Table 48: Overview of structure and parameters used in previously published cost-effectiveness models

Factor	Chosen values/approach	References
Model structure	Markov: 29 studies	(34, 198, 200, 205-230)
	Patient level simulation: 5 studies	(231-235)
	Direct analysis: 20 studies	(180, 236-254)
	Decision tree: 2 studies	(255, 256)
	Not explicitly descriptive: 10 studies	(202, 237, 257-264)
Intervention	Ivabradine plus standard care: 15 studies	(34, 198, 202, 208, 209, 212, 213, 216, 220, 222-225, 229, 258)
	Eplerenone: 9 studies	(200, 205, 218, 233, 239, 250, 251, 253, 254)
	Valsartan: 5 studies	(226, 234, 236, 248, 263)
	Enalapril: 5 studies	(214, 230, 256, 259, 262)
	Other drug treatments or treatment combinations: 32 studies	(180, 206, 207, 210, 211, 215, 217, 219, 221, 227, 228, 231, 232, 235, 237, 238, 240-247, 249, 252, 255, 257, 260, 261, 264, 265)
Comparator	Standard care: 30 studies	(34, 180, 198, 202, 203, 207-212, 216, 220-222, 224, 225, 228-230, 234-236, 239-241, 246, 258, 260, 263)
	Placebo: 26 studies	(205, 213-215, 219, 223, 226, 227, 231, 232, 242-245, 248, 250-254, 256, 257, 259, 261, 262, 264)
	Other: 9 studies	(200, 206, 218, 237, 238, 247, 249, 255, 265)
Health states (Markov models only)	Alive or dead: 9 studies	(198, 202, 205-207, 212, 216, 220, 229)
	Severe heart failure, severe heart failure with hospitalisation or dead: 2 studies	(213, 227)
	Other: 18 studies	(200, 208-211, 214, 215, 217-219, 221-226, 228, 230)
Time horizon (Markov models only)	1.25 years to lifetime (n=29)	(34, 198, 200, 205-230)

5.1.3 *Please provide a complete quality assessment for each cost-effectiveness study identified.*

Quality assessments, based on Drummond and Jefferson, 1996 (266), are provided in the Appendices (Section 8.9). Based on the quality assessment we consider all studies to be of good quality. The studies often reported the sources of effectiveness estimates, the discount rates used, the major outcomes in a disaggregated and aggregated form, and the approach to sensitivity analyses.

5.2 *De novo analysis*

Patient population

5.2.1 *State which patient groups are included in the economic evaluation and how they reflect the population defined in the scope and decision*

problem for the NICE technology appraisal, marketing authorisation/CE marking, and the population from the trials.

The population considered for this economic model is the same as that considered in PARADIGM-HF; that is, patients with HFrEF (see Section 4.3.1). This reflects the population specified in the NICE scope and the anticipated marketing authorisation.

Whilst the PARADIGM-HF trial protocol states that the study will evaluate the effect of sacubitril valsartan compared with enalapril in patients in NYHA classes II-IV (267), and whilst all patients screened at study admittance fell into that category, it should be noted that a small number of patients had an improvement in their NYHA class between screening and randomisation and so 5% of randomised patients were NYHA class I (see Table 13 (10)).

Model structure

5.2.2 *Describe the model structure and provide a diagram of the model submitted*

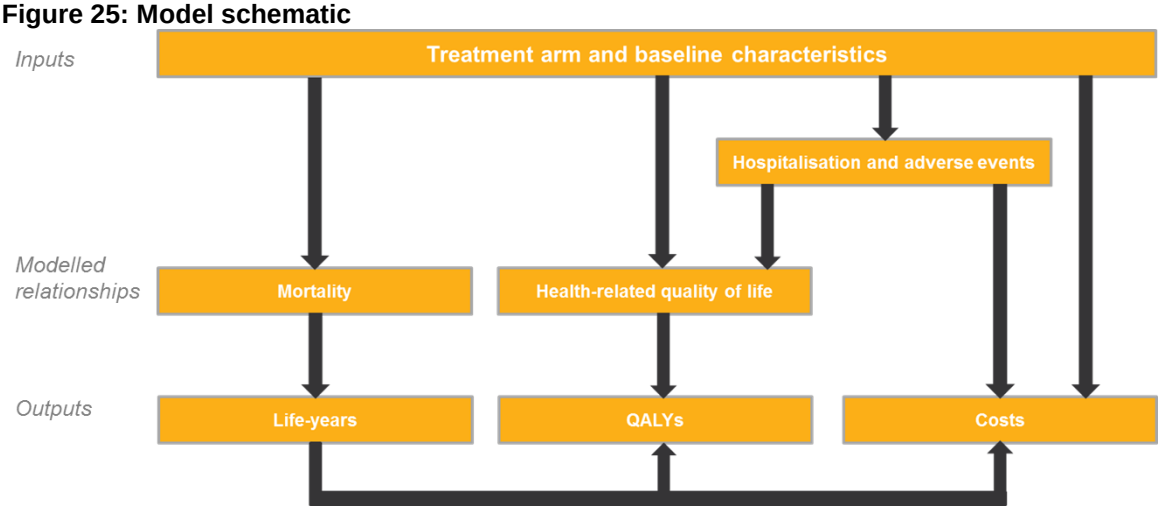
Type of de novo analysis

A decision analytic model was constructed in MS® Excel®. The economic model is structured as a two-state Markov model (with health states defined as alive and dead), with hospitalisation rates, EQ-5D and adverse event rates estimated within the alive health state. Models with similar structures, including the model submitted to NICE as part of TA267 have been published previously (216, 234, 235). Figure 25 below provides a model schematic.

The model was run once using the baseline characteristics of each patient from the PARADIGM-HF study; in practice this means that the model was run using the characteristics – and associated risks – of each patient in turn, and the resulting outcomes recorded. Outcomes were obtained for the cohort as a whole by averaging across the entire patient group (n=8,399)[c]. It should be noted that this approach differs from a patient-level simulation, as the model is evaluated analytically, and not stochastically. Similar approaches have been adopted previously in economic evaluations in CV conditions (216, 268, 269), and allow the characterisation of the distribution of costs and benefits across a heterogeneous cohort. The model may also be run using the 'mean' patient (i.e. using the mean characteristics of the PARADIGM-HF cohort); however, this approach does not account for non-linearities within the model and is therefore considered less accurate. Since model results are reasonably congruent between the two approaches, the 'mean' patient approach was only used for analyses in which use of the patient-level approach was considered impractical.

c Note that 43 patients who underwent randomisation were not allocated to treatment arms, and so were not included in the final analysis set (see Figure 4)

Figure 25: Model schematic



Note in the base case, all-cause mortality and all-cause hospitalisation is assumed
Abbreviation: QALYs, Quality Adjusted Life Years

Model structure capturing aspects of HF

The choice of events and outcomes used in the model was based on the most patient-relevant effects of HF on patients, carers and society (Sections 3.1 and 1.2). Deterioration of heart function in HF patients is chronic and progressive; therefore, according to HF guidelines (Section 3.4), treatment aims to prevent or slow the worsening of HF in order to reduce mortality, hospitalisation and symptoms. This is aligned with the decision problem, as described in Section 1.2. The following aspects of HF were therefore captured in the model:

- All-cause mortality, which was estimated using parametric survival curves (see Section 5.3.1, base-case analysis)
    - An alternative mortality analysis is presented in which CV mortality is estimated using parametric survival curves and UK life tables inform non-CV mortality (see Section 5.3.1)
- All-cause hospitalisation rates, which were estimated using a negative binomial regression model (see Section 5.3.1)
- HRQoL, which was estimated via a longitudinal analysis of EQ-5D values using a mixed-effects regression model (see Section 5.3.1)
- Adverse event rates, which were estimated from PARADIGM-HF assuming a constant rate (see Section 5.3.1)

Model structure in line with clinical care pathway.

The model structure as described in this section is aligned with the clinical care pathway as detailed in Section 3.5, reflecting the anticipated first-line positioning of sacubitril valsartan by comparing against current therapies (ACEis and ARBs for patients intolerant to ACEis) as recommended in NICE clinical guidelines (7).

Cycle length and half-cycle correction

A one-month cycle length was selected as the shortest cycle length considered practical (270), given the frequency of within-trial data collection and a lifetime time horizon. This

cycle length was also adopted in TA267 (34) and in a number of previously published economic evaluations in HF (216, 234, 235).

Half-cycle correction was implemented using the life-table method (271). The time in a given cycle is estimated by taking the average of the number of people at the start and end of the cycle.

5.2.3 *Complete the table below presenting the features of the de novo analysis.*

Table 49 provides an outline of the key features of the de novo cost-effectiveness model.

Table 49: Features of the de novo analysis

Factor	Chosen values	Justification
Time horizon	Lifetime	Long enough to reflect all important differences in costs or outcomes between the technologies being compared [NICE reference case (204)]. HF is a chronic condition requiring treatment for the duration of remaining lifetime.
Cycle length	One month	This was the shortest cycle length considered practical, given the frequency of within-trial data collection and a lifetime time horizon. This cycle length was also adopted in TA267 (34), and in a number of previously published economic evaluations in HF (216, 234, 235)
Half-cycle correction	A half-cycle correction was implemented using the life-table method (271)	In their review of guidelines for good practice in decision-analytic modelling in health technology assessment, Philips et al, 2004 (272), state that a half-cycle correction should be included “to adjust for the implicit bias of the assumption that transitions are occurring at the end or the beginning of the cycle”.
Were health effects measured in QALYs; if not, what was used?	Health effects expressed in QALYs. EQ-5D is the measure of HRQoL	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults [NICE reference case (204)]
Discount of 3.5% for utilities and costs	The same annual rate for both costs and health effects (currently 3.5%)	As specified in the NICE reference case (204)
Perspective (NHS/PSS)	NHS and PSS	NHS and PSS [NICE reference case (204)]

Abbreviations: HF, heart failure; HRQoL, health-related quality of life; NICE, National Institute for Health and Care Excellence; NHS, National Health Service; PSS, personal social services; QALYs, quality-adjusted life years; TA, technology appraisal.

Intervention technology and comparators

5.2.4 *Interventions considered*

The primary analysis in our submission compares sacubitril valsartan with ACEi (both in combination with standard care). A secondary analysis compares sacubitril valsartan against ARBs.

Primary comparison with the ACEi enalapril

- ACEi is widely used in the treatment of HFrEF. In England, the National Heart Failure Audit (2013) states that 73% of patients discharged for HFrEF are treated with ACEi (6)
- Most identified clinical guidelines, including those issued by NICE, recommend ACEi as the first-line therapeutic option in HFrEF (7, 20, 35) and sacubitril valsartan is anticipated to replace current first-line therapy
- NICE Scientific Advice to Novartis (273) states that: "NICE understands that the proposed positioning of sacubitril valsartan in the treatment pathway for heart failure patients is as first-line therapy. Therefore it is appropriate that an ACEi is the comparator in the trial (and the economic analysis)"

The ACEi comparator arm in the model is informed by efficacy data from the enalapril arm of PARADIGM-HF. Enalapril was selected as the comparator in PARADIGM-HF because it is the most well-studied ACEi with well-documented mortality benefits in HF across the largest number of patients (8, 9).

In a SR and NMA, Chatterjee et al (185) find that "benefits of ACEi in patients with HF appear to be due to a class effect" and note that "there is currently no statistical evidence in support of the superiority of any single agent over the others". As such, enalapril is assumed to be clinically representative of all ACEis, and therefore the economic evaluation aims to estimate the class effect between ACEi and sacubitril valsartan, a first-in-class ARNI.

Secondary comparison with ARBs

A secondary analysis included in this submission compares sacubitril valsartan with ARB (both in combination with standard care). Although ACEi in combination with standard care is recommended as first-line therapy in patients with HFrEF, a proportion of the patient population who are intolerant to ACEi will receive an ARB. In England, the National Heart Failure Audit (2013) reports that 18% of discharged patients with HF are treated with ARBs (6). Of the 8,399 subjects in the PARADIGM-HF FAS, 22.9% were treated with an ARB prior to entering the study (11).

'Standard care' and background therapies

In line with NICE clinical guidelines, the majority of patients who receive an ACEi as a first-line therapy (or ARB in those who are intolerant to ACEi) for HF might also receive additional standard care therapies for HF including:

- Beta blockers (recommended for all patients)
- Aldosterone antagonists (recommended for patients who remain symptomatic)

In England, 82% and 49% of patients receive beta blockers and aldosterone antagonists, respectively (6). This is aligned with the use of these therapies in PARADIGM-HF (93% and 56% of patients were receiving beta blockers and aldosterone antagonists, respectively (11)) (See Section 4.7.1 and Table 50).

Additional background therapies have also been considered, due to the high proportion of PARADIGM-HF subjects using such therapies at baseline (173) (see Table 50). These

therapies are typically used in the treatment of common comorbidities of HF. These include:

- Fluid retention: diuretics
- Atrial fibrillation: digoxin
- Prevention of CVD including coronary disease and AF: Anticoagulants, Aspirin, ADP antagonists and lipid lowering medications (e.g. atorvastatin),.

Table 50: Background therapy use in PARADIGM-HF at randomisation (173)

Treatment	%
Diuretic	80
Beta blocker	93
Aldosterone antagonist	56†
Digoxin	30
Anticoagulant	32
Aspirin	52
Adenosine diphosphate antagonist	15
Lipid lowering	56

† As reported by McMurray et al (10)

5.2.5 *If the intervention and comparator(s) are not implemented in the model as per their marketing authorisations/CE marking, describe how and why there are differences.*

The intervention and comparators (including both ACEi and ARB) were implemented in the model as per their marketing authorisations. Sacubitril valsartan and enalapril were both included as studied in PARADIGM-HF, and this is in accordance with the marketing authorisations for enalapril and the anticipated licensed indication for sacubitril valsartan. Dosing in PARADIGM-HF is described in Section 4.3. Dosing for ARB was determined based on recommendations in the BNF (274).

5.2.6 *If a treatment continuation rule has been assumed for the intervention and comparator(s), provide the rationale for the continuation rule and where it is referenced.*

No stopping rule or similar is applied.

5.3 *Clinical parameters and variables*

5.3.1 *Describe how the clinical data were incorporated into the model.*

PARADIGM-HF (detailed in Section 3) is the principal source of evidence for the economic model, informing key clinical events and outcomes including all-cause mortality, all-cause hospitalisation, HRQoL and adverse events. No intermediate outcome measures linked to final clinical outcomes were considered in the economic model.

Overview of analyses

Patient-level data analyses of PARADIGM-HF were used to inform:

- Baseline characteristics
- Estimates of all-cause mortality (and CV-mortality for the alternative mortality analysis)
- Estimates of all-cause hospitalisation rate
- Estimates of EQ-5D over time
- Adverse event rates were derived from published data (10).

These analyses were performed and reported in accordance with NICE Decision Support Unit (DSU) methodologies where relevant (275, 276). This approach is also consistent with the analyses presented in TA267 (34, 216), and where possible is consistent with the methods employed in the primary analysis of PARADIGM-HF.

All analyses were based on the FAS population of PARADIGM-HF. It is noted that adverse event rates in the clinical section are based on the SAF (Section 4.4.1) and will differ from those presented in the economic section. The FAS remains the population of interest within the economic evaluation, as the evaluation considers all patients prescribed sacubitril valsartan.

Mortality

The base case analysis models all-cause mortality data from PARADIGM-HF. It is noted that the primary endpoint in PARADIGM-HF was a composite of CV mortality and HF hospitalisation, with deaths due to CV causes being the primary driver of mortality within PARADIGM-HF (81% of all deaths) (10). Sacubitril valsartan was not associated with a significant difference in non-CV mortality compared with enalapril (p=0.53) (175). An alternative analysis is therefore considered in which CV mortality is modelled using parametric survival curves derived from PARADIGM-HF, and augmented with non-CV mortality data based on adjusted UK life tables. This approach aligns with the approach taken by the manufacturer of ivabradine in TA267 (34, 216), but generates more optimistic survival estimates, and thus a less conservative ICER. Table 51 summarises the strengths and limitations of both mortality approaches explored in the economic model.

Table 51: Strengths and limitations of mortality approaches explored in model

	Strengths	Limitation
Base case analysis – All-cause mortality	Clear application of data from PARADIGM-HF in the cost-effectiveness model Fewer data sources required to model mortality Non-CV mortality is sourced from a HFrEF population	Exclusion of patients from trial with presence of other disease with life expectancy < 5 years may lead to lower rates of non-CV mortality Rates of non-CV mortality are not statistically significantly different between sacubitril valsartan and ACEi enalapril All-cause mortality is a secondary endpoint of the trial
Alternative mortality analysis – CV mortality	CV mortality is the key driver of mortality benefit in the PARADIGM-HF patient population CV mortality is a component of the composite primary endpoint This approach aligns with the approach taken in TA267 Life-tables will reflect local non-CV mortality rates	Introducing uncertainty in model by combining RCT data and life tables No reliable estimates of non-CV mortality are available in HF patients, which is likely to underestimate mortality

Abbreviations: CV, cardiovascular, HF, heart failure, RCT, randomised controlled trials; TA, technology appraisal

All-cause mortality – base case analysis

All-cause mortality was modelled using parametric survival curves derived from PARADIGM-HF. Predicted all-cause mortality is based on treatment arm, baseline characteristics, and time from randomisation.

Extrapolation: In order to reflect that the mortality benefits of sacubitril valsartan (relative to ACEi) are expected to extend beyond the timeframe of the PARADIGM-HF follow-up (10), it was necessary to extrapolate these data beyond the timeframe of the trial.

The assumption of proportional hazards was deemed reasonable as the results of plotting the log cumulative hazards (Figure 26) were considered to be relatively parallel. In addition, Figure 27 presents the cumulative hazard, as recommended by Bagust and Beale, 2013 (277). Results from this analysis did not identify any discernible non-linear trends, and the risk of all-cause mortality appears to be relatively constant over the observed study follow-up. A single model of all-cause mortality (including a treatment effect for sacubitril valsartan) was therefore assumed in all subsequent analyses.

Figure 26: Log-cumulative hazard plot of all-cause mortality in PARADIGM-HF

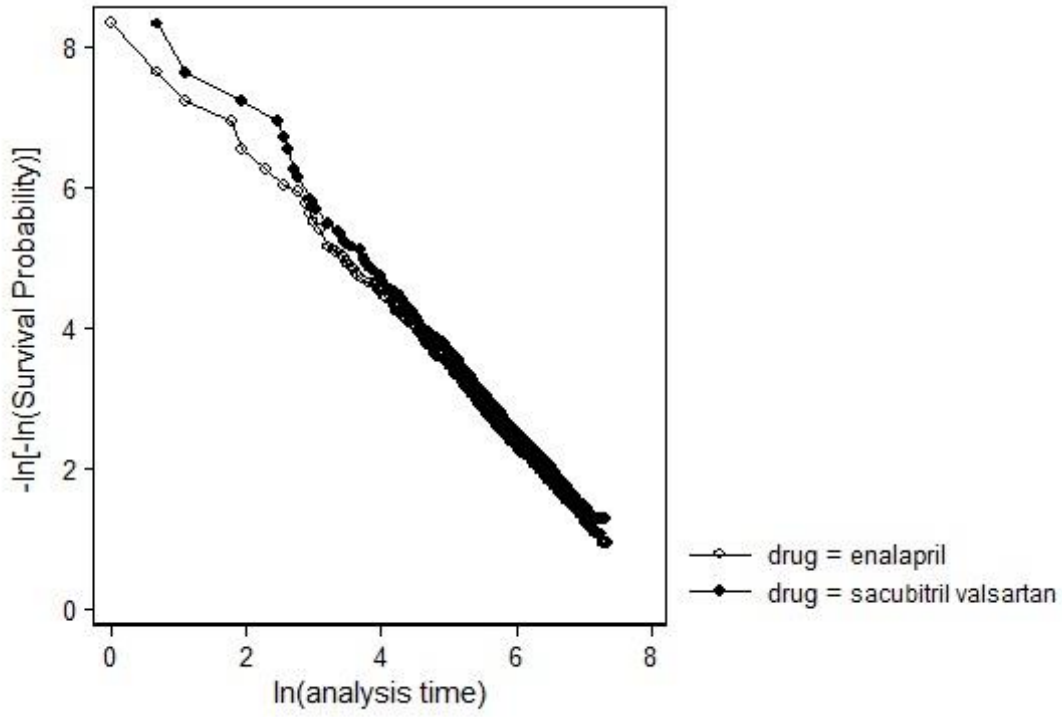
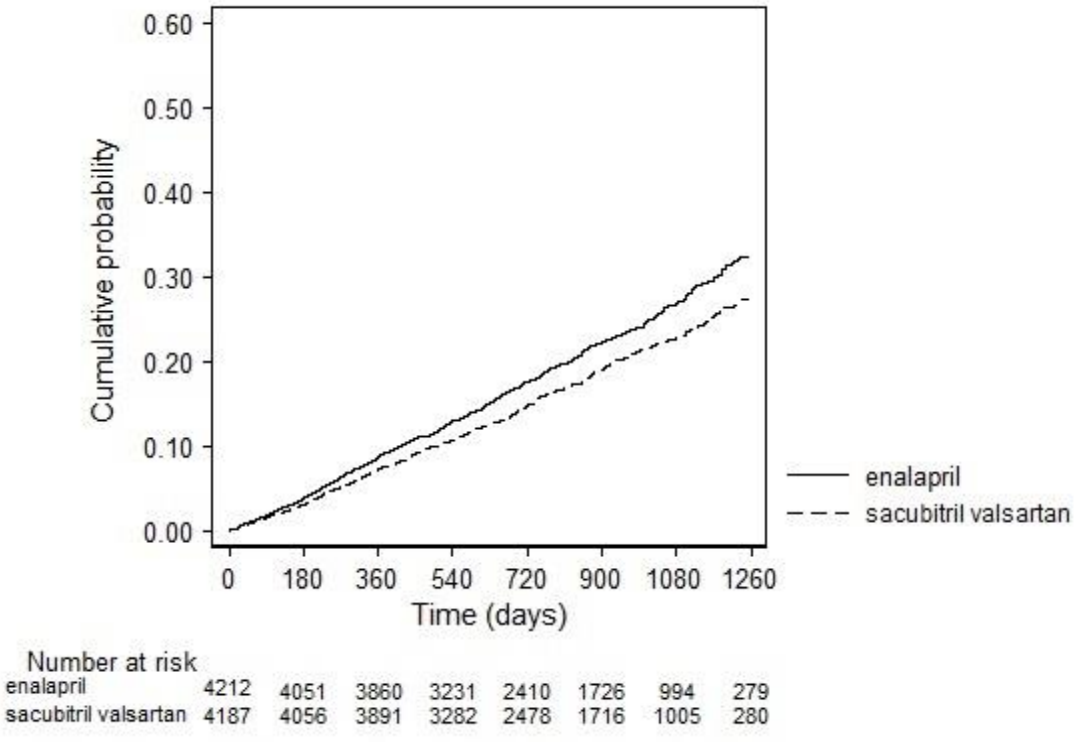


Figure 27: Cumulative hazard of all-cause mortality in PARADIGM-HF to day 1260 (10)



Distribution selection: Six parametric distributions were estimated (exponential, Weibull, generalised gamma, log-logistic, lognormal, Gompertz) (276).

Summary statistics including the Akaike information criterion (AIC) and the Bayesian Information criterion (BIC) for each distribution are reported in Table 52. There were few

meaningful differences between the candidate distributions, with the exception of the lognormal distribution, which had poorer performance than other candidate distributions on both the AIC and BIC measures. Differences between the remaining candidate distributions were modest and these scores were not considered sufficiently different to discriminate between distributions.

Table 52: All-cause mortality, summary statistics for alternative parametric distributions†

Model	Obs	ll(null)	ll(model)	df	AIC	BIC
Gompertz	8399	-5435	-5429	3	10864	10886
Weibull	8399	-5433	-5427	3	10860	10881
Exponential	8399	-5438	-5433	2	10869	10883
Gamma	8399	-5432	-5427	4	10862	10890
Loglogistic	8399	-5433	-5428	3	10861	10882
Lognormal	8399	-5459	-5453	3	10912	10933

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; df, degrees of freedom; ll, log-likelihood; obs, observations.
† Estimated using treatment and region variables only, as pre-specified for the statistical models in the primary analysis of PARADIGM-HF.

The NICE DSU (276) warn that AIC and BIC tests are based only on the relative fit to the observed data, and "[do] not tell us anything about how suitable a parametric model is for the time period beyond the final trial follow-up". The DSU recommend that "when the survival data require substantial extrapolation it is important to attempt to validate the predictions made by the fitted models by other means" (276).

The alternative extrapolation assumptions were presented to UK clinical experts (sacubitril valsartan UK advisory board 2; Section 5.3.4) to determine the clinical plausibility of each survival model. Examples of the plots presented to clinical experts are presented in the Appendix, Section 8.14.

- It was determined that the log-logistic and log-normal models (both accelerated failure time models) produced extrapolations with large proportions of patients alive at long time horizons. This feature is caused by the assumption that mortality increases at a decreasing rate. These models were judged to provide unrealistic extrapolation assumptions and were not considered further.
- Of the remaining models, it was noted that the Gompertz model is especially suited to the modelling of human survival, as mortality is assumed to increase at an increasing rate
- Clinical experts confirmed that the extrapolation using the Gompertz model is clinically plausible
- Use of the Gompertz model provided the shortest survival times, and thus provides the most conservative estimate of mortality benefit

The Gompertz distribution was therefore selected as the distribution for the extrapolation of all-cause mortality. This is further supported by the fact that the same distribution was used in the model of CV mortality presented in the ivabradine NICE submission (34).

Candidate covariates: The mortality risk equations include baseline characteristics; these are included to allow for the estimation of different absolute mortality rates based on alternative patient characteristics, including variables which inform subgroups (see Section 5.2.1). The inclusion of covariates in the mortality model enables patient-level heterogeneity to be captured; survival may be estimated for each individual patient in PARADIGM-HF, and overall survival obtained by averaging across the cohort.

Possible covariates to be included in the risk equation were selected from the subgroups listed a priori in the statistical analysis plan (SAP) for PARADIGM-HF (278). Clinical experts at the sacubitril valsartan UK advisory board 2 (Section 5.3.4) noted that background medications frequently act as markers of disease severity and therefore inclusion of these variables produces non-intuitive estimates of mortality effects. This is a recognised limitation of the approach adopted, but was retained on the basis that, if selected, this is indicative of improved predictive performance of the model.

In addition, other variables identified in the ivabradine manufacturer's submission to NICE as potential modifiers of baseline CV mortality risk or all-cause hospitalisation (but not listed above) were considered (34), as were variables suggested by clinical experts during UK advisory boards 1 and 2 (Section 5.3.4) and subsequent telephone interviews.

Table 53: Candidate covariates

Candidate covariates based on pre-specified subgroups in PARADIGM-HF	Candidate covariates based on the ivabradine manufacturer submission to NICE & suggestions by clinical experts
• Age • Gender: male, female • Race: Caucasian, Black, Asian, Other • Region: North America, Latin America, Western Europe, Central Europe, Asia/Pacific and other • NYHA Class: I/II, III/IV† • eGFR • Diabetic: yes, no • SBP • LVEF • AF based on ECG at Visit 5: yes, no • NT-proBNP • Hypertension: yes, no • Prior use of ACEi: yes, no • Prior use of ARB: yes, no • Use of AA: yes, no • Time since diagnosis of HF: ≤1 year, 1–5 years, >5 years • Prior HF hospitalisation: yes, no	• Digitalis use: yes, no • Lipid medications: yes, no • Heart rate, bpm • BB use: yes, no • Prior stroke: yes, no • Sodium • Potassium • Allopurinol: yes, no • Current smoker: yes, no • Ischaemic aetiology: yes, no • Baseline EQ-5D • QRS on ECG duration • Bundle branch block: yes, no • Prior cancer: yes, no • Prior angina: yes, no • BMI

Abbreviations: AA, aldosterone antagonist; ACEi, angiotensin converting enzyme inhibitor; AF, atrial fibrillation; ARB, Angiotensin II receptor blocker; BB, beta blocker; BMI, body mass index; bpm, beats per minute; ECG; electrocardiogram; eGFR, estimated glomerular filtration rate; HF, heart failure; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association; SBP, systolic blood pressure

† Please note that the full four category version of this variable was retained for the EQ-5D analysis.

Continuous variables were centred on their mean values. The functional form and potential presence of non-linearities of continuous variables were explored by visual inspection of Martingale residuals. NT-proBNP, eGFR and age exhibited non-linear trends; consequently the natural logarithm of NT-proBNP and eGFR was taken, and a quadratic transformation of age (age^2) was included in addition to the non-transformed variable. These transformations were selected based on a ladder of powers approach which seeks transformations that convert a variable into a normally distributed variable.

Covariate selection: No variables were identified *a priori* as being of special interest. Tests of interaction between subgroups suggested no difference in treatment effect between subgroups for the primary end point and death from CV causes[d] from the PARADIGM-HF study (10). In the absence of evidence of heterogeneity between subgroups, the most appropriate statistical interpretation of the data presented is to apply the overall result to each subgroup, and therefore interactions between such variables and the sacubitril valsartan treatment effect were not considered. The basic covariate identification procedure performed was:

- An initial set of covariates was identified using backwards stepwise elimination (using a p-value of <0.1).
- This was validated using forwards stepwise selection (using a p-value of <0.1).
- The interim statistical model was reviewed by clinical experts at sacubitril valsartan UK advisory board 2 (Section 5.3.4).
    - In addition to suggesting alternative parameters for inclusion, clinical experts recommended that potassium be removed from the predictive model due to unexpected directional effects

Table 54 presents the results of the Gompertz model of all-cause mortality. Sacubitril valsartan was associated with a HR of 0.85 (95% CI: 0.77, 0.94; p=0.002), which is consistent with the results of the primary statistical analysis of PARADIGM-HF, which reported a HR of 0.84 (95% CI: 0.76, 0.93; p<0.001, two-sided).

The final model of all-cause mortality exhibited a concordance measure of 68% (95% CI: 67%, 70%). This was in line with that of the model of CV mortality submitted by the manufacturer of ivabradine in TA267 (34).

[d] A nominally significant interaction between NYHA class at randomisation and the effect of treatment on the primary composite end point (p= 0.03, without adjustment for multiple comparisons) was not seen for the interaction between NYHA class and the effect on death from cardiovascular causes (p = 0.76)

Table 54: Gompertz regression model for all-cause mortality (n=8,399)

Mortality	HR	Coef.	SE	z	P>z	95% CI	
Sacubitril valsartan	0.851	-0.161	0.051	-3.15	0.002	-0.261	-0.061
Age†	0.903	-0.102	0.016	-6.30	0.000	-0.134	-0.070
Age^2*	1.001	0.001	0.000	6.86	0.000	0.001	0.001
Female	0.681	-0.384	0.069	-5.52	0.000	-0.520	-0.247
Region							
Latin America	1.719	0.542	0.127	4.28	0.000	0.294	0.790
Western Europe	1.139	0.130	0.112	1.17	0.243	-0.088	0.349
Central Europe	1.439	0.364	0.114	3.18	0.001	0.140	0.588
Asia-Pacific	0.820	-0.199	0.298	-0.67	0.505	-0.784	0.386
Race							
Black	1.343	0.295	0.130	2.27	0.023	0.040	0.550
Asian	2.045	0.715	0.283	2.52	0.012	0.160	1.271
Other	1.091	0.087	0.110	0.79	0.430	-0.129	0.302
NYHA III/IV	1.239	0.214	0.061	3.52	0.000	0.095	0.334
Ejection fraction†	0.987	-0.014	0.004	-3.25	0.001	-0.022	-0.005
Heart rate†	1.006	0.006	0.002	2.62	0.009	0.001	0.010
(log) eGFR†	0.796	-0.228	0.095	-2.39	0.017	-0.415	-0.041
(log) NT-proBNP†	1.478	0.391	0.027	14.34	0.000	0.337	0.444
Sodium†	0.969	-0.031	0.009	-3.50	0.000	-0.049	-0.014
QRS duration	1.002	0.002	0.001	3.07	0.002	0.001	0.003
Diabetes	1.230	0.207	0.054	3.83	0.000	0.101	0.313
BB use	0.749	-0.289	0.088	-3.28	0.001	-0.461	-0.116
Time since diagnosis of HF							
1-5 years	1.227	0.204	0.067	3.03	0.002	0.072	0.336
> 5 years	1.338	0.291	0.072	4.02	0.000	0.149	0.434
Ischaemic disease	1.171	0.158	0.057	2.80	0.005	0.047	0.269
Prior stroke	1.182	0.168	0.083	2.03	0.043	0.005	0.330
Prior HF hosp.	1.165	0.153	0.055	2.76	0.006	0.044	0.261
Baseline EQ-5D	0.587	-0.532	0.115	-4.61	0.000	-0.758	-0.306
Constant	-	-12.840	0.579	-22.17	0.000	-13.976	-11.705
Gamma	-	0.000	0.000	4.57	0.000	0.000	0.001

†Variable centred on mean

* Age exhibited a non-linear effect, and therefore a quadratic transformation was included.

Abbreviations: BB, beta blocker; CI, confidence interval; coef, coefficient; eGFR, estimated glomerular filtration rate; HF, heart failure; hosp., hospitalisation; HR, hazard ratio; NT-proBNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association; SE, standard error.

Alternative mortality analysis – CV mortality

In this alternative analysis, CV mortality is modelled using parametric survival curves derived from PARADIGM-HF, and non-CV mortality is based on all-cause mortality life tables, adjusted (using cause-specific life tables) to remove CV mortality (this process is described in detail in Section 8.16).

Extrapolation, distribution selection, and covariate selection for the CV mortality model followed the same approach as for all-cause mortality. The selected model is presented in Appendix 16, Table 128. The Gompertz model of CV mortality demonstrated that sacubitril valsartan was associated with a hazard ratio of 0.81 (95% CI: 0.72, 0.90; p<0.001), which is consistent with the results of the primary statistical analysis of PARADIGM-HF, which reported a hazard ratio of 0.80 (95% CI: 0.71, 0.89; p<0.001 two-sided) (10). The final model exhibited a concordance measure of 70% (95% CI: 68%, 71%). This was in line with that of the model of CV mortality submitted by the manufacturer of ivabradine in TA267 (34).

Hospitalisation

Sacubitril valsartan was associated with a statistically significant reduction in all-cause, HF, CV, and non-CV hospitalisation (Section 4.7.1). The use of all-cause hospitalisation in the model was therefore considered appropriate.

The cost-effectiveness model predicts the rate of all-cause hospitalisation using a negative binomial regression model derived from PARADIGM-HF data. Predicted hospitalisation rates are based on:

- Treatment arm
- Baseline characteristics

Although all-cause hospitalisation is expected to incorporate the costs of serious adverse events, the costs of less serious adverse events are also considered independently (see below Section ‘Adverse events’).

The negative binomial model was the pre-specified model used in the primary analysis of PARADIGM-HF for hospitalisation counts, and was therefore preferred over alternative approaches such as Poisson regression. Negative binomial models have been used to model hospitalisation rates in HF patients in multiple previously published analyses (147, 279-281). Negative binomial models are typically employed when overdispersion is present; in all models, the dispersion parameter alpha was observed to be significantly greater than zero (p=0.000). The outputs of this model provide annual hospitalisation rates, permitting extrapolation beyond the end of PARADIGM-HF.

Baseline variables considered for selection included all those listed earlier in this section (under the heading “Candidate covariates”). Selection of covariates used the same stepwise procedure as described for all-cause mortality.

The predictive model of hospitalisation is presented in Table 55. Based on common explanatory variables, the resulting model was consistent with the results presented in TA267 (34, 216). The predicted rate ratio for sacubitril valsartan was 0.84 (95% CI: 0.78, 0.91; p<0.0001). This is consistent with the results of the primary statistical analysis, in which the rate ratio was 0.84 (95% CI: 0.78, 0.91; p<0.0001) (129).

Table 55: Negative binomial regression for all-cause hospitalisation

Mortality	IRR	Coef.	SE	z	P>z	95% CI	
Sacubitril valsartan	0.84	-0.173	0.038	-4.550	0.000	-0.247	-0.098
Age†	0.95	-0.054	0.013	-4.080	0.000	-0.081	-0.028
Age^2*	1.00	0.000	0.000	4.290	0.000	0.000	0.001
Female	0.74	-0.297	0.049	-6.020	0.000	-0.393	-0.200
Region							
Latin America	0.70	-0.362	0.084	-4.300	0.000	-0.528	-0.197
Western Europe	1.02	0.017	0.074	0.230	0.820	-0.128	0.162
Central Europe	0.73	-0.322	0.075	-4.260	0.000	-0.470	-0.174
Asia-Pacific	0.71	-0.350	0.085	-4.120	0.000	-0.516	-0.183
Heart rate†	1.01	0.007	0.002	4.290	0.000	0.004	0.010
Log (eGFR)†	0.62	-0.477	0.072	-6.600	0.000	-0.618	-0.335
Log (NT-proBNP)†	1.26	0.228	0.020	11.250	0.000	0.188	0.268
Sodium†	0.98	-0.021	0.007	-3.210	0.001	-0.034	-0.008
QRS duration†	1.00	0.003	0.001	5.330	0.000	0.002	0.004
Diabetes	1.40	0.333	0.040	8.250	0.000	0.254	0.412
Prior ACEi use	0.90	-0.104	0.047	-2.230	0.026	-0.196	-0.013
BB use	0.72	-0.328	0.073	-4.520	0.000	-0.470	-0.185
Lipid lowering medication use	1.08	0.073	0.043	1.690	0.091	-0.012	0.157
Time since HF diagnosis							
1-5 years	1.30	0.265	0.049	5.390	0.000	0.168	0.361
>5 years	1.49	0.402	0.052	7.720	0.000	0.300	0.503
Ischaemic disease	1.09	0.085	0.044	1.920	0.054	-0.002	0.172
Prior stroke	1.16	0.147	0.065	2.270	0.023	0.020	0.275
AF	1.10	0.095	0.042	2.280	0.023	0.013	0.176
Prior cancer	1.18	0.164	0.088	1.870	0.061	-0.008	0.336
Current smoker	1.23	0.209	0.054	3.880	0.000	0.103	0.314
Prior HF hosp.	1.40	0.334	0.041	8.230	0.000	0.254	0.413
Baseline EQ-5D†	0.62	-0.487	0.089	-5.440	0.000	-0.662	-0.311
Constant	-	-2.844	0.473	-6.010	0.000	-3.772	-1.917

†Variable centred on mean
* Age exhibited a non-linear effect, and therefore a quadratic transformation was included.
Abbreviations: ACEi, angiotensin converting enzyme inhibitor; AF, atrial fibrillation; BB, beta blocker; Coef, coefficient; CI, confidence interval; eGFR, estimated glomerular filtration rate; HF, heart failure; hosp., hospitalisation; IRR, incidence rate ratio; NT-proBNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association; SE, standard error.

Adverse events

Adverse event selection

All-cause hospitalisation is expected to incorporate the costs of serious adverse events; the costs of less serious adverse events are also considered independently (See above section 'Hospitalisation'). Adverse events included were the pre-specified safety events for PARADIGM-HF, as reported by McMurray et al (10): hypotension, elevated serum creatinine, elevated serum potassium, cough and angioedema. UK clinical expert feedback at UK Advisory Board 1 (See Section 5.3.4) confirmed these as events that have been or might be associated with ACEi, ARBs (valsartan in sacubitril valsartan), or neprilysin inhibitor (sacubitril) based on their mechanism of action (see Section 4.12).

Adverse events were based on the FAS population (see Section 5.2.2), as opposed to the Safety Set presented in Section 4.12, in order to reflect rates of adverse events in the population prescribed sacubitril valsartan.

Adverse events modelling

Adverse events were modelled simplistically assuming a constant rate for each. A simplistic approach was considered to be appropriate because the included adverse events have low cost, low incidence and limited impact on HRQoL, and are therefore not expected to be a major determinant of cost-effectiveness.

Adverse event rates were calculated using total numbers of patients experiencing each pre-specified safety event (10) (hypotension, elevated serum creatinine, elevated serum potassium, cough and angioedema) and total exposure time for each of the sacubitril valsartan and ACEi arms of the trial (9,308 and 9,235 years respectively (11)). Annual rates were converted to monthly probabilities using the actuarial formula.

Table 56: Derivation of monthly probabilities of adverse events

Event	Sacubitril valsartan (n=4187)			ACEi (n=4212)		
	Num -ber†	Mean annual rate	Mean monthly probability	Number†	Mean annual rate	Mean monthly probability
Hypotension	588	0.063	0.52%	388	0.042	0.35%
Elevated serum creatinine	139	0.015	0.12%	188	0.020	0.17%
Elevated serum potassium	674	0.072	0.61%	727	0.079	0.66%
Cough	474	0.051	0.42%	601	0.065	0.54%
Angioedema	19	0.002	0.02%	10	0.001	0.01%

†Absolute number of each adverse event, taken from McMurray et al (10)
Abbreviations: ACEi, angiotensin-converting enzyme inhibitor.

Mean durations of hypotension and cough were calculated using patient-level data from PARADIGM-HF as 64.9 days and 73.3 days, respectively, in order to incorporate the effects of these adverse events within estimates of HRQoL (see below, Section 'Health-related quality of life').

Health-related quality of life

Utility values are typically attached to model health states, with (for example) EQ-5D changing as patients experience disease progression or alternate between health states.

The possibility of modelling EQ-5D progression using NYHA class was explored but rejected; the reasons for this are discussed in Section 8.11.

In this analysis, HRQoL is modelled using a mixed-effects model, derived from patient-level EQ-5D data (from PARADIGM-HF), to account for repeated observations (see Section 5.4 for further detail). Predicted EQ-5D is based on:

- Treatment arm (See Section 5.4.9)
- Baseline characteristics (including baseline EQ-5D)
- Hospitalisation (see Section 5.4.7 'Role of hospitalisation in HRQoL')
- Adverse events (see Section 5.4.7)
- Time from randomisation (See Section 5.4.9)

Missing data in statistical analyses

For mortality and hospitalisation models, missing data at baseline were imputed deterministically using region-specific mean (continuous variables) or median values (categorical variables). As per the primary SAP for PARADIGM-HF (278), missing EQ-5D observations were assumed to be missing at random in the mixed-effects model. In general, loss to follow-up was very low (20 patients out of 8,442 patients randomised) and the quantity of missing data was low.

Clinical inputs for the secondary comparison versus ARBs

A NMA was conducted to generate clinical evidence for the secondary comparison of sacubitril valsartan versus ARBs (Section 4.10) as no head-to-head trial data exists for sacubitril valsartan against ARBs. The three outcomes analysed in the NMA were 1) all-cause mortality, 2) all-cause hospitalisation and 3) CV mortality.

In the base case analysis for the ARB comparison, all-cause mortality and all-cause hospitalisation were based on the core NMA which pooled studies on the basis of the investigational intervention of interest, irrespective of concomitant standard care therapies (including beta blockers and aldosterone antagonists).

Table 29 in Section 4.10.14 shows the relative effects applied in the model for the ARB comparison. For this comparison, HRQoL in the ARB arm was assumed to be equivalent to the ACEi arm as modelled in the primary analysis comparing sacubitril valsartan and ACEi. Adverse events in the ARB arm were assumed to be equivalent to the sacubitril valsartan arm, as both molecules include valsartan.

5.3.2 *Demonstrate how the transition probabilities were calculated from the clinical data. If appropriate, provide the transition matrix and describe the details of the transformation of clinical outcomes or any other relevant details here.*

Transition probabilities between the formal 'alive' and 'dead' health states were derived from parametric survival curves, assuming a Gompertz distribution. Cumulative survival of all-cause mortality for subject j with a vector of baseline characteristics $\mathbf{X}_j$, at time t, is given as:

$$S(t|\mathbf{X}_j) = exp\left[-\gamma^{-1}\exp(\beta_0 + \mathbf{X}_j\boldsymbol{\beta}_x)\{\exp(\gamma t) - 1\}\right]$$

Where γ is the ancillary parameter and controls the shape of the baseline hazard, and $\boldsymbol{\beta}_x$ is the vector of coefficients for each baseline characteristic.

Hospitalisation rates, adverse event rates and decline in EQ-5D over time are not based on transitions between formal health states, and so do not utilise transition probabilities *per se*. Multivariable regression models are used to estimate hospitalisation rates and EQ-5D; adverse event rates are taken from PARADIGM-HF, and assumed to be constant for simplicity (see Section 5.2.2 'Type of de novo analysis').

The annual rate of hospitalisation $r(y)$ is given as

$$r\left(y\middle|\mathbf{X}_j\right) = \exp(\beta_0 + \mathbf{X}_j\boldsymbol{\beta}_x)$$

And this rate r is converted into a monthly probability of hospitalisation p_j using the actuarial formula; this formula is also used to estimate monthly probabilities of adverse events.

$$p_j = 1 - \exp(-\frac{r}{12})$$

EQ-5D at time t is given as the linear predictor of the fixed effects portion of the mixed model:

$$EQ5D\left(t\middle|\mathbf{X}_j\right) = \beta_0 + \mathbf{X}_j\boldsymbol{\beta}_x + \mathbf{AE_j}\boldsymbol{\beta_{AE}} + t\beta_t + p_j\beta_{hos\,0-30} + p_j\beta_{hos\,30-90}$$

Where β_t is the coefficient on time (in years; i.e. the annual change in EQ-5D), $\beta_{hos\,0-30}$ and $\beta_{hos\,30-90}$are the coefficients (utility decrements) associated with hospitalisation in days 0-30 and 30-90, respectively. $\mathbf{AE_j}$ is the vector of monthly probability of adverse events(cough and hypotension), and $\boldsymbol{\beta_{AE}}$ are the respective coefficients (utility decrements) associated with each adverse event.

5.3.3 *If there is evidence that (transition) probabilities may change over time for the treatment effect, condition or disease, confirm whether this has been included in the evaluation. If there is evidence that this is the case, but it has not been included, provide an explanation of why it has been excluded.*

The baseline risk of mortality may be expected to vary over time, and the model explicitly incorporates this time dependency. Changes in HRQoL over time are also incorporated (see Section 5.4.9). In the base case, hospitalisation was assumed to be constant over time, as assumed in TA267 (34), however a scenario was considered in which the rate of hospitalisation was assumed to increase over time (see Section 5.8.8).

The extent to which the treatment effect for sacubitril valsartan on all-cause mortality varies over time was explored quantitatively by augmenting the Cox proportional hazards model used in the primary statistical analysis of PARADIGM-HF with a time-varying sacubitril valsartan covariate (i.e. including a time and sacubitril valsartan interaction term). The analysis found no evidence that the treatment effect for sacubitril valsartan varied over time (HR for interaction 1.00; p=0.989).

5.3.4 *Clinical expert assessment of applicability of clinical parameters*

UK expert opinion was sought to provide validation of proposed methods and statistical models, and to provide estimates of resource use associated with adverse events. The programme of advisory boards is presented in Table 57. An overview of the information

provided to experts is given in the Appendix, Section 8.14. Further telephone interviews were performed with advisory board participants to validate statistical models and present modifications made to the economic evaluation. In addition, further interviews with external health economic experts have been conducted in various jurisdictions to discuss methodological aspects of model development, but such interviews were not used to inform parameter estimates or validate statistical models.

Table 57: Sacubitril valsartan cost-effectiveness model advisory board programme

Name in document	Date held	External Attendees†	Topics of discussion
Sacubitril valsartan UK advisory board 1	25/6/14	1 x UK Consultant Cardiologist, 2 x Health Economists	Model methods
Sacubitril valsartan UK advisory board 2	21/10/14	2 x UK Consultant Cardiologists, 2 x Health Economists	Model methods, validation of statistical models, estimates of resource use for adverse events

† Attendees who were neither direct employees of Novartis nor direct employees of Novartis-commissioned vendor

5.4 *Measurement and valuation of health effects*

Health-related quality-of-life data from clinical trials

5.4.1 *Provide details of the health-related quality-of-life data available from the clinical trials.*

A primary objective of PARADIGM-HF was to test whether sacubitril valsartan, compared with enalapril, improves the clinical summary score for HF symptoms and physical limitations, as assessed by the KCCQ, at 8 months. Exploratory outcomes included HRQoL outcomes assessed by total score and individual scores of the sub-domains from the KCCQ and total score of the EQ-5D for health status. Results of the EQ-5D and other measures of HRQoL in PARADIGM-HF are detailed in Section 4.7.1, Exploratory outcomes of interest. Table 58 summarises the collection of HRQoL measures in PARADIGM-HF.

Table 58: Collection of HRQoL measures during double blind phase of PARADIGM-HF

Phase	Double blind treatment						
Visit	**5/777‡**	**9**	**10**	**11**	**14**	**17**	**778¶**
Months (m)	**0**	**4m**	**8m**	**12m**	**24m**	**36m**	**EOS**
EQ-5D	x	x	x	x	x	x	x
KCCQ	x	x	x	x	x	x	x

Abbreviation: EOS, end of study; HRQoL, Health Related Quality of Life; KCCQ, Kansas City Cardiomyopathy Questionnaire; m, month
‡ Visit 5/777 (end of run-in visit) was completed for patients upon completing or discontinuing from the run-in period.
¶ 778 (final visit: End of Study [EOS]) scheduled upon the decision to close the study

5.4.2 *If health-related quality-of-life (HRQoL) data were collected in the clinical trials identified in section 4, comment on whether the data are consistent with the reference case.*

Responses to EQ-5D index were converted to utility values using the UK tariff (282) as presented by Dolan (283), which uses a time-trade-off (TTO) methodology to elicit preferences from the general population (see Section 5.4.13). This is consistent with the

NICE reference case (204). A summary of EQ-5D over time in PARADIGM-HF is presented in Table 59 and Figure 28. KCCQ is not a preference-based measure and is therefore not used in the economic evaluation.

Figure 28: EQ-5D index (UK) change from baseline (282)

Table 59: EQ-5D index (UK) by visit in PARADIGM-HF

Month	Sacubitril valsartan			Enalapril			Sacubitril valsartan vs. enalapril			
	n	CFB	SE	n	CFB	SE	Mean diff.	95% ll	95% ul	p-value*
4	[redacted]									
8	[redacted]									
12	[redacted]									
24	[redacted]									
36	[redacted]									

Abbreviations: CFB, change from baseline; diff., difference; ll, lower limit; SE, standard error; ul, upper limit
*p-values are two-sided
Mean difference = Mean difference of [CFB (sacubitril valsartan) - CFB (Enalapril)].
The analysis is performed with a repeated measures mixed-effects model including treatment, region, visit, and treatment-by-visit interaction as fixed effect factors and baseline EQ-5D value as a covariate, with a common unstructured covariance for each treatment group.

Mapping

5.4.3 *If applicable, describe the mapping methods used to estimate health state utility values from the quality-of-life data collected in clinical trials.*

Mapping was not required, as EQ-5D data was available directly from PARADIGM-HF. Statistical analysis of EQ-5D from PARADIGM-HF is described in Section 5.4.13, Table 61.

Health-related quality-of-life studies

5.4.4 *Describe how systematic searches for relevant HRQoL data were done.*

A SR was conducted to identify HRQoL studies from the published literature relevant to the decision problem; in particular EQ-5D health state utility values (HSUVs) (in line with the NICE preferred method) relating to patients with chronic HF.

The following databases were searched using OVID:

- MEDLINE (R) 1946 to present (via OVID) & Ovid MEDLINE In-Process and Other Non-Indexed Citations
- EMBASE (Ovid) 1980 to present.
- Cochrane library(Ovid) to present, searching the following databases
- Econlit (Ovid) 1969 to present
- Electronic searches were supplemented by hand searching the following sources: primary sources of utilities used in economic evaluations, manufacturer databases, Research Papers in Economics (RePEc), the EQ-5D website, the CEA Registry, conference proceedings and NICE HTA submissions.

Full details of the systematic review including search strategy and flow diagram are provided in the Appendix, Section 8.10.

5.4.5 *Tabulate the details of the studies in which HRQoL was measured.*

Please see Appendices (Section 8.10.7).

5.4.6 *Highlight any key differences between the values derived from the literature search and those reported in or mapped from the clinical trials.*

Utility values identified in the literature search were broadly consistent with baseline utility values in PARADIGM-HF, although most identified studies summarised utility values by health state (for example NYHA class, which is not modelled in the cost-effectiveness analysis presented here, see Appendix, Section 8.12). Model utility values were derived from a patient-level analysis of PARADIGM-HF data; this approach was considered to have the following advantages over using HSUVs identified in the published literature:

- EQ-5D may be derived from the same population as the clinical efficacy data
- Change in EQ-5D over time may be considered

- Utility decrements associated with hospitalisation and adverse events may be incorporated
- Significant differences associated with sacubitril valsartan may be incorporated
- Baseline characteristics of individuals from PARADIGM-HF may be used to predict EQ-5D scores
- EQ-5D index scores elicited in PARADIGM-HF are from the period 2009 to 2014, and so are considered to be reasonably current

Adverse reactions

5.4.7 *Describe how adverse reactions affect HRQoL.*

Section 5.3.1 'Adverse events' describes the adverse events included in the model; clinician-reported adverse events of cough and hypotension were incorporated in the statistical models of HRQoL, the construction of which is described in Section 5.4.13, Table 61. Cough and hypotension were consistently associated with modest statistically significant reductions in HRQoL (-0.028 and -0.029, respectively, see Table 61).

Elevated serum potassium and serum creatinine were assumed to have no impact on HRQoL[e], while too few angioedema events were observed to make inference regarding the effects on HRQoL.

Serious adverse events requiring hospitalisation are assumed to be captured in the utility decrements associated with hospitalisation, which were 0.105 ($p<0.001$) and 0.054 ($p<0.001$) in days 0-30 and 30-90 post-hospitalisation, respectively (see Section 5.3.1 'Hospitalisation').

Role of hospitalisation in HRQoL

The following explanatory variables were considered in an attempt to capture the effects (both short and medium-term) of hospitalisation:

- Hospitalisation in the 30 days before EQ-5D measurement
    - This variable is designed to capture the acute effects of hospitalisation
    - This visit window was selected as a more conservative alternative to that presented during TA267, in which hospitalisation +/- 30 days of the EQ-5D visit was considered (34)
- Hospitalisation 30 - 90 days before EQ-5D measurement
    - This variable is designed to capture any longer-term effects during rehabilitation

[e] This is considered to be a conservative assumption, given that sacubitril valsartan is associated with reduced rates of elevated serum creatinine and elevated serum potassium vs. ACEi (see Section 5.3.1 'Adverse events')

Hospitalisation is assumed to be associated with a decrement of -0.105 during Day 0-30, and -0.054 during Day 30-90 (See Table 61). The effect of excluding utility decrements for hospitalisation was considered in a scenario analysis (see Section 5.8.8, Effect of hospitalisation on HRQoL).

5.4.8 *Define what a patient experiences in the health states in terms of HRQoL in the cost-effectiveness analysis. Explain how this relates to the aspects of the disease or condition that most affect patients' quality of life.*

In this analysis, a patient's HRQoL is assumed to be a function of:

- Their baseline characteristics (including baseline EQ-5D)
- Time spent alive in the model
- Their risk of hospitalisation
- Their risk of adverse events
- Treatment arm

HFrEF is a chronic, progressive condition. The explicit inclusion of time is therefore expected to capture the progressive nature of HFrEF; indeed, duration of HF has been shown to be an independent predictor of poorer HRQoL (284).

Hospitalisation has been shown to be associated with reduced HRQoL in HF patients and was therefore included within the statistical model of EQ-5D (34); utility decrements associated with less serious (non-hospitalised) adverse events were also included in the model of EQ-5D, and found to be associated with statistically significant reductions in HRQoL (see Table 60).

Baseline characteristics have been included to capture heterogeneity between patients. Such characteristics included NYHA class, which has been shown previously to be a statistically significant predictor of HRQoL (2, 285).

Details of how HRQoL is predicted over time are described in Section 5.3.2.

5.4.9 *Clarify whether HRQoL is assumed to be constant over time in the cost-effectiveness analysis. If not, provide details of how HRQoL changes over the course of the disease or condition.*

In order to determine the extent to which EQ-5D changes over time, four mixed model specifications were developed which considered alternative covariates and assumptions. Table 60 presents these alternative analyses.

Model 2 demonstrates that subjects receiving sacubitril valsartan experienced better HRQoL post-baseline than subjects receiving enalapril ($p<0.001$ for difference). Model 3 includes interaction effects between treatment and time and suggests a non-significant difference in the rate at which EQ-5D changes over time between sacubitril valsartan and enalapril ($p=0.1318$), though there remained a significant overall difference between sacubitril valsartan and enalapril ($p=0.0219$). We attempted to explain the difference between sacubitril valsartan and enalapril by further adding time-varying effects to Model 2, including the proximity of the EQ-5D visit (in time) to hospitalisation and the incidence of adverse events (Model 4). These inclusions did not alter the conclusions observed in Model 2. The benefit of sacubitril valsartan on HRQoL cannot therefore be explained

solely by reduced numbers of hospitalisations, or differences in adverse event profiles. It is hypothesised that the remaining benefit may be attributed to improvements in symptoms with sacubitril valsartan. Scenario analysis considered omission of the treatment effect on EQ-5D (see Section 5.8.8.2).

The resulting model was conservative, in that it assumes that the rate of decline in EQ-5D is the same between sacubitril valsartan and enalapril. Although evidence from Model 3 does not support the alternative assumption of different rates of decline, graphical evidence presented in Figure 28 does suggest a divergence in EQ-5D over time. These assumptions are also conservative when compared with those submitted by the manufacturer in TA267 (34), which, by assuming constant NYHA beyond the observed data, effectively assumed constant EQ-5D beyond the observed data (see Appendix, Section 8.12).

Table 60: Results of longitudinal analysis of EQ-5D over time†

Variable	Model 1	Model 2	Model 3	Model 4
	Baseline characteristics only	Baseline characteristics and treatment	Baseline characteristics, treatment x time and interaction	Baseline characteristics, and treatment x time, hospitalisation and adverse event effects
Time (years)	-0.008***	-0.008***	-0.009***	-0.008***
Sacubitril valsartan		0.011***	0.008*	0.011***
Sacubitril valsartan*Time			0.003	
Hosp. previous 30 days				-0.105***
Hosp. previous 30-90 days				-0.054***
Cough				-0.028***
Hypotension				-0.029***
p-value for sacubitril valsartan effect	NA	<0.001***	0.0219*	<0.001***
Implied annual change				
ACEi	-0.008	-0.008	-0.009	-0.008
Sacubitril valsartan			-0.006	
p-value for comparison of slopes	NA	NA	0.1318	NA
n	34,208	34,208	34,208	34,208
AIC	-23604	-23615	-23615	-24153

* p< 0.1, ** p< 0.01, ***p<0.001
Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; AIC, Akaike information criterion; Hosp, hospitalisation.
† All models control for age, gender, region, NYHA class, heart rate, NT-proBNP, sodium, BMI, diabetes, duration of heart failure, ischaemic aetiology, previous stroke, current smoker and EQ-5D at baseline.

5.4.10 ***If appropriate, describe whether the baseline HRQoL assumed in the cost-effectiveness analysis is different from the utility values used for each of the health states. State whether quality-of-life events were taken from this baseline.***

Utility values implemented in the analysis are taken from the model of EQ-5D in which HRQoL is assumed to decline over time (see Section 5.4.9), and therefore differ from baseline EQ-5D values. Baseline EQ-5D is used as a covariate in models of all-cause mortality, all-cause hospitalisation and EQ-5D over time, and is taken directly from PARADIGM-HF for each individual.

5.4.11 ***If the health state utility values used in the cost-effectiveness analysis have been adjusted, describe how and why they have been adjusted, including the methodologies used.***

The approach to modelling EQ-5D is described in Section 5.3.1 'Health-related quality of life', Sections 5.4.7 and 5.4.9. Results of model selection are presented in 5.4.13. Utility values are adjusted for treatment arm, time from randomisation, baseline characteristics, adverse events and hospitalisations.

Baseline characteristics considered include those listed in Section 5.3.1 ' All-cause mortality – base case analysis (candidate covariates). Covariate selection was based on a similar process to that described for mortality (but was performed manually by the analyst; see Section 5.3.1 'All-cause mortality – base case analysis' (covariate selection)).

5.4.12 ***Identify any health effects found in the literature or clinical trials that were excluded from the cost effectiveness analysis and explain their exclusion.***

In a recent review of HRQoL studies in patients with HF, Coelho et al (286) note that a number of additional patient characteristics not captured within the EQ-5D may be associated with poorer HRQoL. These include:

- Social factors such as lack of support and isolation
- Socio-economic status

[redacted]

These characteristics were not available from PARADIGM-HF, and were therefore not included. Sacubitril valsartan is not expected to substantially alter these factors, and therefore the exclusion of these effects would not be expected to have a notable effect on the outcomes of the analysis.

5.4.13 ***In a table, summarise the utility values chosen for the cost-effectiveness analysis***

As the model was run once using the baseline characteristics of each patient from the PARADIGM-HF study, utility values are different for each patient (see 5.2.2 'Type of de novo analysis') (282). The mean EQ-5D in PARADIGM-HF at randomisation was 0.780 (SD 0.22).

Predicted utility for each patient is modelled using a mixed-effects model, derived from patient-level EQ-5D data (from PARADIGM-HF), to account for repeated observations. The final model is presented in Table 61.

The key utility assumptions and modelling outcomes (see Section 5.4.9) are:

- Treatment effect: After controlling for the effects of hospitalisation and adverse events, sacubitril valsartan was associated with a small (0.011) but statistically significant effect on EQ-5D (p=0.001). This was assumed to persist for the duration of the time horizon.
- Time from randomisation: EQ-5D declines at a constant rate over the modelled time horizon; this rate of decline is the same irrespective of baseline characteristics. The implied annual change in EQ-5D is -0.008.
    - This compares to a rate of change in EQ-5D reported by Berg et al, 2015 (287) of -0.006.[f]
- Hospitalisation (see Section 5.4.7 'Role of hospitalisation in HRQoL'): For simplicity, both the acute and mid-term hospitalisation utility decrements are applied in the model cycle in which the patient is hospitalised. Hospitalisation is assumed to be associated with a decrement of -0.105 during Day 0-30, and -0.054 during Day 30-90.
- Adverse events (see Section 5.4.7): Utility decrements for hypotension and cough are applied in the model cycle in which the adverse event occurs. Cough and hypotension were consistently associated with modest statistically significant reductions in HRQoL (-0.028 [p<0.001] and -0.029 [p<0.001], respectively
    - Serious adverse events requiring hospitalisation are assumed to be captured in the utility decrements associated with hospitalisation

[f] Berg et al report that "Mean utility was 0.840 (0.126) after 1 year compared with 0.846 (0.127) for the same patients at inclusion"

Table 61: Final mixed model of EQ-5D index score with individual-level random effect

EQ-5D	Coef.	SE	z	P>z	95% CI	
Sacubitril valsartan	0.011	0.003	3.35	0.001	0.004	0.017
Age†	-0.001	0.000	-4.96	0.000	-0.001	0.000
Female	-0.031	0.004	-7.8	0.000	-0.039	-0.023
Region						
Sacubitril valsartan	0.011	0.003	3.35	0.001	0.004	0.017
Latin America	0.041	0.007	5.72	0.000	0.027	0.055
Western Europe	0.013	0.007	1.86	0.063	-0.001	0.026
Central Europe	0.000	0.007	-0.04	0.969	-0.014	0.013
Asia-Pacific	0.041	0.008	5.37	0.000	0.026	0.056
NYHA						
II (vs. I)	-0.009	0.008	-1.22	0.224	-0.024	0.006
III (vs. I)	-0.051	0.008	-6.05	0.000	-0.067	-0.034
IV (vs. I)	-0.092	0.021	-4.46	0.000	-0.132	-0.051
Heart rate†	0.000	0.000	-1.97	0.049	-0.001	0.000
(log) NT-proBNP†	-0.009	0.002	-5.35	0.000	-0.013	-0.006
Sodium†	0.001	0.001	1.8	0.071	0.000	0.002
BMI	-0.002	0.000	-6	0.000	-0.003	-0.001
Diabetes	-0.014	0.003	-4.02	0.000	-0.021	-0.007
Time since diagnosis of HF						
1-5 years	-0.017	0.004	-4.21	0.000	-0.024	-0.009
> 5 years	-0.023	0.004	-5.34	0.000	-0.031	-0.014
Ischaemic aetiology	-0.007	0.003	-2.13	0.033	-0.014	-0.001
Prior stroke	-0.012	0.006	-2.06	0.039	-0.023	-0.001
Current smoker	-0.013	0.005	-2.8	0.005	-0.022	-0.004
Baseline EQ-5D†	0.488	0.008	61.39	0.000	0.473	0.504
Hosp 0 – 30 days	-0.105	0.006	-18.31	0.000	-0.116	-0.094
Hosp 30 – 90 days	-0.054	0.004	-12.43	0.000	-0.062	-0.045
AE – cough	-0.028	0.007	-4.33	0.000	-0.041	-0.015
AE – hypotension	-0.029	0.006	-4.63	0.000	-0.042	-0.017
Time (years)	-0.008	0.001	-8.56	0.000	-0.010	-0.006
Constant	0.822	0.010	79.67	0.000	0.802	0.843

† Variable centred on the mean
Abbreviations: AE, adverse event; BMI, body mass index; Coef, coefficient; CI, confidence interval; HF, heart failure; Hosp, hospitalisation; NT-proBNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association; SE, standard error.

5.4.14 *If clinical experts assessed the applicability of the health state utility values available or approximated any of values, provide the details (see section 5.3.4).*

Expert opinion was sought to provide validation of all statistical models, including the statistical model of EQ-5D.

The details of this process have been described previously in Section 5.3.4.

5.5 *Cost and healthcare resource use identification, measurement and valuation*

Resource identification, measurement and valuation studies

5.5.1 *Describe how relevant cost and healthcare resource use data for England were identified.*

Relevant costs were taken from publicly available sources. These are detailed in Section 5.5.2.

A resource use SR was performed, and is detailed in the Appendix, Section 8.11. Although potentially relevant studies were identified, it was considered that estimates of background resource use would be most reliably and appropriately informed by the Novartis commissioned analysis of the Clinical Practice Research Datalink (CPRD) dataset (16) for the following reasons:

- The CPRD dataset covers the English NHS, and so better reflects the population considered by NICE than studies considering resource use outside of England, or within smaller subpopulations
- The CPRD analysis is reasonably current (study period: 1 January 2008 to 31 December 2011), while a number of alternative studies are based on data from the 1990s
- Bespoke data tables considering resource use excluding hospitalisation and pharmacological therapies are available from the CPRD analysis, as is necessary in order to avoid double counting

5.5.2 *When describing how relevant unit costs were identified, comment on whether NHS reference costs or payment-by-results (PbR) tariffs are appropriate for costing the intervention being appraised. Describe how the clinical management of the condition is currently costed in the NHS in terms of reference costs and the PbR tariff. Provide the relevant Healthcare Resource Groups and PbR codes and justify their selection with reference to section 2.*

NHS Reference Costs are used to estimate the costs of hospitalisation and the cost of outpatient attendances, and for some peripheral costing items such as laboratory tests and A&E visits associated with adverse events. The Healthcare Resource Group (HRG) codes used and the methods applied are described in the Appendix, Section 8.12.

Outpatient cardiology appointments (service code 320) have an average cost of £130.86 (14). Hospitalisations in patients with HFrEF are included under the PbR tariff and under NHS reference costs. The costs of acute HF events are presented in Table 62. Other

HRGs used in the estimation of the costs of hospitalisation are presented in Section 8.12.

Table 62: Unit costs for acute heart failure (total HRG activity excluding excess bed days) (14)

HRG	Currency description	Activity	Unit cost
EB03A	Heart Failure or Shock, with CC Score 14+	5,678	£4,015
EB03B	Heart Failure or Shock, with CC Score 11-13	21,285	£3,151
EB03C	Heart Failure or Shock, with CC Score 8-10	33,895	£2,217
EB03D	Heart Failure or Shock, with CC Score 4-7	49,820	£1,597
EB03E	Heart Failure or Shock, with CC Score 0-3	12,307	£1,184

Abbreviations: CC, complication and comorbidity; HRG, Healthcare Resource Group.

5.5.3 *If clinical experts assessed the applicability of the cost and healthcare resource use values available, or approximated any of the values used in the cost-effectiveness analysis, provide the details (see section 5.3.4).*

UK expert opinion was sought to provide estimates of resource use associated with adverse events.

The details of this process have been described previously in Section 5.3.4.

Intervention and comparators' costs and resource use

5.5.4 *In a table, summarise the cost and associated healthcare resource use of each treatment.*

Pharmacological therapies

In the base case analysis, the daily cost of ACEi is based on the observed enalapril dose from PARADIGM-HF (18.9 mg per day) (10); it is noted that the target dose as defined in the PARADIGM-HF trial protocol is 10 mg bid (267), and so a daily cost based on the target dose is included in a scenario analysis. The most commonly used ACEi in England is ramipril, and so a further scenario is considered in which the costs of ramipril are applied. Since ramipril is associated with higher acquisition costs than enalapril, the base case assumption is considered to be conservative.

The daily cost of sacubitril valsartan is based on the observed dose of sacubitril valsartan from PARADIGM-HF (375 mg) (10). A daily cost based on the pre-specified target dose of 200 mg bid is expected to be the same as that of the observed dose, considering the flat pricing structure of sacubitril valsartan.

Typical costs of standard care (including beta blockers and aldosterone antagonists) and background medications (See Section 5.2.4) are based on recommended doses. See Section 5.2.4 for the definition of standard care, as used in this economic evaluation. Daily costs for primary and background therapies are presented in Table 63.

Table 63: Daily costs of primary and background therapies

Therapy	Daily cost[§]	Daily dose assumptions	Source of daily dose assumption
Sacubitril valsartan[†]	£3.27	375 mg[‡]	PARADIGM-HF (10)
Enalapril[†]	£0.07	18.9 mg[‡]	PARADIGM-HF (10)
Ramipril	£0.09	Two 5 mg tabs	BNF (274)
Perindopril	£0.05	One 4 mg tab	BNF (274)
Lisinopril	£0.11	One 20 mg tab, one 10 mg tab and one 5 mg tab	BNF (274)
Losartan	£0.10	One 100 mg tab and one 50 mg tab	BNF (274)
Candesartan[¶]	£0.08	One 32 mg tab	BNF (274)
Valsartan	£1.32	Two 160 mg tabs	BNF (274)
Carvedilol[†]	£0.11	Two 25 mg tabs	BNF (274)
Bisoprolol	£0.04	One 10 mg tab	BNF (274)
Spironolactone*	£0.07	One 50 mg tab	BNF (274)
Digoxin[†]	£0.05	One 62.5 µg or 125 µg tab	BNF (274)
Atorvastatin[†]	£0.05	One 20 mg tab	BNF (274)
Simvastatin	£0.07	One 80 mg tab	BNF (274)
Furosemide[†]	£0.03	One 20 mg or 40 mg tab	BNF (274)
Aspirin[†]	£0.03	One 75 mg tab	Bermingham 2014 (288)
Warfarin[†]	£0.04	One 5 mg tab	Drugs.com (289)
Clopidogrel[†]	£0.07	One 75 mg tab	BNF (274)

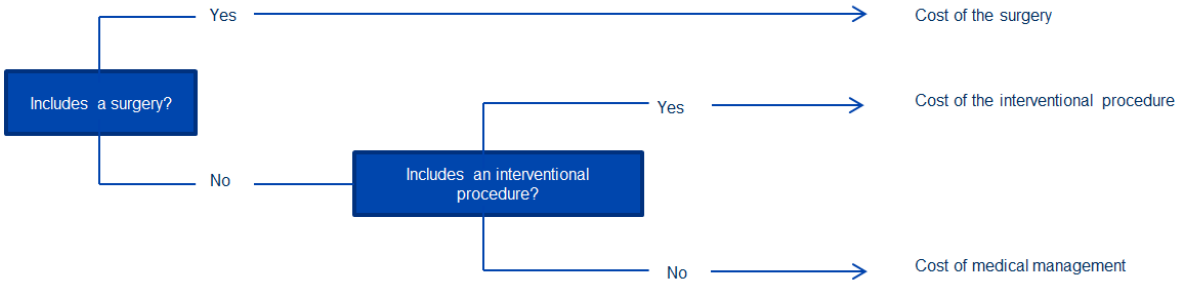
†Cost used in the base case
‡Average sacubitril valsartan dose is 375 mg daily in PARADIGM-HF; average enalapril dose is 18.9 mg daily in PARADIGM-HF (10).
§Using list prices all taken from BNF other than sacubitril valsartan
¶Cost used in the base case comparison vs. ARB

Hospitalisation

Costs for hospitalisation are taken from the NHS National Schedule of Reference Costs 2013-2014 (14). NHS reference costs provide unit costs for a hospitalisation event, and not a cost per day. This method is considered to be aligned with the process through which care is reimbursed in England.

The proportion of each type of hospitalisation is taken from PARADIGM-HF. A scenario is included in which these proportions are derived from patients in Western Europe only (approximately 2000 patients), in order to better reflect the kinds of surgical and interventional procedures that are performed in the UK. In the UK, hospitalisations are costed according to HRG code – hospitalisations including a surgery or interventional procedure are costed separately and include the costs of medical management incurred before and after the procedure. Hospitalisations observed during PARADIGM-HF are therefore costed according to the algorithm presented in Figure 29.

Figure 29: Algorithm to determine how each hospitalisation is costed



The proportions of each type of hospitalisation are presented in Table 64.

Table 64: Proportions of hospitalisations that are surgeries, interventional procedures and medical management alone (11)

Hospitalisation type	Proportion of hospitalisations
Surgical procedures	3%
Interventional procedures	7%
Medical management	91%

For practicality, hospitalisations for medical management were only included for diagnoses with >30 reported cases. Physician-reported diagnoses are mapped to the most appropriate HRG codes, and a weighted average is calculated using NHS activity as reported in the NHS National Schedule of Reference Costs (2013-2014). Details of the proportion of each physician reported diagnosis observed in PARADIGM-HF – and the associated HRG codes – are provided in the Appendix, Section 8.12. The HFrEF population is likely to have higher levels of comorbidities than the general population, and therefore inclusion of comorbidities at the same rate as the general population is likely to represent a conservative estimate of hospitalisation costs.

Table 65: Cost per hospitalisation (weighted average of relevant HRG codes)

Event	Cost per event	Source
Hospitalisation	£2,866.35	NHS National Schedule of Reference Costs, 2013-2014 (14)

Abbreviations: NHS, National Health Service; HRG, Healthcare Resource Group.

Background medical resource use

Because of the protocol-driven nature of resource use in PARADIGM-HF, estimates of background resource use are taken from relevant national sources.

Estimates of background resource use include A&E referrals, outpatient contacts and GP visits. Mean annual use is taken from a study using data from the CPRD (16); unit costs are taken from published national sources (Table 66). Levels of background resource use are assumed to be the same between both arms of the model.

Table 66: Background medical resource use

		Mean annual use*	Unit cost	Source of unit cost
A&E Visits	GP emergency visits	[redacted]	£35.00	PSSRU 2014 (13)
	A&E referrals	[redacted]	£123.67	NHS National Schedule of Reference Costs, 2013-2014 (14)
Outpatient office physician visits	GP visits	[redacted]	£35.00	PSSRU 2014 (13)
	Cardiologist visits	[redacted]	£130.86	NHS National Schedule of Reference Costs, 2013-2014 (14)
	Other physician visits	[redacted]	£35.00	PSSRU 2014 (13)
Other GP visits or contacts	GP home visits	[redacted]	£35.00	PSSRU 2014 (13)
	GP hospital visits	[redacted]	£35.00	PSSRU 2014 (13)
	GP nursing home visits	[redacted]	£35.00	PSSRU 2014 (13)
	GP residential home visits	[redacted]	£35.00	PSSRU 2014 (13)
	GP phone calls to patient	[redacted]	£35.00	PSSRU 2014 (13)
	GP visits with third parties	[redacted]	£35.00	PSSRU 2014 (13)

Abbreviations: A&E, accident and emergency; GP, general practitioner, NHS, National Health Service; PSSRU, Personal Social Services Research Unit.
* Mean annual use based on CPRD data (16)

Initial costs associated with titrating sacubitril valsartan

Once the health care professional has decided to initiate a patient on sacubitril valsartan, the patient would require one or two initial visits for titration of sacubitril valsartan based on the draft SmPC.

- In RAAS naïve patients, sacubitril valsartan would be initiated at a dose of 50mg twice daily. Sacubitril valsartan would then be titrated up to a dose of 100 mg twice daily then titrated again to maintenance dose of 200 mg twice daily.
- Previously treated patients would be initiated on 100 mg twice daily of sacubitril valsartan then titrated up to 200 mg twice daily.

However, no additional visits are required compared to initiation with ACEis or ARBs, where uptitration is also required (290, 291). Hence, the base case analysis assumes that no additional cost is associated with initiation of sacubitril valsartan.

A scenario analysis has been included to estimate the impact of cost associated with two additional visits. As the titration can be conducted by a GP, HF specialist nurse, or a cardiologist each with a different cost to the NHS, the scenario analysis is conservatively based on the maximum number of visits (two) and the most expensive visit (cardiologist outpatient appointment, see Table 67).

Table 67: Unit costs associated with titration

Resource use	Cost	Source
Cardiology outpatient contact	£130.86	NHS National Schedule of Reference Costs, 2013-2014 (14)

Abbreviations: NHS, National Health Service

Health-state costs and resource use

5.5.5 *Summarise and tabulate the costs included in each health state.*

For costs associated with the "alive" state, please see Sections 5.5.4 and 5.5.6. The "dead" state does not incur any costs.

Adverse reaction unit costs and resource use

5.5.6 *Summarise and tabulate the costs for each adverse reaction listed in section 4.12 and included in the de novo cost-effectiveness analysis.*

Adverse events for enalapril and sacubitril valsartan which are included in the economic model (based on FAS population as observed in PARADIGM-HF, and reported by McMurray et al (10)) are presented in Section 5.3.1 'Adverse event selection'. Estimates of resource use associated with adverse events were taken from UK clinical opinion (as supplied at the UK Advisory Board 2, Section 5.3.4), and are presented in Table 68. Unit costs associated with adverse events are presented in Table 69.

Table 68: Resource use and cost for adverse event

Event	Resource use*	Cost
Hypotension	• 2 GP visits	£70.00
Cough	• 2 GP visits • blood test	£73.00
Elevated serum creatinine	• 2 GP visits • blood test	£73.00
Elevated serum potassium	• 2 GP visits • blood test	£73.00
Angioedema		£221.58†
Mild – 60%	• 2 cardiologist outpatient visits • Antihistamine treatment	
Severe – 40%	• A&E visit • GP visit • Glucocorticoid treatment	
Hospitalisation	• NA (captured in hospitalisation model)	NA

Abbreviations: GP, General Practitioner; A&E, accident and emergency, NA, not applicable
*Estimates of resource use sourced from UK clinical opinion from a UK advisory board (Section 5.3.4)
†Weighted average cost of mild and severe angioedema based on ratio observed in PARADIGM-HF

Table 69: Unit costs associated with adverse events

Resource use	Cost	Source
GP visit (patient contact lasting 11.7 min)	£35.00	PSSRU (13)
Lab test (haematology)	£3.00	NHS National Schedule of Reference Costs, 2013-2014 (14)
Outpatient contact	£130.86	NHS National Schedule of Reference Costs, 2013-2014 (14)
Daily cost of antihistamines (cetirizine od, 10 mg, assumed taken for 14 days)	£0.04	BNF (274)
A&E visit	£123.67	NHS National Schedule of Reference Costs, 2013-2014 (14)
Daily cost of glucocorticoids (prednisolone, 40 mg, assumed taken for 5 days)	£0.37	BNF (274)

Abbreviations: A&E, accident and emergency; BNF, British National Formulary; GP, General Practitioner; , NHS, National Health Service; PSSRU, Personal Social Services Research Unit.

Miscellaneous unit costs and resource use

5.5.7 *Describe and tabulate any additional costs and healthcare resource use that have not been covered elsewhere*

All costs and healthcare resource use have been described in Sections 5.5.4 and 5.5.6.

5.6 *Summary of base case de novo analysis inputs and assumptions*

5.6.1 *Summary of base case de novo analysis inputs*

Please see the Appendix, Section 8.15 for full details of model input parameters. Table 70 summarises model inputs, sources and analyses.

Table 70: Summary of model inputs

Area of model	Source of data	Analysis	Section
All-cause mortality	PARADIGM-HF	Gompertz model of all-cause mortality with baseline characteristics and treatment as explanatory variables	5.3.1
All-cause hospitalisation		Negative binomial model with total number of all-cause hospitalisations as dependent variable and baseline characteristics and treatment as explanatory variables	5.3.1
Health-related quality of life		Mixed model of EQ-5D, including baseline characteristics, time, treatment, AEs, hospitalisation as explanatory variables	5.3.1
AEs		Simple rate of AEs observed in PARADIGM-HF assumed for all patients	5.3.1
Resource use		Costs of hospitalisation: proportion of surgical procedures, interventions, and medical management based on those observed in PARADIGM-HF	5.5.4
	CPRD	Cost of HF management: annualised rates of contact for GP, cardiologist, and A&E visits.	5.5.4
	Clinical expert opinion	Estimates of resource use for AEs was provided by clinical expert opinion	5.5.6
Unit costs	NHS Reference costs, PSSRU, BNF	Unit costs applied to estimates of resource use as described above.	5.5

Abbreviations: AE, adverse event; A&E, accident and emergency; BNF, British National Formulary; CPRD, Clinical Practice Research Datalink; HF, heart failure; GP, general practitioner; PSSRU, Personal Social Services Research Unit – unit costs of health.

5.6.2 *Assumptions*

A list of the key assumptions for the economic analysis is provided in Table 71.

Table 71: Summary of key assumptions applied in the economic model

Model area	Applicable to	Assumption	Rationale
PARADIGM-HF	Generalisability	The PARADIGM-HF population is representative of the English HFrEF population	PARADIGM-HF was a large RCT with a comparable patient population to those seen in other studies (173) and represents the best data currently available to inform the economic evaluation. However, subjects in PARADIGM-HF were younger and more likely to be male, as compared with the English HFrEF population. However, 1500 patients (19%) were over 75 years old (See Section 4.5.2). The topic is considered further in a scenario analysis which reweights the PARADIGM-HF population to better match the English population (see Section 5.8.8.1).
Regression models	Global assumptions	Sacubitril valsartan treatment effects are the same across patient populations	Tests of interaction found no evidence of treatment-effect modifiers for pre-defined subgroups for the primary endpoint and CV mortality (10). (See Section 5.3.1, Mortality.)
		Sacubitril valsartan treatment effects persist over the modelled time horizon	Long-term data from SOLVD showed that the treatment effect of enalapril persisted over 15 years of follow-up (182). It is therefore considered reasonable to assume that the treatment effects of HF treatments persist beyond trial duration. It is noted that the treatment effect of ivabradine was assumed to persist over a lifetime time horizon in the model submitted as part of TA267 (34, 216).
	Mortality	Survival follows a Gompertz distribution, estimated using proportional hazards (for both all-cause and CV mortality approaches)	The Gompertz distribution was preferred by clinical experts, provides the most conservative estimate of survival benefit, and has been used previously (34). See Section 5.3.1, Mortality.
	Hospitalisation	The rate of hospitalisation is constant over time	This assumption is made for simplicity and has been employed in previous economic evaluations of therapies in HFrEF (34, 216). A scenario is included in which hospitalisation rates are assumed to increase annually by 10%.

Model area	Applicable to	Assumption	Rationale
		Hospitalisation rates as observed in PARADIGM-HF are representative of hospitalisation rates seen in English patients with HFrEF	Baseline hospitalisation rates are expected to be higher in clinical practice than observed in PARADIGM-HF. A scenario analysis is included in which hospitalisation costs are doubled (see Section 5.8.8). Results of this analysis and calibration of the model against estimates of hospitalisation risk from CPRD (see Section 5.8.8.1) suggest that increasing the baseline risk of hospitalisation improves the cost-effectiveness of sacubitril valsartan, and thus the base-case assumption is considered conservative.
	EQ-5D	EQ-5D declines at a constant rate over the modelled time horizon (and is the same irrespective of baseline characteristics)	Current data are limited to that observed in PARADIGM-HF, and longitudinal data from Berg et al (287) which suggests an annual decrease in EQ-5D of -0.006. As such, there remains uncertainty regarding long-term time trends in EQ-5D. In order to explore this, scenario analyses are considered which halve and double the rate of change in EQ-5D over time and in which EQ-5D is assumed to remain constant from baseline and after 5 and 10 years (see Section 5.8.8).
		Both the acute and mid-term hospitalisation utility decrements are applied in the model cycle in which the patient is hospitalised	This simplifying assumption is made in order to reduce model complexity. A scenario in which hospitalisation utility decrements are not included is considered (see Section 5.8.8).
		Utility decrements for hypotension and cough are applied in the model cycle in which the adverse event occurs	This simplifying assumption is made in order to reduce model complexity. A scenario in which adverse event rates are set to zero is considered (see Section 5.8.8).
Costs	Pharmacological therapy	Daily costs of ACEi and sacubitril valsartan are based on observed doses from PARADIGM-HF	PARADIGM-HF represents the best available data source for dosing of sacubitril valsartan and ACEi in clinical practice, and efficacy data are based on these observed doses. A scenario analysis is included in which recommended doses are used (see Section 5.8.8).
		Costs and recommended doses of representative background therapies based on BNF	Recommended doses presented in the BNF are expected to be representative of doses used in clinical practice. Costs of background therapies represent a low proportion of total costs.

Model area	Applicable to	Assumption	Rationale
		Use of background therapies is the same between model arms	Sacubitril valsartan is not expected to modify the use of background therapies. Costs of background therapies represent a low proportion of total costs.
		Use of background therapies in PARADIGM-HF is representative of that seen in English clinical practice	Efficacy data are based on background therapy regimens observed in PARADIGM-HF; as such, it is appropriate that resource use data be based on the same population. Use of BB and AA in PARADIGM-HF is broadly reflective of English clinical practice: In England, 82% and 49% of patients receive BB and AA, respectively (6), as compared with 93% and 56% in PARADIGM-HF.
	Hospitalisation	Cost per hospitalisation based on HRGs mapped from physician-reported diagnoses; surgeries and interventional procedures that could be classified, and medical management hospitalisations with > 30 instances considered.	Resulting costs of hospitalisation are similar to those reported previously (34, 216). Scenario analyses are included in which hospitalisation costs are doubled and halved, and in which the proportion of each hospitalisation type is taken from patients in Western Europe only (see Section 5.8.8.),
	Background medical resource use	Background medical resource use is the same between model arms	Patients in the sacubitril valsartan arm of PARADIGM-HF experience a lower hospitalisation rate, which is expected to be correlated with lower levels of background resource use. As such, this is expected to be a conservative assumption.
	Adverse events	Cost per adverse event based on estimates of resource use provided by UK cardiologists	In the absence of alternative data sources, this was considered a reasonable approach. AE costs represent a low proportion of total costs.
	Initial costs associated with titrating sacubitril valsartan	No additional cost is associated with titration of sacubitril valsartan	Although additional visits are required, these are not additional compared with ACEis and ARBs. A scenario analysis is included, assuming the maximum number of visits and the maximum cost per visit (2 outpatient cardiology visits, see Section 5.8.8)

Abbreviations: AA, aldosterone antagonist; ACEi, angiotensin converting enzyme inhibitor; AE, adverse event; ARB, Angiotensin II Receptor Blocker; BB, beta blocker; BNF, British National Formulary; CPRD, Clinical Practice Research Datalink; CV, cardiovascular; HF, heart failure; HFrEF, Heart Failure with reduced Ejection Fraction; HRG, Healthcare Resource Group; RCT, randomised controlled trial; TA, Technology Appraisal.

5.7 *Base case results*

Table 70 and Table 71 above summarise the model inputs and key assumptions that have been used to determine the base case results.

5.7.1 *Base case incremental cost effectiveness analysis results – all-cause mortality*

5.7.1.1 Base case results – primary comparison versus ACEi

Table 72 presents the results of the primary analysis of sacubitril valsartan in combination with standard care vs. ACEi in combination with standard care sacubitril valsartan is associated with incremental costs of £7,448 and incremental QALYs of 0.41 resulting in an ICER of £18,187.

Table 72: Base case results vs. ACEi

Technologies	Total			Incremental			ICER (£) vs. ACEi
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	
ACEi	£13,286	6.03	4.46	-	-	-	-
Sacubitril valsartan	£20,734	6.51	4.87	£7,448	0.48	0.41	£18,187

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

Clinical outcomes

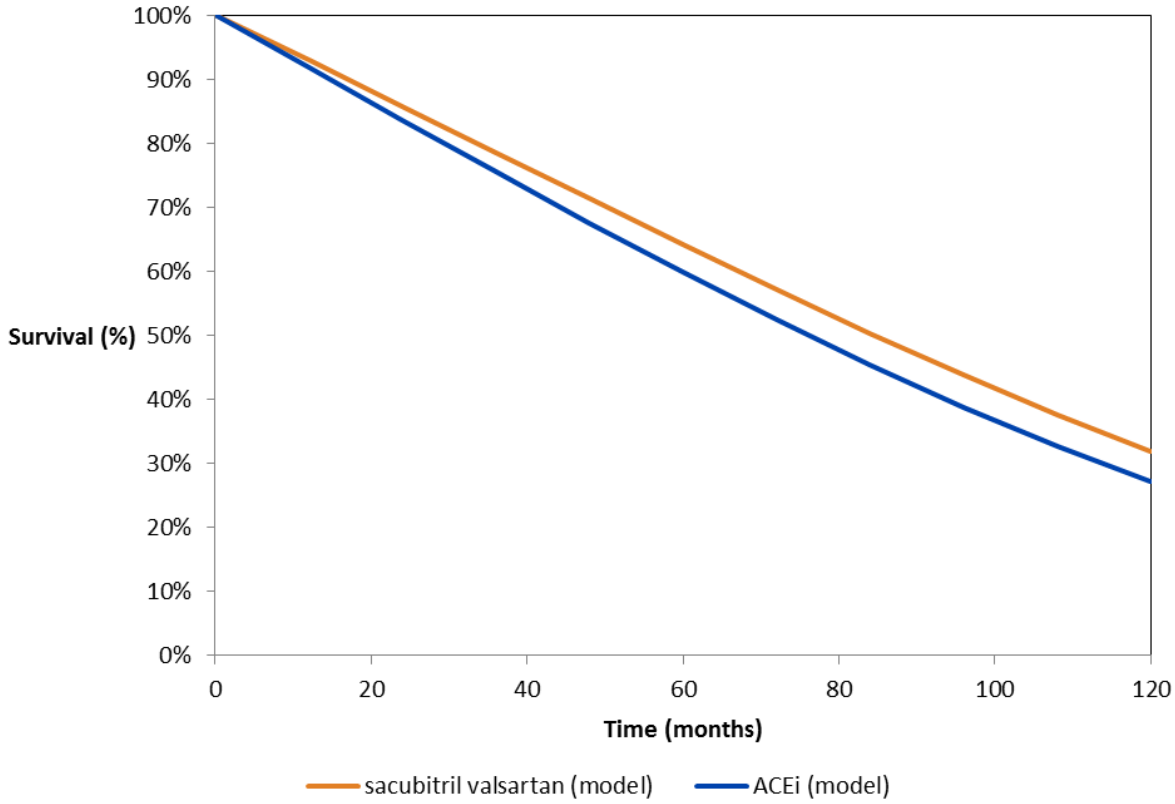
Table 74 (and Figure 30) and Table 73 (and Figure 31) present the model outcomes for both therapies. The results show increased survival, and a modest decrease in the expected number of hospitalisations associated with sacubitril valsartan.

Table 73: Mortality outcomes

Component	ACEi	Sacubitril valsartan	Incremental†
CV mortality (%) at year 2	14%	11%	-2%
CV mortality (%) at year 5	33%	28%	-5%
CV mortality (%) at year 10	61%	53%	-7%
All-cause mortality (%) at year 2	16%	14%	-2%
All-cause mortality (%) at year 5	40%	36%	-4%
All-cause mortality (%) at year 10	73%	68%	-5%
Expected survival (years)	7.16	7.82	0.66

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; CV, cardiovascular;.
†Values shown in the 'Incremental' column are absolute differences (i.e. differences in percentage points) and not relative percentage changes.

Figure 30: Visual representation of the model mortality outcomes



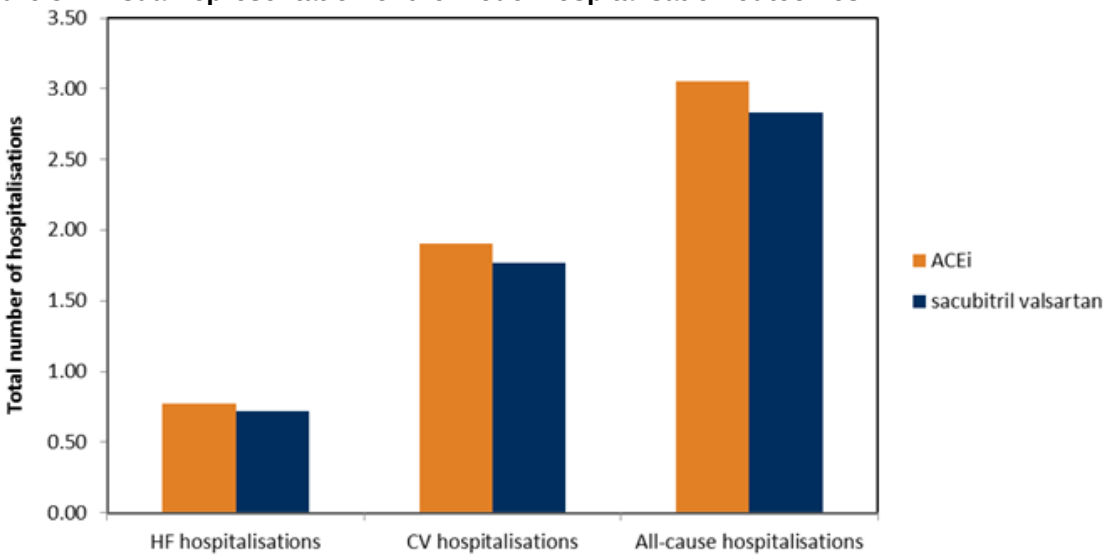
Abbreviations: ACEi, angiotensin-converting enzyme inhibitor;

Table 74: Hospitalisation outcomes

Component	ACEi	Sacubitril valsartan	Incremental
HF hospitalisations	0.77	0.72	-0.06
CV hospitalisations	1.91	1.77	-0.14
All-cause hospitalisations	3.05	2.83	-0.22
No. of hospitalisations per year	0.43	0.36	-0.06

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; CV, cardiovascular; HF, heart failure.

Figure 31: Visual representation of the model hospitalisation outcomes



Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; CV, cardiovascular; HF, heart failure.

5.7.1.2 Base case results - secondary comparison versus ARBs

Table 75 presents the results of the secondary comparison versus ARB, informed by the NMA described in Section 4.10. In the base case analysis ARB comparison, described in Section 5.2.4, sacubitril valsartan is associated with incremental costs of £8,453 and incremental QALYs of 0.50, resulting in an ICER of £16,753.

Table 75: Summary of incremental cost-effectiveness vs. ARB

Technologies	Total			Incremental			ICER (£)
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	vs. ARB
ARB	£12,281	5.89	4.37	-	-	-	-
Sacubitril valsartan	£20,734	6.51	4.87	£8,453	0.62	0.50	£16,753

Abbreviations: ARB, angiotensin receptor blocker; ICER, incremental cost-effectiveness ratio; LYG, Life Years Gained; QALYs, Quality Adjusted Life Years

Clinical outcomes

Table 76 and Table 77 present the model outcomes for both therapies for the base-case analysis for the ARB comparison. The results show increased survival, and a comparable number of hospitalisations associated with sacubitril valsartan.

Table 76: Mortality outcomes for comparison vs. ARB

Component	ARB	Sacubitril valsartan	Incremental†
CV mortality (%) at year 2	14%	11%	-3%
CV mortality (%) at year 5	34%	28%	-6%
CV mortality (%) at year 10	62%	53%	-8%
All-cause mortality (%) at year 2	17%	14%	-3%
All-cause mortality (%) at year 5	42%	36%	-6%
All-cause mortality (%) at year 10	74%	68%	-6%
Expected survival (years)	6.98	7.82	0.85

Abbreviations: ARB, angiotensin receptor blocker; CV, cardiovascular.
†Values shown in the 'Incremental' column are absolute differences (i.e. differences in percentage points) and not relative percentage changes.

Table 77: Hospitalisation outcomes for comparison vs. ARB

Component	ARB	Sacubitril valsartan	Incremental
HF hospitalisations	0.68	0.72	0.04
CV hospitalisations	1.67	1.77	0.10
All-cause hospitalisations	2.68	2.83	0.15
No. of hospitalisations per year	0.38	0.36	-0.02

Abbreviations: ARB, angiotensin receptor blocker ; CV, cardiovascular; HF, heart failure.
Note: Hospitalisations are lower in the ARB arm compared to sacubitril valsartan as this is based on 'lifetime' hospitalisations and patients on ARB have a lower life expectancy. Number of hospitalisation per year is reduced with sacubitril valsartan as was shown in the NMA (Table 29).

5.7.2 *For the outcomes highlighted in the decision problem (see section 3), provide the corresponding outcomes from the model and compare them with clinically important outcomes such as those reported in clinical trials, as suggested in the table below. Discuss reasons for any differences between the modelled results in the cost-effectiveness analysis and the observed results in the clinical trials (for example, adjustment for crossover*

Mortality

Table 78, Table 79 and Figure 32 present the comparisons between mortality predicted by the model, and mortality as observed in PARADIGM-HF. It can be seen that the model closely reflects the observed data within the trial period.

Table 78: Predicted vs. observed survival for sacubitril valsartan

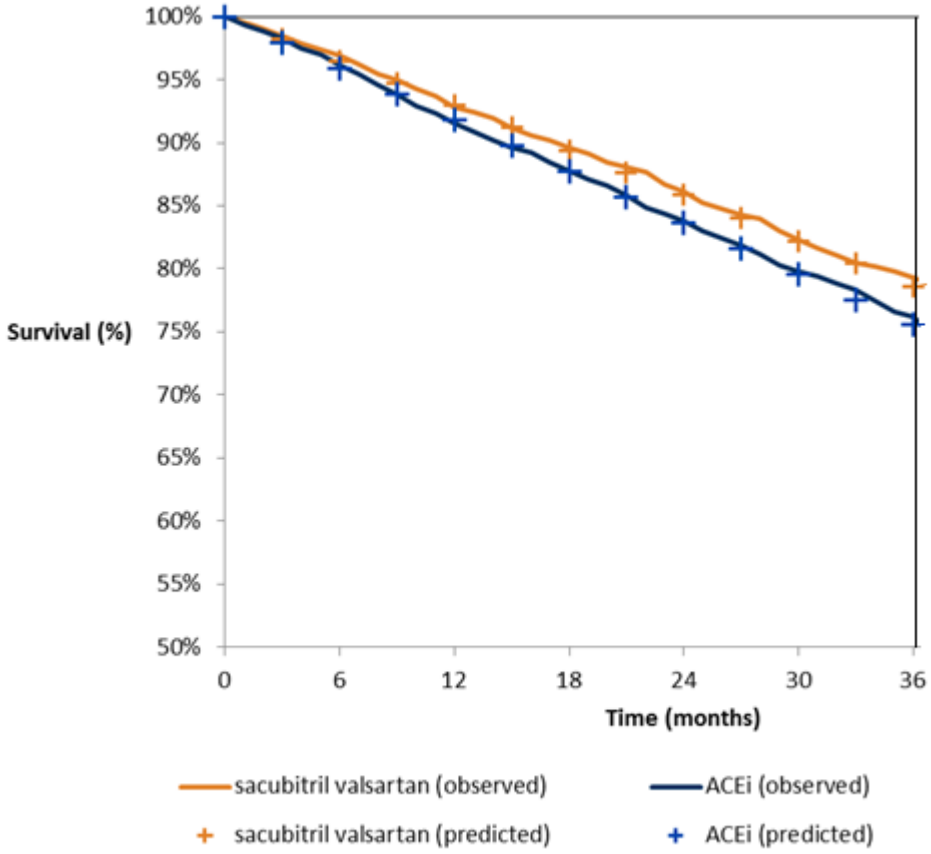
Month	Predicted survival from model (Sacubitril valsartan)	Observed survival from PARADIGM-HF (Sacubitril valsartan)
0	100%	100%
3	98%	98%
6	97%	97%
9	95%	95%
12	93%	93%
15	91%	91%
18	89%	90%
21	88%	88%
24	86%	86%
27	84%	84%
30	82%	82%
33	80%	81%
36	79%	79%

Table 79: Predicted vs. observed survival for ACEi

Month	Predicted survival from model (ACEi)	Observed survival from PARADIGM-HF (ACEi)
0	100%	100%
3	98%	98%
6	96%	96%
9	94%	94%
12	92%	92%
15	90%	90%
18	88%	88%
21	86%	86%
24	84%	84%
27	82%	82%
30	80%	80%
33	78%	78%
36	76%	76%

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor

Figure 32: Predicted vs. observed survival for sacubitril valsartan and ACEi



Abbreviations: ACEi, angiotensin-converting enzyme inhibitor.

Hospitalisation

Table 80 presents a comparison of hospitalisation rates as predicted by the model, and as observed in PARADIGM-HF. Model predicted rates are consistent with those generated by the negative binomial model used in the primary analysis of PARADIGM-HF (0.43 and 0.51 for sacubitril valsartan and ACEi, respectively, compared with comparable figures from PARADIGM-HF of 0.43 and 0.50).

Table 80: Summary of model results compared with clinical data

Outcome	PARADIGM-HF clinical trial result		Model result
	Unadjusted estimated rate	Estimated rate from NB model†	
Annual hospitalisation rate (Sacubitril valsartan)	0.38	0.42	0.43
Annual hospitalisation rate (ACEi)	0.44	0.50	0.51

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; NB, negative binomial.
† Negative binomial (NB) regression model, adjusted for treatment and region. Log(follow-up duration) is the offset variable.

5.7.3 *Provide (if appropriate) the proportion of the cohort in the health state over time (Markov trace) for each state, supplying 1 for each comparator*

Table 81 presents the proportion of the cohort in the 'alive' health state over time for sacubitril valsartan and ACEi, respectively.

Table 81: Proportion of cohort in alive health state

Year	% in Alive health state	
	Sacubitril valsartan	ACEi
0	100%	100%
1	93%	92%
2	86%	84%
3	79%	76%
4	72%	68%
5	64%	60%
6	57%	52%
7	50%	45%
8	44%	39%
9	37%	33%
10	32%	27%
11	27%	22%
12	22%	17%
13	17%	14%
14	14%	11%
15	11%	8%

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor

5.7.4 *Provide details of how the model assumes QALYs accrued over time*

Table 82 and Table 83 present the QALYs accrued over time for sacubitril valsartan and ACEi, respectively.

Table 82: QALYs accrued over time, sacubitril valsartan

Year	QALYs	Hospitalisation decrements	AE decrements	Total
1	0.7382	-0.0066	-0.0006	0.7311
2	0.6559	-0.0053	-0.0005	0.6501
3	0.5783	-0.0042	-0.0004	0.5737
4	0.5057	-0.0033	-0.0003	0.5021
5	0.4382	-0.0026	-0.0003	0.4354
6	0.3761	-0.0020	-0.0002	0.3739
7	0.3193	-0.0015	-0.0002	0.3177
8	0.2681	-0.0011	-0.0001	0.2669
9	0.2223	-0.0008	-0.0001	0.2215
10	0.1820	-0.0006	-0.0001	0.1813
11	0.1468	-0.0004	-0.0001	0.1464
12	0.1167	-0.0003	0.0000	0.1164
13	0.0912	-0.0002	0.0000	0.0910
14	0.0701	-0.0001	0.0000	0.0700
15	0.0529	-0.0001	0.0000	0.0528

Abbreviations: AE, adverse event; QALY, quality-adjusted life year.

Table 83: QALYs accrued over time, ACEi

Year	QALYs	Hospitalisation decrements	AE decrements	Total
1	0.7240	-0.0077	-0.0005	0.7157
2	0.6352	-0.0060	-0.0004	0.6288
3	0.5527	-0.0046	-0.0003	0.5478
4	0.4766	-0.0035	-0.0003	0.4728
5	0.4069	-0.0027	-0.0002	0.4040
6	0.3437	-0.0020	-0.0002	0.3416
7	0.2871	-0.0014	-0.0001	0.2855
8	0.2368	-0.0010	-0.0001	0.2356
9	0.1927	-0.0007	-0.0001	0.1919
10	0.1546	-0.0005	-0.0001	0.1541
11	0.1222	-0.0003	0.0000	0.1218
12	0.0949	-0.0002	0.0000	0.0947
13	0.0725	-0.0002	0.0000	0.0723
14	0.0543	-0.0001	0.0000	0.0542
15	0.0399	-0.0001	0.0000	0.0398

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; AE, adverse event; QALY, quality-adjusted life year.

5.7.5 *Provide details of the disaggregated QALYs and costs by health state, and of resource use predicted by the model in the base case incremental cost effectiveness analysis by category of cost*

Table 84 presents the disaggregated costs accrued in each model arm. The most significant cost difference is associated with the cost of primary drug therapy. Additional costs are also accrued for background therapy and HF management due to the additional resource use associated with extended survival. Although sacubitril valsartan is associated with a significant reduction in the hospitalisation rate, the associated reduction in costs is somewhat offset by

Table 84: Base case results – disaggregated costs for ACEi comparison (lifetime time horizon)

Component	ACEi	Sacubitril valsartan	Incremental
Primary therapy	£152	£7,774	£7,622
Background therapy	£540	£583	£43
Hospitalisation	£7,489	£6,868	-£622
HF management	£5,015	£5,413	£399
Adverse events	£91	£97	£6
Total costs	**£13,286**	**£20,734**	**£7,448**

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; HF, heart failure.

The model does not have health states *per se*, and therefore all QALYs are accrued in the 'alive' state. Similarly all resource use is incurred in this single state.

5.7.6 *Alternative analysis – CV mortality approach*

5.7.6.1 Alternative results vs ACEi

Table 85 presents the results of the alternative analysis vs. ACEi in which CV mortality is modelled (See Alternative mortality analysis – CV mortality' section and Section 8.16 for further details on the alternative analysis). Sacubitril valsartan is associated with incremental costs of £8,583 and incremental QALYs of 0.51, resulting in an ICER of £16,894.

Table 85: Summary of incremental cost-effectiveness vs. ACEi – alternative analysis

Technologies	Total			Incremental			ICER (£)
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	vs. ACEi
ACEi	£14,823	6.73	4.93	-	-	-	-
Sacubitril valsartan	£23,405	7.34	5.44	£8,583	0.62	0.51	£16,894

Abbreviations: ACEi, angiotensin converting enzyme inhibitor; ICER, incremental cost-effectiveness ratio; LYG, life adjusted years; QALYs; quality adjusted life years.

5.7.7 *Alternative results vs ARBs*

The ARB comparison using CV mortality was also explored (see Table 86). See Section 5.2.4 for further details on the ARB comparison, description of the assumptions employed and the rationale for each assumption.

Table 86: Summary of incremental cost-effectiveness vs. ARB – alternative analysis

Technologies	Total			Incremental			ICER (£)
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	vs. ARB
ARB	£13,837	6.63	4.87	-	-	-	-
Sacubitril valsartan	£23,405	7.34	5.44	£9,569	0.71	0.57	£16,817

Abbreviations: ARB, angiotensin receptor blocker; Inc, incremental; ICER, incremental cost-effectiveness ratio LYG, life adjusted years; QALYs; quality adjusted life years

5.8 *Sensitivity analyses*

Probabilistic sensitivity analysis

5.8.1 ***The mean value, distribution around the mean and the source and rationale for the supporting evidence should be clearly described for each parameter included in the model. The distributions for probabilistic sensitivity analysis should not be arbitrarily chosen, but should represent the available evidence on the parameter of interest, and their use should be justified.***

Joint parameter uncertainty is explored through probabilistic sensitivity analysis (PSA) whereby all parameters are assigned distributions and varied jointly. 1,000 Monte Carlo simulations were performed and recorded (292). Where the covariance structure between parameters was known, correlated random draws were sampled from a multivariate normal distribution. Sampling from multivariate distributions is performed using code developed by the Centre for Bayesian Statistics in Health Economics (293). Results were plotted on the cost-effectiveness plane (CEP) (294, 295), and a cost-effectiveness acceptability curve (CEAC) was constructed. Confidence intervals around expected ICERs were estimated using Fieller's theorem.

Model parameters included in probabilistic sensitivity analysis (and their respective probability distributions) are shown in Section 8.15.

5.8.2 ***The distributions and their sources for each parameters should be clearly stated if different from those presented in section 5.5, including the derivation and value of any 'priors'. If any parameters or variables were omitted from the probabilistic sensitivity analysis, please provide the rationale for the omission(s).***

Parameters were assigned distributions based on best practice guidance (295). Where data were available, correlation between parameters was preserved by assuming multivariate normal distributions (295). Distributions assumed and related parameters are provided in Section 8.15. Unit costs were not varied where there was a lack of information regarding uncertainty around these quantities.

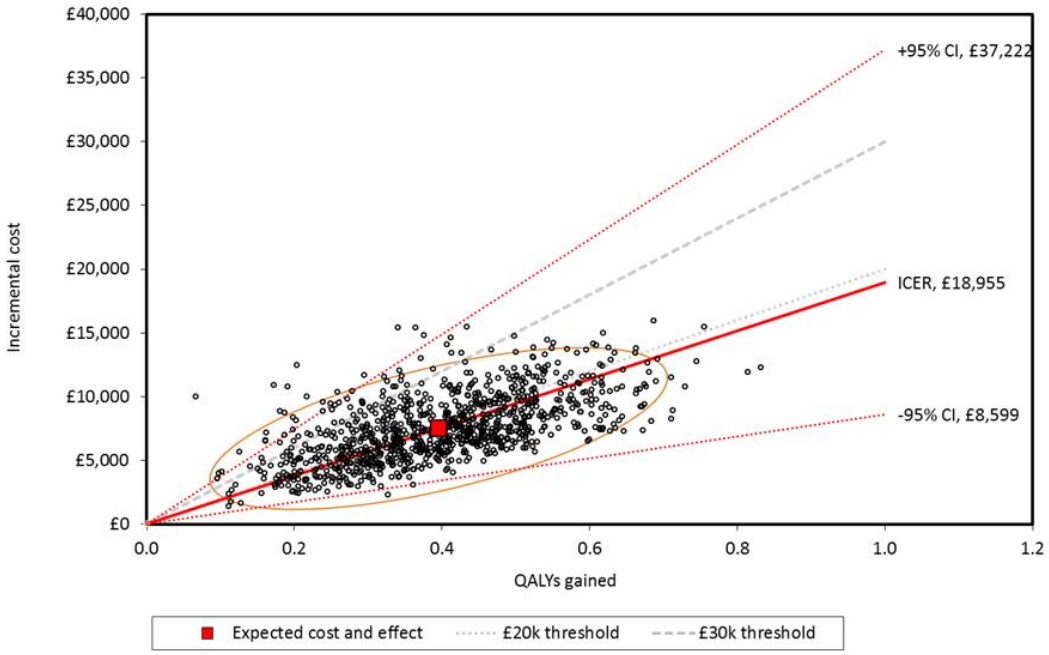
5.8.3 ***Present the incremental cost effectiveness results of a probabilistic sensitivity analysis (including 95% confidence intervals).***

5.8.3.1 Primary comparison vs ACEi

The results of 1,000 simulations were plotted on the CEP (Figure 33), and the CEAC was calculated (Figure 34). It is noted that all simulation results lie in the north-east quadrant of the cost-effectiveness plane, i.e. sacubitril valsartan is always more expensive and more effective than ACEi. The probabilistic ICER is £18,955 (95% CI: £8,599, £37,222).

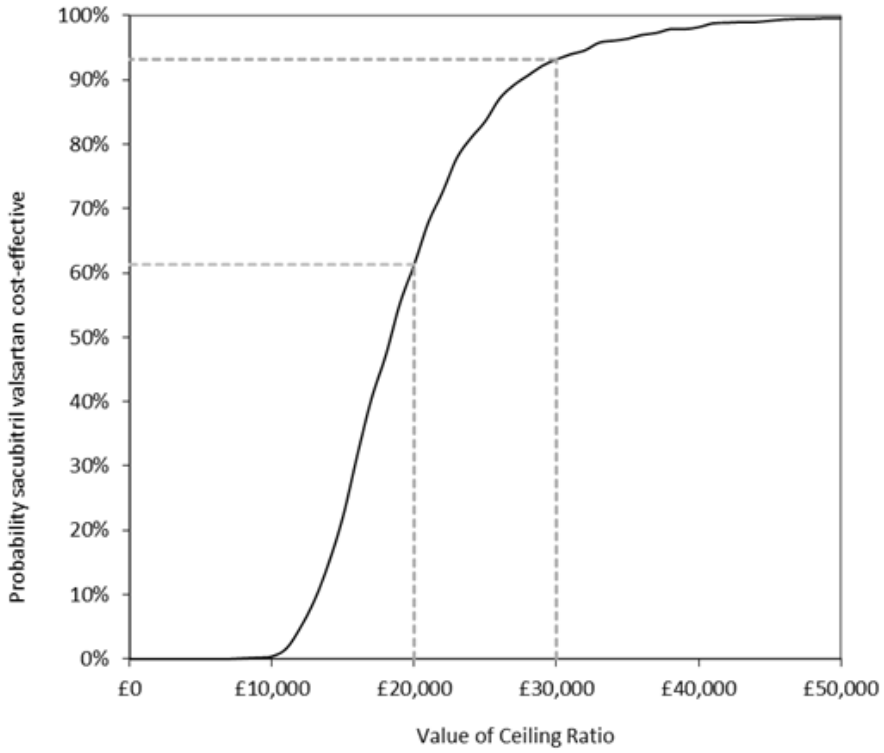
The CEAC (Figure 34) presents the probability that sacubitril valsartan is a cost-effective treatment option at various values of the ceiling ratio, or various willingness-to-pay thresholds. The probabilities of sacubitril valsartan being cost-effective at the lifetime time horizon at thresholds of £20,000 and £30,000 are 61% and 93%, respectively.

Figure 33: Cost-effectiveness plane and 95% confidence ellipse – ACEi comparison



Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; CI, confidence interval; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year.

Figure 34: Cost-effectiveness acceptability curve – ACEi comparison

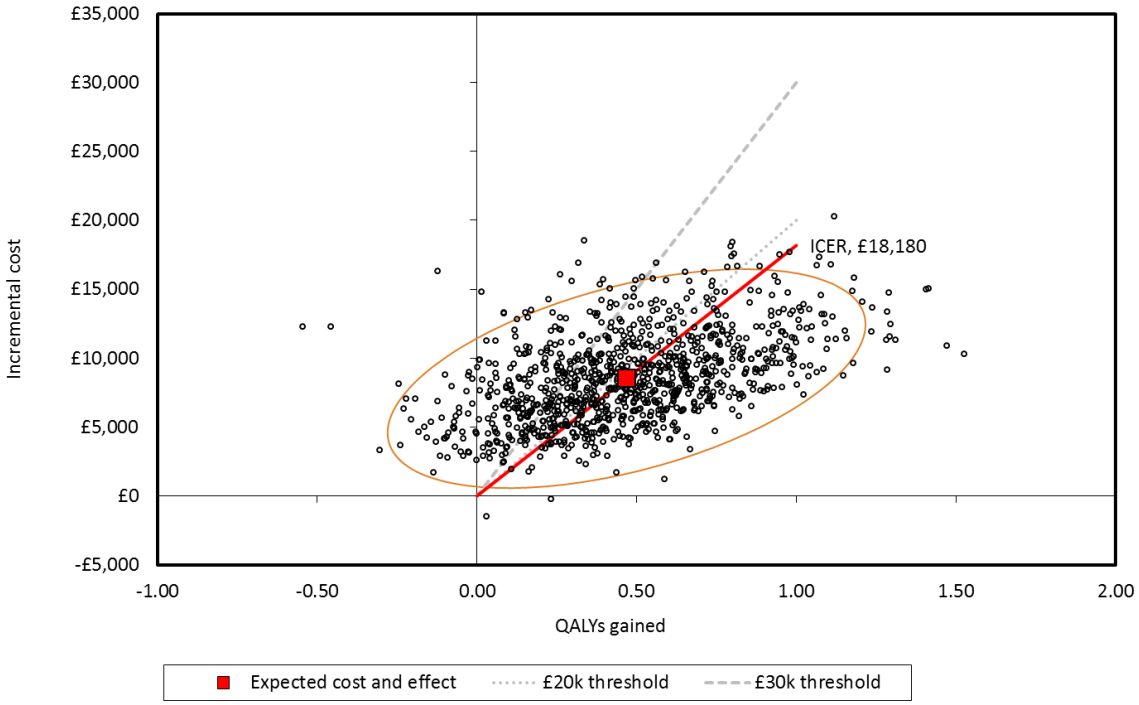


Abbreviations: ACEi, angiotensin-converting enzyme inhibitor.

5.8.3.2 Secondary comparison vs ARBs

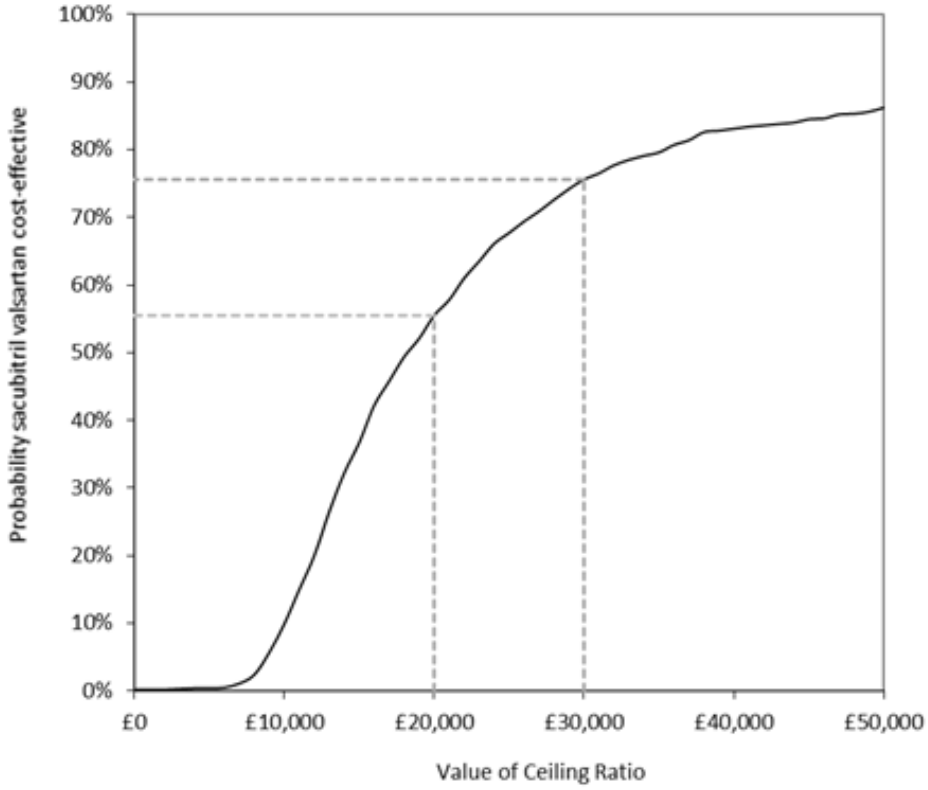
The results of 1,000 simulations were plotted on the CEP (Figure 35), and the CEAC was calculated (Figure 36). The comparison against ARBs is subject to greater uncertainty than the comparison against ACEis, driven by uncertainty in the results of the NMA. The probabilistic ICER is £18,180. The 95% CIs for the probabilistic ICER were undefined because the lower limit lies in the north-east quadrant and the upper limit lies in the north-west quadrant of the CEP (See Figure 35). The probabilities of sacubitril valsartan being cost-effective at the lifetime time horizon at thresholds of £20,000 and £30,000 are 56% and 76%, respectively.

Figure 35: Cost-effectiveness plane and 95% confidence ellipse – ARB comparison



Abbreviations: ARB, angiotensin II receptor blocker; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year.

Figure 36: Cost-effectiveness acceptability curve – ARB comparison



Abbreviations: ARB, angiotensin II receptor blocker.

5.8.4 ***Describe and explain, if any, the variation between the incremental cost effectiveness analysis results estimated from the base case analysis (section 5.6) and the probabilistic sensitivity analysis.***

The probabilistic ICER vs. ACEi from PSA was £18,955. This compares to a base case deterministic ICER vs. ACEi of £18,187. The outcomes of the two analyses were therefore considered congruent.

Deterministic sensitivity analysis

5.8.5 ***Identify which variables were subject to deterministic sensitivity analysis, how they were varied, and the rationale behind this. If any parameters or variables listed in section 5.6.1 were omitted from sensitivity analysis, please provide the rationale.***

Model parameters included in deterministic sensitivity analysis (and their upper and lower values) are shown in Section 8.15. Parameters were systematically and independently varied over a plausible range determined by a) the 95% confidence interval surrounding the point estimate or b) upper and lower values of ±25% (where confidence intervals are not available). The deterministic sensitivity analysis was first run using mean patient characteristics (as opposed to the patient-level cohort approach used in the base case results) to identify the ten most influential parameters using a less computationally burdensome approach. The ICERs were then recorded at the upper and lower values for these ten parameters using the patient-level approach to produce a tornado diagram.

5.8.6 ***Present the results of deterministic sensitivity analysis. Consider the use of tornado diagrams.***

Deterministic sensitivity analysis was performed for the primary comparison vs ACEi. The most influential parameters related to all-cause mortality, with the treatment effect of sacubitril valsartan, the baseline mortality rate, and the coefficient for age (squared) on all-cause mortality having the greatest effects on the ICER.

Table 87 and Figure 37 present the deterministic sensitivity analysis results using the ten most influential parameters. The most influential parameter was the treatment effect term (that is, the log hazard ratio) in the statistical model of all-cause mortality. This parameter determines the difference in all-cause mortality between the two arms of the model. At the upper bound of the 95% CI (the smallest difference in expected survival), the ICER increases to £32,900. At the lower bound (largest difference in expected survival), the ICER is reduced to £13,506.

The second most influential parameter was the constant term in the statistical model of all-cause mortality. This parameter determines the baseline risk of all-cause mortality. At the lower bound of the 95% CI (the highest expected survival), the ICER increases to £23,613. At the upper bound (lower expected survival) the ICER is reduced to £14,551.

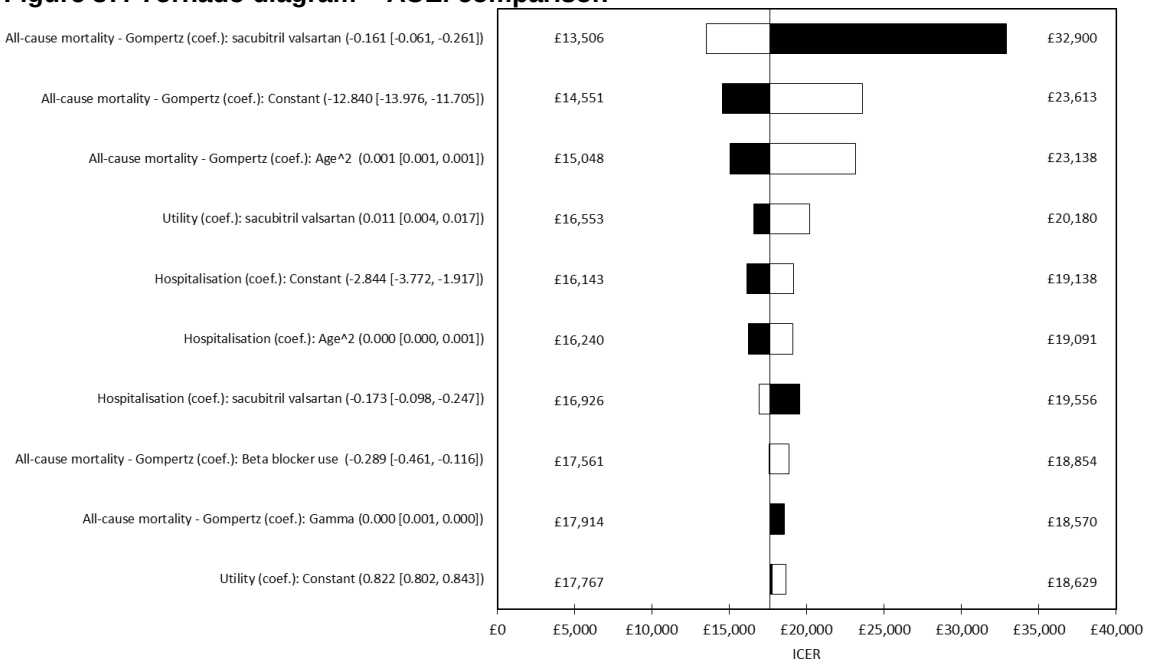
The coefficient for age (squared) was associated with changes of a similar order of magnitude, as this coefficient has a disproportionately large impact on expected survival compared with coefficients for other baseline characteristics. The non-transformed age coefficient is also included as a covariate in all models. Other coefficients in the model of all-cause mortality were also influential, such as the coefficients for beta blocker use at baseline. The treatment effects for sacubitril valsartan for utility and hospitalisation were associated with modest changes in the ICER.

Table 87: Deterministic sensitivity analysis using patient-level analysis – ACEi comparison

Parameter	Mean (range varied between)	ICER with low value	ICER with high value
All-cause mortality - Gompertz (coef.): sacubitril valsartan	-0.161 (-0.061, -0.261)	£13,506	£32,900
All-cause mortality - Gompertz (coef.): Constant	-12.840 (-13.976, -11.705)	£23,613	£14,551
All-cause mortality - Gompertz (coef.): Age^2*	0.001 (0.001, 0.001)	£23,138	£15,048
Utility (coef.): Sacubitril valsartan	0.011 (0.004, 0.017)	£20,180	£16,553
Hospitalisation (coef.): Constant	-2.844 (-3.772, -1.917)	£19,138	£16,143
Hospitalisation (coef.): Age^2*	0.000 (0.000, 0.001)	£19,091	£16,240
Hospitalisation (coef.): Sacubitril valsartan	-0.173 (-0.098, -0.247)	£16,926	£19,556
All-cause mortality - Gompertz (coef.): BB use	-0.289 (-0.461, -0.116)	£18,854	£17,561
All-cause mortality - Gompertz (coef.): Gamma	0.000 (0.001, 0.000)	£17,914	£18,570
Utility (coef.): Constant	0.822 (0.802, 0.843)	£18,629	£17,767

* Age exhibited a non-linear effect, and therefore a quadratic transformation was included.
Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; BB, beta blocker; coef., coefficient; ICER, incremental cost-effectiveness ratio.

Figure 37: Tornado diagram – ACEi comparison†



† Black shading is used to signify where the low value of the parameter has been used; white shading is used to signify where the high value of the parameter has been used
Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; coef, coefficient. ICER, incremental cost-effectiveness ratio.

Deterministic sensitivity analysis was also performed for the comparison against ARB (Table 88 and Figure 38). Findings were consistent of the results with the analysis vs

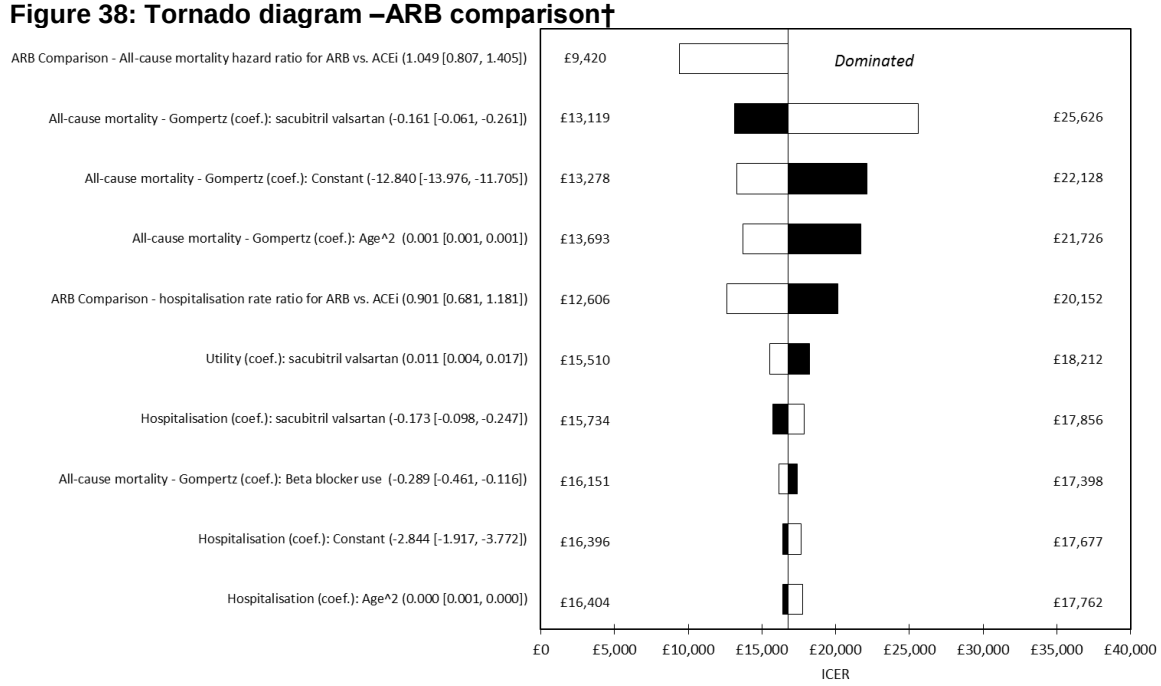
ACEi, except the all-cause mortality hazard ratio for ARB vs ACEi from the NMA was the most influential parameter. This parameter is subject to a high degree of uncertainty due to the wide credible intervals generated by the NMA, which is associated with the heterogeneity of included NMA studies: at the lower 95% credible interval (in which ARB is most effective vs ACEi and sacubitril valsartan) ARB was the dominant treatment strategy; at the upper 95% credible interval (in which ARB is less effective vs ACEi and sacubitril valsartan) the ICER was £9,420. It is of note that the comparison against ARB is achieved by varying the outcomes of the ACEi arm, and therefore parameters from the statistical models of all-cause mortality, all-cause hospitalisation, and HRQoL continue to be influential parameters.

Table 88: Deterministic sensitivity analysis using patient-level analysis – ARB comparison

Parameter	Mean (range varied between)	ICER with low value	ICER with high value
ARB Comparison - All-cause mortality hazard ratio for ARB vs. ACEi	1.049 (0.807, 1.405)	Dominated	£9,420
All-cause mortality - Gompertz (coef.): sacubitril valsartan	-0.161 (-0.061, -0.261)	£13,119	£25,626
All-cause mortality - Gompertz (coef.): Constant	-12.840 (-13.976, -11.705)	£22,128	£13,278
All-cause mortality - Gompertz (coef.): Age^2*	0.001 (0.001, 0.001)	£21,726	£13,693
ARB Comparison - hospitalisation rate ratio for ARB vs. ACEi	0.901 (0.681, 1.181)	£20,152	£12,606
Utility (coef.): sacubitril valsartan	0.011 (0.004, 0.017)	£18,212	£15,510
Hospitalisation (coef.): sacubitril valsartan	-0.173 (-0.098, -0.247)	£15,734	£17,856
All-cause mortality - Gompertz (coef.): BB use	-0.289 (-0.461, -0.116)	£17,398	£16,151
Hospitalisation (coef.): Constant	-2.844 (-1.917, -3.772)	£16,396	£17,677
Hospitalisation (coef.): Age^2*	0.000 (0.001, 0.000)	£16,404	£17,762

* Age exhibited a non-linear effect, and therefore a quadratic transformation was included.
Abbreviation: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BB, beta blocker; coef., coefficient; ICER, incremental cost-effectiveness ratio.

Figure 38: Tornado diagram –ARB comparison†



†Black shading is used to signify where the low value of the parameter has been used; white shading is used to signify where the high value of the parameter has been used
Abbreviations: ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; coef., coefficient; ICER, incremental cost-effectiveness ratio.

5.8.7 *For technologies whose final price or acquisition cost has not been confirmed, sensitivity analysis should be done over a plausible range of prices. This may also include the price of a comparator that includes a confidential patient access scheme.*

Not applicable (See Section 2.1)

5.8.8 *Scenario analysis*

Scenario analyses are performed in which key structural assumptions were varied and ICERs reported. Further scenario analyses were performed using data from analysis of CPRD in order to illustrate how model outcomes may vary compared to English clinical practice (296). These scenarios are detailed in Table 89.

Table 89: Scenario analyses included

Area of uncertainty	Scenario
Structural scenarios	
Time horizon	All time horizons from 1 to 30 years
Discount rates	Discount rate: 1.5% benefits; 6% costs†
Mortality	Model all-cause mortality using Weibull distribution
Mortality	Model all-cause mortality using exponential distribution
HRQoL time trend	Time trend halved
HRQoL time trend	Time trend doubled
HRQoL time trend	No decrease in HRQoL over time
HRQoL time trend	HRQoL constant at 5 years
HRQoL time trend	HRQoL constant at 10 years
Treatment effect on HRQoL	No absolute benefit in HRQoL for sacubitril valsartan
Treatment effect on hospitalisation	Sacubitril valsartan treatment effect applied only to HF hospitalisations
Treatment effect on hospitalisation	Sacubitril valsartan treatment effect applied only to CV hospitalisations
Effect of hospitalisation on HRQoL	Decrements for hospitalisation set to zero
Extrapolation of treatment effects	All treatment effects cease at year 5
Extrapolation of treatment effects	All treatment effects cease at year 10
Discontinuation	Include discontinuation
Discontinuation	No discontinuation after year 3
Discontinuation	Discontinuation included; no loss of efficacy
Hospitalisation costs	Double cost per hospitalisation
Hospitalisation costs	Halve cost per hospitalisation
Hospitalisation costs	Hospitalisation proportions derived using Western Europe population only
Adverse event rates	All adverse event rates set to zero
Cost of primary therapies	Cost of ACEi/ sacubitril valsartan based on PARADIGM-HF target doses
Cost of primary therapies	Cost of ramipril applied
Inclusion of titration costs	Titration cost assumed in sacubitril valsartan arm only (2 x cardiologist cost)
Increased risk of hospitalisation over time	10% annual increase in baseline risk of hospitalisation
CPRD scenarios	
Generalisability	Re-weighting of PARADIGM-HF patient characteristics
Generalisability	Calibration of model to CPRD outcomes

Abbreviations: ACEi, angiotensin converting enzyme inhibitor; CPRD, Clinical Practice Research Datalink; CV, cardiovascular; HF, heart failure; HRQoL, health-related quality of life.
†Historic NICE discounting scenario

5.8.8.1 CPRD analysis

Data from the CPRD database was accessed to assess the generalisability characteristics and outcomes from PARADIGM-HF to the English HF population (296). For further details on the methodology of the CPRD database analysis please see data on file (296) The analysis allowed the identification of subjects with HFrEF[g] to determine the generalisability of PARADIGM-HF to English clinical practice. Subjects in PARADIGM-HF were generally younger, more likely to be male, and more likely to be current smokers than those in CPRD (Table 90).

These differences have consequences for estimating, amongst other things, the baseline mortality rate. Because cost-effectiveness is determined by absolute differences in costs and effects, this may affect the cost-effectiveness of sacubitril valsartan in clinical practice. In order to provide estimates of cost-effectiveness more representative of clinical practice, several scenario analyses are included in which the cohort of subjects in PARADIGM-HF is weighted in such a way as to make them more generalisable. For the English CPRD analysis, this requires over-sampling of older and female subjects.

Raking (or sample-balancing) adjusts sampling weights across subjects such that the marginal totals of the adjusted weights on specified characteristics agree with the corresponding totals for the population. All propensity-score methods assume that balance of the observed variables leads to balance across unobserved variables i.e. there are no unobserved confounding factors that remain unbalanced.

Table 90 presents baseline characteristics prior to and following raking. Two alternative sets of weights are generated; one in which only age and gender are used for weighting, and another in which, in addition to age and gender, other clinical variables (current smoking status, prior stroke and eGFR <60 mL/min) available for a limited subset of patients in CPRD are also included. The resulting distribution of subjects after weighting closely resembles that of the CPRD HFrEF cohort. The reweighting of age and gender only generates a population that is slightly more severe with regards to smoking, prior stroke, and eGFR <60 mL/min which may imply that the population in PARADIGM-HF although imbalanced with regards to age and gender is not per se a less severe population. The weights obtained are used to reweight the estimated costs and effects across the PARADIGM-HF population.

[g] HFrEF defined by following read codes: G581.00 Left ventricular failure, G581000 Acute left ventricular failure, 585f.00 Echocardiogram shows left ventricular

Table 90: Comparison of PARADIGM-HF and CPRD characteristics and model characteristic after reweighting of subjects

Variable	PARADIGM-HF	CPRD	Re-weighted PARADIGM-HF from model	
			Age and gender only	All available variables
18-49 years	11	[redacted]	[redacted]	[redacted]
50-54 years	9	[redacted]	[redacted]	[redacted]
55-64 years	32	[redacted]	[redacted]	[redacted]
65-69 years	16	[redacted]	[redacted]	[redacted]
70-74 years	15	[redacted]	[redacted]	[redacted]
75-84 years	17	[redacted]	[redacted]	[redacted]
85+ years	1	[redacted]	[redacted]	[redacted]
Mean age (SD)	63.8 (11)	[redacted]	[redacted]	[redacted]
Gender (% female)	22	[redacted]	[redacted]	[redacted]
Prior stroke (%)	8.6	[redacted]	[redacted]	[redacted]
eGFR <60 mL/min (%)	36.4	[redacted]	[redacted]	[redacted]
Current smoker (%)	14.4	[redacted]	[redacted]	[redacted]

Abbreviations: CPRD, Clinical Practice Research Datalink; eGFR, estimated glomerular filtration rate; SD, standard deviation.
† New HF patients and LVSD within 6 months of HF diagnosis in CPRD, 2005-2013 (n=18,028)
‡ Characteristics of patients with HFrEF, based on CPRD-HES linked data set, 2005-2013, at index date (n=10,646)

The effect of re-weighting is to assume alternative baseline characteristics of the sampled cohort. Figure 40 presents how this process adjusts the rate of survival predicted by the model when compared against the data observed in PARADIGM-HF.

Figure 39: Observed vs predicted survival after re-weighting (all available variables analysis)

Abbreviation: ACEi, angiotensin converting enzyme inhibitor.

Observed vs predicted outcomes are compared quantitatively in Table 91. All-cause mortality is compared graphically in Figure 40. Mortality in CPRD was higher than observed in PARADIGM-HF, and therefore under the base-case assumptions of the model. After re-weighting on all available variables, mortality outcomes from the model matched CPRD outcomes more closely.

Table 91: Comparison of outcomes between CPRD, PARADIGM-HF and model outcomes (base-case and reweighted)

Outcome	CPRD‡	PARADIGM-HF observed (enalapril)	Model predicted outcomes		
			Base-case (enalapril arm)	Re-weighted PARADIGM-HF (enalapril)	
				Age and gender only	All available variables
All-cause mortality (cumulative per year)					
Year 1	[redacted]	8.5	8.2	[redacted]	[redacted]
Year 2	[redacted]	16.3	16.3	[redacted]	[redacted]
Year 3	[redacted]	23.8	24.5	[redacted]	[redacted]
Year 4	[redacted]	32.3	32.4	[redacted]	[redacted]
Annualised all-cause hospitalisation rate	[redacted]	0.50†	0.51	[redacted]	[redacted]

Abbreviations: CPRD, Clinical Practice Research Datalink.
† Negative binomial (NB) regression model, adjusted for treatment and region. Log(follow-up duration) is the offset variable.
‡ Outcomes based on follow-up of HFrEF patients alive on 1 Jan 2010 (n=4,190). 1 Jan 2010 was considered the first day 'at risk' in this analysis.

Figure 40: All-cause mortality in PARADIGM-HF (enalapril arm) and CPRD with model predictions, before and after re-weighting (enalapril arm)

Abbreviations: CRPD, Clinical Practice Research Datalink.

Estimates of cost-effectiveness of sacubitril valsartan compared to ACEi for the re-weighted cohort were consistent with the base-case ICER irrespective of which of the weighting schemes were used (see Section 5.7), though total costs and QALYs varied more noticeably (Table 92 and Table 93). This suggests that the cost-effectiveness is relatively linear with respect to the effect of changes in survival; i.e. because reduced survival reduces QALYs and costs in similar proportions, the effect on the ICER is broadly neutral.

Table 92: Reweighted base-case vs results using age and gender only

Therapy	Total costs	Total QALYs	Inc costs	Inc QALYs	ICER
ACEi	£13,079	3.89	--	--	--
Sacubitril valsartan	£19,853	4.26	£6,775	0.37	£18,142

Abbreviations: ACEi, angiotensin-converting-enzyme inhibitor; CPRD, Clinical Practice Research Datalink; QALYs, quality-adjusted life-years; ICER, incremental cost-effectiveness ratio; Inc, incremental.

Table 93: Reweighted results using all variables available in CPRD

Therapy	Total costs	Total QALYs	Inc costs	Inc QALYs	ICER
ACEi	£12,721	4.09	--	--	--
Sacubitril valsartan	£19,818	4.47	£7,097	0.39	£18,432

Abbreviations: ACEi, angiotensin-converting-enzyme inhibitor; CPRD, Clinical Practice Research Datalink; QALYs, quality-adjusted life-years; ICER, incremental cost-effectiveness ratio; Inc, incremental.

Although re-weighting led to estimates of mortality which more closely matched those from CPRD, the rate of all-cause hospitalisation is markedly different between CPRD and PARADIGM-HF, and re-weighting was unable to completely address this discrepancy. [redacted]. This was achieved by varying the constant terms of the regression models used to predict hospitalisation and all-cause mortality (see Section 5.3.1) using the MS Excel inbuilt 'goal-seek' functionality; this analysis therefore required the use of the 'mean' patient approach[h] (as opposed to a patient-level cohort approach). The results of the calibrated analysis (Table 94) show improved cost-effectiveness of sacubitril valsartan (compared to the base case analysis using the mean patient characteristics approach in Table 95), driven principally by greater cost-savings achieved through reduced hospitalisations.

[h]Running model results using the patient-level cohort approach uses a macro which loops through each patient in turn and records the relevant outcomes; model results using the 'mean' patient are calculated within the spreadsheet. Since the 'goal-seek' functionality works within the spreadsheet, it was necessary to perform this analysis using the 'mean' patient. After setting the model to use the 'mean patient characteristics' on the 'Population' sheet, the analysis requires the user to 'goal-seek' 1-Engine_ACEi!Y65 (all-cause mortality at year 4) and Hospitalisation!Q57 (yearly hospitalisation rate) to the corresponding values using the constant terms of the regression models for all-cause mortality and all-cause hospitalisation, respectively.

Table 94: Results following calibration of model using outcomes from CPRD analysis (mean patient characteristics approach)

Therapy	Total costs*	Total QALYs	Inc costs	Inc QALYs	ICER
ACEi	£28,962	3.338	--	--	--
Sacubitril valsartan	£33,676	3.712	£4,714	0.374	£12,595

Abbreviations: ACEi, angiotensin-converting-enzyme inhibitor; QALYs, quality-adjusted life-years; ICER, incremental cost-effectiveness ratio; Inc, incremental.

[redacted]

Table 95: Base case results using mean patient characteristics approach

Therapy	Total costs	Total QALYs	Inc costs	Inc QALYs	ICER
ACEi	£12,735	4.32	--	--	--
Sacubitril valsartan	£20,079	4.74	£7,343	0.42	£17,624

Abbreviations: ACEi, angiotensin-converting-enzyme inhibitor; QALYs, quality-adjusted life-years; ICER, incremental cost-effectiveness ratio; Inc, incremental.

All of the above analyses assume that the treatment effect of sacubitril valsartan is the same in clinical practice as observed in PARADIGM-HF; this is supported by the observation that no significant interactions between subgroups membership and treatment effect on the primary composite endpoint of CV mortality were observed in the primary statistical analysis of PARADIGM-HF (10). Furthermore, the re-weighting analyses assume that balance on the presented variables achieves balance on the unobserved variables. Table 90 demonstrates that this is unlikely to be the case, however sensitivity analysis suggests that age is the most influential baseline characteristic on the estimated cost-effectiveness (see Section 5.8.6). Therefore by including age in the reweighting it is believed that the most important difference (in terms of cost-effectiveness) between the patients of PARADIGM-HF and English clinical practice is being controlled for.

These analyses suggest that although baseline characteristics of PARADIGM-HF vary from those seen in English clinical practice, this is unlikely to adversely affect the cost-effectiveness of sacubitril valsartan. Indeed, if the baseline rate of hospitalisations assumed in the base-case analysis is markedly lower than that observed in clinical practice, the predicted ICER may overestimate the 'true' ICER representative of English clinical practice.

5.8.8.2 Other scenario analyses

Time horizon

The SR of economic evaluations in HF (see Section 5.1) found that a range of time horizons were adopted. The ICER is therefore calculated for time horizons of between 1 and 30 years, and presented graphically.

Discount rates

NICE currently require that both costs and outcomes are discounted at a rate of 3.5%, but historic discount rates were set at 6% for costs and 1.5% for outcomes in a scenario analysis (204, 297).

Mortality

The choice of distribution (Gompertz) for long-term extrapolation is subject to a high degree of uncertainty, considering the absence of long-term mortality data in HF patients; models of all-cause mortality assuming the Weibull and exponential distributions are included in scenario analyses.

HRQoL time trend

In the absence of long-term EQ-5D data in patients with HFrEF, the base case analysis assumes that EQ-5D declines linearly over the modelled time horizon. To establish the effect of this assumption on model outcomes, several approaches to modelling the HRQoL time trend are employed in scenario analyses:

- Annual rate of decline in EQ-5D halved
- Annual rate of decline in EQ-5D doubled
- No time trend (i.e. EQ-5D is constant)
- EQ-5D constant (no decline) after 5 years
- EQ-5D constant (no decline) after 10 years

Treatment effect on HRQoL

The mixed effects model of EQ-5D (presented in Section 5.4.13 displays a small but statistically significant positive effect associated with sacubitril valsartan (0.011; p=0.001), beyond the benefit due to differences in hospitalisation and adverse events. This effect is thought to be due to improvements in symptoms in sacubitril valsartan patients. To test the effect of including this small absolute benefit, a scenario is included in which it is set to be zero.

Treatment effect on hospitalisation

Although sacubitril valsartan is a HF medication, it is associated with a reduced incidence of non-HF hospitalisation (rate ratio: 0.88; p=0.002). As such, all-cause hospitalisation is modelled, and the relevant treatment effect applied to both HF and non-HF hospitalisations. To test the effect of including a treatment effect for all-cause hospitalisation, scenario analyses are included in which the relevant treatment effect is applied only to HF hospitalisations, or only to CV hospitalisations.

Practically, the treatment effect coefficient for the HF (or CV) hospitalisation is weighted by the proportion of hospitalisations with HF (or CV) cause, and used as the all-cause hospitalisation treatment effect coefficient. Derivations of the all-cause hospitalisation treatment effect coefficient, assuming no treatment effect on non-HF hospitalisations, and no treatment effect on non-CV hospitalisations, are presented in Table 96 and Table 97, respectively.

Table 96: Derivation of all-cause hospitalisation treatment effect coefficient, assuming no treatment effect on non-HF hospitalisations

	% of hospitalisations	Treatment effect coefficient	Incidence rate ratio for treatment
HF hospitalisation	25.3	-0.257	0.773
Non-HF hospitalisation	74.7	0†	1
All-cause hospitalisation	-	*-0.065*§	*0.937*§

Abbreviations: HF, heart failure
†Assumption
§ Treatment effect and IRR for all-cause hospitalisation are calculated as weighted averages of the respective treatment effects and IRRs for HF and non-HF hospitalisation as assumed in this scenario

Table 97: Derivation of all-cause hospitalisation treatment effect coefficient, assuming no treatment effect on non-CV hospitalisations

	% of hospitalisations	Treatment effect coefficient	Incidence rate ratio for treatment
CV hospitalisation	62.4	-0.179	0.836
Non-CV hospitalisation	37.6	0†	1
All-cause hospitalisation	-	*-0.112*§	*0.894*§

Abbreviations: CV, cardiovascular
†Assumption
§ Treatment effect and IRR for all-cause hospitalisation are calculated as weighted averages of the respective treatment effects and IRRs for HF and non-HF hospitalisation as assumed in this scenario

Effect of hospitalisation on HRQoL

The mixed model of EQ-5D includes utility decrements for hospitalisation in the previous 30 days, or in the previous 30-90 days (See Section 5.4.7). Since hospitalisation decrements are not typically included beyond hospital discharge, a scenario analysis is included in which these utility decrements are set to zero.

Extrapolation of treatment effects

Median follow-up time in PARADIGM-HF is 27 months (10); in the absence of long-term data, it has been assumed that the treatment effect of sacubitril valsartan on mortality, hospitalisation and EQ-5D continues over a lifetime time horizon. Scenarios are therefore included in which all sacubitril valsartan treatment effects cease after 5 and 10 years, which represent a conservative assumption.

Discontinuation

Other than discontinuations due to death, treatment was discontinued in 17.8% of patients receiving sacubitril valsartan, and 19.8% of patients receiving enalapril (10). Data analysis was performed following the ITT principle (see Section 4.4.1 for details of patient populations used in the statistical analysis). Therefore, efficacy estimates are assumed to reflect mean efficacy for the population under consideration, including those who discontinue the study drug. However, treatment discontinuation continues

throughout the trial, and is not restricted to an initial period. It is expected that further patients will discontinue beyond the trial follow-up period.

Assumptions employed in the base case are conservative. The efficacy in discontinued patients is incorporated under an ITT approach to estimating the treatment effect of sacubitril valsartan, but the increased costs of sacubitril valsartan are still applied to these patients.

In line with NICE guidelines, clinical opinion (see Section 5.3.4) has confirmed that ACEi patients would be expected to transition to an ARB following discontinuation. Although sacubitril valsartan is a new therapy, it is assumed that discontinued patients would switch to an ACEi instead of an ARB give that is the current first-line treatment. In the presence of long-term uncertainty, the economic model allows for discontinuation to be modelled in different ways as scenario analyses. The model considers:

- Discontinuation to be explicitly considered (yes/no)
    - If not considered, efficacy is assumed to continue for all patients based on that observed in PARADIGM-HF. Costs are similarly not adjusted to reflect discontinuation
- Treatment following sacubitril valsartan (ACEi/ARB/no treatment)
    - Costs of primary therapy are determined according to treatment assigned (if any) following discontinuation of the study drug
- Treatment following ACEi (ARB/no treatment)
    - Costs of primary therapy are determined according to treatment assigned (if any) following discontinuation of the study drug
- Time horizon in which discontinuation may occur (user-inputted number of years)
    - Beyond this point, no further discontinuation is permitted
- Sacubitril valsartan patients switch to ACEi efficacy following treatment discontinuation (yes/no)
    - i.e. Patients receiving sacubitril valsartan who discontinue revert to the efficacy of ACEi (mortality, hospitalisation, EQ-5D).

It is noted that a change in efficacy following discontinuation in the ACEi arm is not modelled because it is expected that discontinued patients would transition to an ARB; ARBs have been shown to have comparable efficacy to ACEi (184), which has also been demonstrated in the NMA presented in this submission (Section 4.10).

The scenario analysis therefore assumes an exponential survival model of treatment discontinuation, implying a constant rate of discontinuation. This model was selected for simplicity. The model of discontinuation is presented in Table 98.

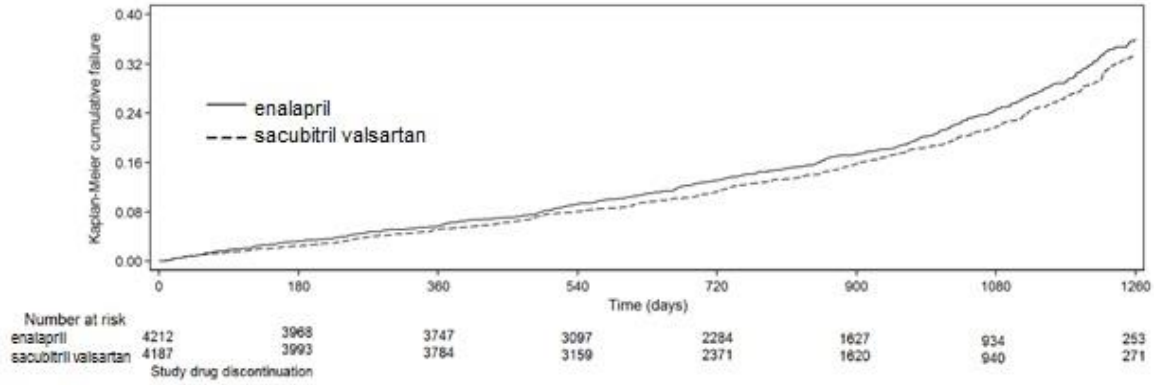
Upon discontinuation, costs and efficacy for sacubitril valsartan patients are assumed to revert to that of ACEi, while costs for discontinued ACEi patients are assumed to be based on those of ARBs (with efficacy assumed to be the same between ACEi and ARBs in this scenario). Please note that this loss of efficacy is assumed for all treatment effects; mortality, hospitalisation, HRQoL and adverse events.

Kaplan-Meier discontinuation (not due to death) for the FAS is presented in Figure 41.

The hazard of discontinuation is observed to increase towards the end of the trial. This increase appears to begin at approximately Month 33 and occurs in both arms of the model. This increasing rate is therefore believed to represent an artefact of the study design and/or reporting.

In order to avoid extrapolation of the trend observed post Month 33, which would be associated with implausibly high rates of discontinuation, an exponential survival distribution was assumed, generating a constant risk of discontinuation over time. Table 98 presents the resulting exponential model of discontinuation. Sacubitril valsartan was associated with a significantly lower rate of discontinuation (not due to death) (HR: 0.89; p=0.027), compared with ACEi.

Figure 41: Kaplan-Meier discontinuation (not due to death) in PARADIGM-HF (FAS)†



† Kaplan-Meier estimator treating death as censoring event
Abbreviations: FAS, full analysis set.

Table 98: Exponential model of treatment discontinuation†

Variable	Coefficient	SE	z	P>z	95% CI	
Sacubitril valsartan	-0.112	0.050	-2.210	0.027	-0.210	-0.013
Region						
Latin America	-0.286	0.098	-2.900	0.004	-0.478	-0.093
Western Europe	-0.108	0.088	-1.220	0.221	-0.280	0.065
Central Europe	-0.409	0.091	-4.490	0.000	-0.588	-0.230
Other	-0.874	0.115	-7.620	0.000	-1.099	-0.649
Heart rate‡	0.007	0.002	3.070	0.002	0.002	0.011
(log) eGFR‡	-0.531	0.090	-5.940	0.000	-0.707	-0.356
(log) NT-proBNP‡	0.204	0.027	7.590	0.000	0.152	0.257
Sodium‡	-0.016	0.009	-1.860	0.063	-0.034	0.001
Diabetes	0.155	0.053	2.900	0.004	0.050	0.259
Beta blocker use	-0.175	0.096	-1.830	0.067	-0.362	0.013
Lipid lowering medication use	-0.191	0.056	-3.430	0.001	-0.301	-0.082
Time since HF diagnosis						
1-5 years	0.102	0.067	1.520	0.130	-0.030	0.234
>5 years	0.288	0.069	4.200	0.000	0.154	0.422
Ischaemic disease	0.131	0.057	2.280	0.022	0.019	0.243
EQ-5D‡	-0.473	0.109	-4.320	0.000	-0.687	-0.258
Constant	-7.994	0.138	-57.840	0.000	-8.265	-7.723

Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate; HF, heart failure; NT-proBNP, N-terminal pre-brain natriuretic peptide; SE, standard error
† The analysis time is 1 day; ‡Variable is centred on the mean

Hospitalisation costs

In order to inform a cost per hospitalisation that is more reflective of English clinical practice, a scenario is included in which proportions of different hospitalisations are derived using only patients from the Western Europe subpopulation of PARADIGM-HF. The cost per hospitalisation in this scenario is £3,139. Scenarios are also included in which the cost per hospitalisation is doubled, and halved.

Adverse event rates

Given that the included adverse events have low incidence, low costs and limited impact on HRQoL, their inclusion is expected to have minimal impact on the ICER. This is tested using a scenario in which all adverse event rates are set to zero.

Costs of primary therapy

Daily costs of sacubitril valsartan and ACEi are based on mean observed daily doses from PARADIGM-HF (see Section 5.5.4). It is noted, however that observed doses were lower than pre-specified target doses for both primary therapies (10). A scenario analysis is included in which the daily costs of sacubitril valsartan and ACEi are based on target doses of 200 mg bid and 10 mg bid, respectively.

Ramipril

A scenario is also included where ACEi is costed based on the cost of the most widely used ACEi in England, ramipril.

Inclusion of titration costs

Although the costs of titration would only be expected to be incremental for sacubitril valsartan patients vs. ACEi patients in those switching from a stable ACEi regimen, a conservative scenario is included in which the cost of titration (2 cardiologist visits) is applied to all patients in the sacubitril valsartan arm.

Increased risk of hospitalisation over time

For simplicity, it is assumed that the rate of hospitalisation is constant over time. However, it may be expected that this rate increases with increased severity of disease; as such, a hypothetical scenario is included in which the baseline annual hospitalisation rate is assumed to increase by 10% of the original baseline rate each year.

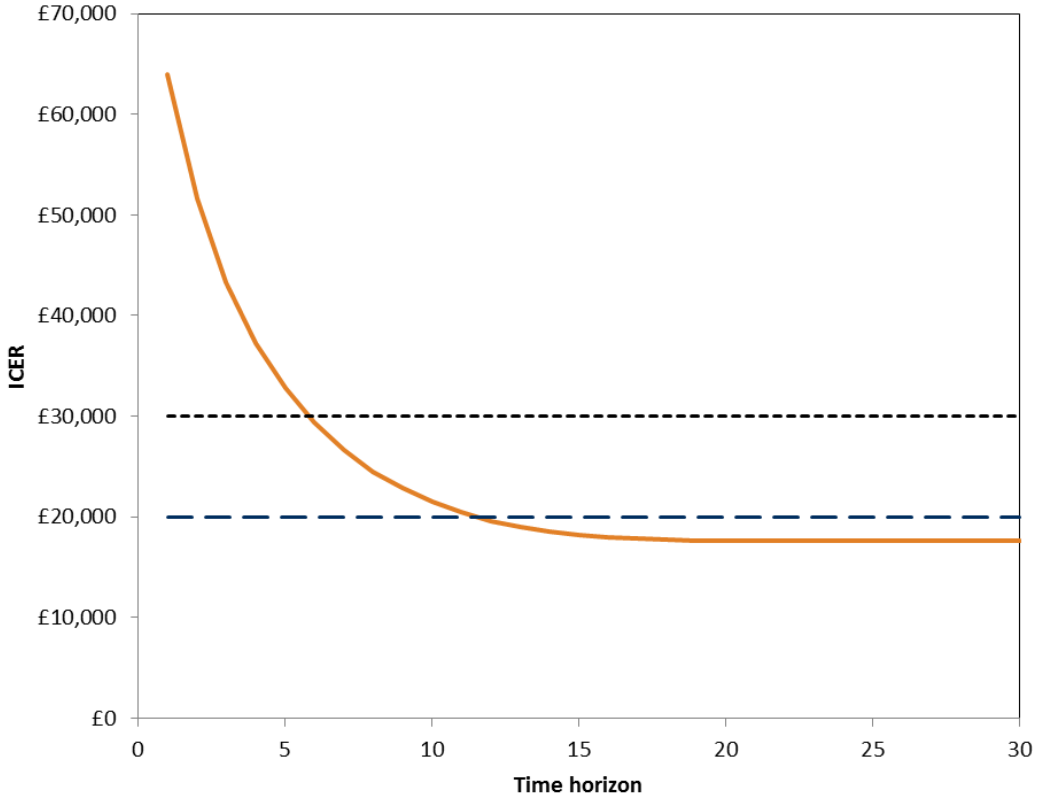
5.8.9 *Present the results of scenario analysis. Include details of structural sensitivity analysis.*

Scenario analysis was performed to test the robustness of the structural assumptions. Results are particularly sensitive to the time horizon; considering that much of the benefit of sacubitril valsartan is attributable to extended survival, this is to be expected. A graphical representation of how the ICER varies with the time horizon is shown in Figure 42.

Results are also sensitive to discounting, and assumptions around the continuation of treatment effect. The only scenarios associated with ICERs over £30,000 per QALY gained were sacubitril valsartan treatment effect assumed to persist for durations of <5 years and modelled time horizon reduced to <5 years. The conservative assumption that the treatment effect of sacubitril valsartan cease at Year 5 is associated with an increase of 76% in the ICER. Long-term data from SOLVD showed that the treatment effect of enalapril persisted over 15 years of follow-up (182). It is therefore considered reasonable to assume that the treatment effect of HF treatments persist beyond trial duration (See Section 5.6.2). It is noted that the treatment effect of ivabradine was assumed to persist over a lifetime time horizon in the model submitted as part of TA267 (34, 216). The modelled time horizon reduced to less than 5 years is not an adequate time horizon to model the costs and benefits associated with a lifelong treatment for a chronic condition.

Assuming no direct benefit of sacubitril valsartan on HRQoL led to an increase of 20% in the ICER leading to an ICER slightly above £20,000. Although the HRQoL benefit of sacubitril valsartan over enalapril is small (Coefficient 0.011; See Section 5.4.13, Table 61), this is consistently significant and increases over time as observed based on the EQ-5D data from the PARADIGM-HF trial (See Section 5.8.9, Figure 28). Hence this is assumed a conservative scenario. Other assumptions surrounding the rate of change in EQ-5D over time were less influential. Assuming an extreme scenario in which EQ-5D declines at twice the rate of the base case provided an increase in the ICER of 9%. The inclusion of discontinuation suggested the model was relatively linear to this, with a 1% change in the ICER. Only in the extremely optimistic scenario in which discontinuation was associated with a reduction in costs but not efficacy of sacubitril valsartan was the ICER reduced by 29%. The results of all scenario analyses are presented in Table 99.

Figure 42: ICER over a varying time horizon



Abbreviations: ICER, incremental cost-effectiveness ratio.

Table 99: Results of scenario analyses

Scenario name	Costs		QALYs		ICER	% change from base case
	Sacubitril valsartan	ACEi	Sacubitril valsartan	ACEi		
Base case analysis	**£20,734**	**£13,286**	**4.87**	**4.46**	**£18,187**	–
Discount rates altered to reflect historic NICE discount rates of 6% for costs and 1.5% for outcomes	£18,537	£11,986	5.38	4.90	£13,604	-25%
Weibull distribution used in all-cause mortality model	£26,961	£16,982	6.20	5.63	£17,368	-5%
Exponential distribution used in model of all-cause mortality	£29,596	£18,684	6.74	6.13	£17,923	-1%
Annual rate of decline in EQ-5D halved	£20,734	£13,286	5.44	4.93	£17,466	-4%
Annual rate of decline in EQ-5D doubled	£20,734	£13,286	5.00	4.58	£19,826	9%
No decline in EQ-5D over time	£20,734	£13,286	4.61	4.23	£16,799	-8%
No decline in EQ-5D after 5 years	£20,734	£13,286	5.13	4.69	£17,473	-4%
No decline in EQ-5D after 10 years	£20,734	£13,286	4.96	4.53	£17,934	-1%
Effect of sacubitril valsartan on EQ-5D (beyond differences in hospitalisation / adverse event rates) assumed to be zero	£20,734	£13,286	4.89	4.48	£21,877	20%
Effect of sacubitril valsartan on hospitalisation rates assumed to apply to HF hospitalisation only	£21,495	£13,286	4.80	4.46	£20,203	11%
Effect of sacubitril valsartan on hospitalisation rates assumed to apply to CV hospitalisation only	£21,154	£13,286	4.87	4.46	£19,294	6%
Effect of hospitalisation on EQ-5D assumed to be zero	£20,734	£13,286	4.87	4.46	£18,284	1%
Sacubitril valsartan treatment effects assumed to cease at year 5	£20,459	£13,286	4.90	4.49	£32,020	76%
Sacubitril valsartan treatment effects assumed to cease at year 10	£20,614	£13,286	4.69	4.46	£21,159	16%
Treatment discontinuation considered over lifetime time horizon	£18,563	£13,304	4.81	4.46	£18,348	1%
Treatment discontinuation considered up to year 3	£19,478	£13,297	4.75	4.46	£18,156	0%
Treatment discontinuation assumed to result in reduced therapy costs; efficacy estimates as in trial	£18,598	£13,304	4.80	4.46	£12,926	-29%
Hospitalisation costs doubled	£27,602	£20,775	4.87	4.46	£16,669	-8%
Hospitalisation costs halved	£17,301	£9,542	4.87	4.46	£18,946	4%
Proportions of hospitalisation types derived using Western Europe population	£21,442	£14,058	4.87	4.46	£18,031	-1%
All adverse event rates set to zero	£20,638	£13,195	4.87	4.46	£18,157	0%
Primary therapies costed assuming target doses from PARADIGM-HF	£20,734	£13,295	4.87	4.46	£18,166	0%
Cost of ramipril applied to ACEi arm	£20,734	£13,330	4.87	4.46	£18,081	-1%
Cost of titration included	£20,996	£13,286	4.87	4.46	£18,827	4%
Increased risk of hospitalisation over time	£24,011	£16,656	4.86	4.45	£17,960	-1%

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; CV, cardiovascular; HF, heart failure; HRQoL, health-related quality of life; ICER, incremental cost-effectiveness ratio; NICE, National Institute of Health and Care Excellence; QALY, quality-adjusted life-year;

Summary of sensitivity analyses results

5.8.10 *Describe the main findings of the sensitivity analyses, highlighting the key drivers of the cost-effectiveness results.*

The PSA for the ACEi comparison found that the probabilities of sacubitril valsartan being cost-effective at the lifetime time horizon and at thresholds of £20,000 and £30,000 per QALY gained, are 62% and 94%, respectively. The probabilities of sacubitril valsartan being cost-effective at the lifetime time horizon compared to ARBs at thresholds of £20,000 and £30,000 are 56% and 76%, respectively.

Deterministic sensitivity analysis identified the treatment effect due to sacubitril valsartan on all-cause mortality, baseline risk of all-cause mortality and age (due to its impact on expected survival) as key drivers of cost-effectiveness, with higher all-cause mortality risk/shorter life expectancy being associated with lower ICERs. The treatment effects for sacubitril valsartan for utility and hospitalisation were associated with modest changes in the ICER.

The only scenarios associated with ICERs over £30,000 per QALY gained were 1) sacubitril valsartan treatment effect assumed to persist for durations of <5 years, which represents a conservative assumption, and 2) the modelled time horizon was reduced to <5 years, which is not an adequate time horizon to model the costs and benefits associated with a lifelong treatment for a chronic condition. Assuming no direct benefit of sacubitril valsartan on HRQoL led to an increase of 20% in the ICER leading to an ICER slightly above £20,000.

5.9 *Subgroup analysis*

5.9.1 *Please specify whether analysis of subgroups was carried out and how these subgroups were identified, referring to the scope and decision problem specified for the NICE technology appraisal.*

The model was run for 39 subgroups identified a priori in the statistical analysis plan for PARADIGM-HF, or identified post-hoc by clinical experts. As each member of the FAS passes through the model, expected costs and outcomes are estimated for each subject, and averaged across all subjects (see Section 5.2.2). Subgroup analysis is performed by averaging expected outcomes across members of each subgroup only. The use of multivariable regression models allows baseline (or underlying) risks to vary between subjects, allowing estimates of cost-effectiveness by subgroup without the stratification of data. See also Section 5.9.2 for assumptions regarding treatment effects.

5.9.2 *Clearly define the characteristics of patients in the subgroup.*

The patient populations which are considered to potentially be of clinical or economic relevance, and which are therefore included as subgroups in the economic model, are described in Section 4.8.1. Many of these populations were identified *a priori* in the SAP for PARADIGM-HF (278), whilst others, based on clinical recommendations or NICE scientific advice (as issued to Novartis on sacubitril valsartan) (273), represent groups defined post-hoc.

A multivariate approach to subgroup analysis has been adopted; individual patients in the relevant subgroup are passed deterministically through the model, and the resulting expected costs and outcomes averaged across each subgroup.

5.9.3 *Describe how the statistical analysis was carried out.*

A multivariate approach to subgroup analysis has been adopted; individual patients in the relevant subgroup are passed deterministically through the model, and the resulting expected costs and outcomes averaged across each subgroup

5.9.4 *If subgroup analyses were done, please present the results in tables similar to those in section 5.7.*

Results of the incremental analyses are presented in Table 100. Incremental cost-effectiveness typically exhibited low variation, reflecting the assumption of a common treatment effect across subgroups. The greatest variation was observed between baseline NT-proBNP ≤/> median. In the ≤ median NT-proBNP subgroup, the ICER increased by 7%, and in the > median NT-proBNP, the ICER was reduced by 9%. This finding is consistent with the results based on risk quintile, which suggest that the cost-effectiveness of sacubitril valsartan increases as the risk of events increases. This observation is not universal across these univariate subgroups; for example sacubitril valsartan was observed to be slightly less cost-effective in more severe NYHA classes (III/IV) than less severe (I/II), though this difference was modest (5% vs. -1%). The ICER in patients' ≥75 years was decreased by 5% vs. the base case.

Overall, the subgroup analyses do not show notable differences between any of the subgroups and the overall population. ICERs for all subgroups remained under the £20,000 per QALY gained cost-effectiveness threshold.

Table 100: Subgroup analyses

#	Subgroup	Δ Costs	Δ QALYs	ICER	% change from base case
1	Full analysis set	£7,448	0.410	£18,187	0%
2	Baseline age < 65 years	£7,865	0.427	£18,434	1%
3	Baseline age ≥ 65 years	£7,015	0.392	£17,909	-2%
4	Baseline age < 75 years	£7,722	0.420	£18,384	1%
5	Baseline age ≥ 75 years	£6,251	0.364	£17,195	-5%
6	Region - North America	£7,386	0.402	£18,374	1%
7	Region - Latin America	£6,957	0.413	£16,839	-7%
8	Region - Western Europe	£7,862	0.427	£18,415	1%
9	Region - Central Europe	£7,446	0.382	£19,502	7%
10	Region - Asia-Pacific	£7,382	0.438	£16,860	-7%
11	Baseline NYHA class I/ II	£7,775	0.433	£17,941	-1%
12	Baseline NYHA III/ IV	£6,455	0.337	£19,152	5%
13	Baseline LVEF ≤ median	£7,076	0.405	£17,471	-4%
14	Baseline LVEF > median	£7,881	0.415	£19,000	4%
15	Baseline SBP ≤ median	£7,361	0.414	£17,801	-2%
16	Baseline SBP > median	£7,553	0.405	£18,665	3%
17	Baseline eGFR < 60	£6,684	0.384	£17,420	-4%
18	Baseline eGFR ≥ 60	£7,887	0.424	£18,585	2%
19	Baseline NT-proBNP ≤ median	£8,677	0.446	£19,458	7%
20	Baseline NT-proBNP > median	£6,124	0.370	£16,539	-9%
21	Diabetes at baseline	£6,771	0.385	£17,593	-3%
22	No diabetes at baseline	£7,807	0.423	£18,474	2%
23	Hypertension at baseline	£7,366	0.401	£18,371	1%
24	No hypertension at baseline	£7,647	0.430	£17,775	-2%
25	Prior use of ACEi	£7,489	0.410	£18,280	1%
26	Prior use of ARB	£7,304	0.409	£17,862	-2%
27	Use of BB at baseline	£7,537	0.412	£18,301	1%
28	No use of BB at baseline	£6,268	0.379	£16,549	-9%
29	Use of AA at baseline	£7,350	0.406	£18,100	0%
30	No use of AA at baseline	£7,572	0.414	£18,295	1%
31	≤ 1 year since diagnosis of HF	£8,418	0.447	£18,848	4%
32	1-5 years since diagnosis of HF	£7,188	0.399	£18,015	-1%
33	> 5 years since diagnosis of HF	£6,841	0.387	£17,677	-3%
34	Ischaemic aetiology	£7,217	0.398	£18,139	0%
35	Non-ischaemic aetiology	£7,795	0.427	£18,255	0%
36	Prior AF at baseline	£7,077	0.389	£18,170	0%
37	No prior AF at baseline	£7,665	0.421	£18,197	0%
38	Prior HF hospitalisation	£7,155	0.401	£17,855	-2%
39	No prior HF hospitalisation	£7,943	0.424	£18,717	3%

Abbreviations: AA, aldosterone antagonists; ACEi, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin receptor blocker; BB, beta blocker; eGFR, estimated glomerular filtration rate; HF, heart failure; ICER, incremental cost-effectiveness ratio; LVEF, left ventricular ejection fraction; NT-proBNP, N terminal pro-brain natriuretic peptide; NYHA, New York Heart Association; QALYs, quality-adjusted life years; SBP, systolic blood pressure.

5.9.5 *Identify any obvious subgroups that were not considered and explain why.*

Please refer to the subgroups identified in the decision problem in section 3. All pre-specified subgroups were considered.

5.10 *Validation*

Validation of de novo cost-effectiveness analysis

Internal verification of calculations was performed by the primary modeller in the first instance and checked by a second modeller involved with model development (internal peer review); the economic model was examined by two modellers external to the technical model development process (external peer review) (187). Verification techniques included:

- Face validity: testing that the model meets expectations based on simple calculations
- Model behaviour: testing whether varying model inputs has the expected directional effect
- Internal consistency: model outputs will be compared against PARADIGM-HF
- Cell-by-cell checks of calculations: manual inspection of formulae
- Use of logical scenario checks and the rebuilding of important parts of the model
- A complete cross-check of inputs, sources, and supporting documentation

The model produces outcomes at multiple time points to allow comparison against published sources.

External validity

Outcomes from the economic model were compared against the most comparable model identified by the systematic literature review, the model of ivabradine used in TA267 (34). It is noted that patient populations in the pivotal trial SHIfT (the primary source of evidence in TA267) and PARADIGM-HF are not directly comparable. SHIfT trial results were restricted to patients with heart rate >75 bpm, and considered patients requiring therapy in addition to first-line treatment and standard care (to include ACEi/ARB, beta blockers and AA). The ACEi arm of the present model is compared against the standard care arm of the model developed for TA267. Compared with the ivabradine model, the current model predicts total costs that are 41% higher. The additional cost predicted by the present model is attributable to differences in the estimation of follow-up costs, but may also be explained by differences in predicted survival; estimated QALYs are 12% higher and life-years are 7% higher in the present model, which may reflect the more severe patient population considered in the SHIfT study. For example, in PARADIGM-HF, 25% of subjects had NYHA III/IV (173), whereas the corresponding proportion in SHIfT was 52% (34). It is further observed that the ivabradine model predicts slightly poorer survival at Year 5, and that this difference grows to 5% (in absolute terms) at Year 10. Given the differences in data, model design and approaches to the estimation of costs, the extent to which the models aligned was considered reasonable.

Table 101: Comparison of comparator arms in ivabradine and present economic models

Technologies	Standard care ivabradine model‡	ACEi arm in sacubitril valsartan model	Absolute difference	Relative difference
Technology cost†	£642	£691	£49	8%
Follow-up costs	£1,803	£5,106	£3,303	183%
Hospitalisation	£7,001	£7,489	£488	7%
Total costs	**£9,446**	**£13,286**	**£3,840**	**41%**
QALYs	3.99	4.46	0.47	12%
Life-years	5.61	6.03	0.42	7%
Survival Year 5	59%	60%	1%	1%
Survival Year 10	22%	27%	5%	23%

† Therapy titration and drug costs; ‡ As reported in manufacturer submission to NICE (34)
Abbreviations: ACEi, angiotensin converting enzyme inhibitor; QALY, quality-adjusted life year.

It is further possible to compare model outcomes to those observed in CPRD (16). This comparison is presented in Section 5.8.8.1.

5.11 *Interpretation and conclusions of economic evidence*

5.11.1 *Are the results from this economic evaluation consistent with the published economic literature? If not, why do the results from this evaluation differ, and why should the results in the submission be given more credence than those in the published literature?*

No previous cost-effectiveness analyses for sacubitril valsartan exist.

The primary base case cost-effectiveness analysis shows that sacubitril valsartan in combination with standard care (beta blockers and aldosterone antagonists) for the treatment of HFrEF, is cost-effective at a willingness-to-pay threshold of £20,000 (ICER = £18,187 per QALY gained), compared with ACEis in combination with standard care based on head-to-head trial data; this is achieved despite ACEis being low cost generic compounds. Cost-effectiveness is also maintained in the alternative analysis in which CV mortality is modelled from PARADIGM-HF, with an ICER of £16,894 per QALY, slightly lower than in the base case.

The secondary cost-effectiveness analysis for the comparison of sacubitril valsartan versus ARBs results in an ICER of £16,753 per QALY gained based on the results of the NMA. As the ARB comparison is based on an NMA it is associated with greater uncertainty due to heterogeneity of studies compared with the well powered head-to-head trial data available for the ACEi comparison. No previous cost-effectiveness analyses for sacubitril valsartan exist.

The cost-effectiveness findings were robust to changes in most structural assumptions. The only scenarios associated with ICERs over £30,000 per QALY gained were 1) sacubitril valsartan treatment effect assumed to persist for durations of <5 years, which represents a conservative assumption, and 2) modelled time horizon reduced to <5 years, which is not an adequate time horizon to model the costs and benefits associated with a lifelong treatment for a chronic condition. Assuming no direct benefit of sacubitril valsartan on HRQoL led to an increase of 20% in the ICER leading to an ICER slightly above £20,000 per QALY gained. Although the HRQoL benefit of sacubitril valsartan

over enalapril is small (Coefficient 0.011; see Section 5.4.13, Table 61), this observation was highly significant and robust to alternative model specifications (see Section 5.8.9, Figure 28).

Deterministic cost-effectiveness of sacubitril valsartan is driven principally by reductions in mortality, but also by reduction in HRQoL decline over time and reduction in hospitalisations. These results are consistent with the clinical benefit of sacubitril valsartan compared with ACEis within the PARADIGM-HF trial (See Section 4.4.1) and ARBs based on the NMA (See Section 4.10).

Probabilistic sensitivity analysis suggests that the probability that sacubitril valsartan is cost-effective vs ACEi at a £20,000 per QALY threshold is 61%, increasing to 93% at £30,000 per QALY. The probability that sacubitril valsartan is cost-effective versus ARB at a £20,000 per QALY threshold is 56% and 76% at £30,000 per QALY gained. The higher level of uncertainty with the results of the ARB analysis is likely due to larger credible intervals for the relative treatment effect of ARBS based on the NMA compared to the treatment effect from the head-to-head ACEi analysis.

In summary, sacubitril valsartan is a cost-effective option for the treatment of patients with HFrEF compared to ACEis (both in combination with standard care), therefore, these results support sacubitril valsartan replacing ACEi as first-line therapy in England.

5.11.2 *Is the economic evaluation relevant to all groups of patients who could potentially use the technology as identified in the decision problem?*

The economic evaluation considers the cost-effectiveness of sacubitril valsartan in combination with standard care (beta blockers and aldosterone antagonists) in patients with HFrEF based on the patient-level data from the PARADIGM-HF trial. Therefore, the economic evaluation is relevant for all patients who could potentially receive and benefit from sacubitril valsartan based on the current evidence base. This population is aligned with the decision problem and NICE scope (see Section 1.2).

We also observe similar cost-effectiveness across clinically-relevant patient subgroups. This finding is in part a consequence of the assumption of a common sacubitril valsartan treatment effect across all subjects (see Section 5.3.1). This is supported by an analysis conducted by McMurray et al, which found no evidence of treatment effect modifiers for CV mortality in PARADIGM-HF (10).

5.11.3 *How relevant (generalisable) is the analysis to clinical practice in England?*

The PARADIGM-HF trial is the key data source for the cost-effectiveness analysis. Section 4.1.3 presents the characteristics of the PARADIGM-HF study population. In summary, the magnitude of the advantages of sacubitril valsartan over enalapril was highly statistically significant and clinically meaningful, particularly since sacubitril valsartan was compared to an evidence based dose of enalapril that has been shown to reduce mortality in patients with HF, as compared with placebo. The superior outcomes were consistent in all subgroups, which included age, gender, NYHA, LVEF, NT-pro-BNP, and systolic blood pressure (SBP). The standard care and background therapies used in PARADIGM-HF are comparable to standard background therapies used in England. Compared with the English HFrEF population, subjects in PARADIGM-HF were younger, more likely to be male and distributed into milder NYHA classes. In

PARADIGM-HF 49% of patients were ≥65 years of age (n=4120) and 19% of patients were ≥75 years of age (n=1563) with the oldest patient aged 96 at randomisation, and 22% (n=1,832) were female. No difference in treatment effects were seen in subgroup analysis of these patient groups.

The generalisability of the model results to English clinical practice has been thoroughly explored in scenario analyses in the economic evaluation (Section 5.8.8.1). Reweighting the PARADIGM-HF population based on patient characteristics from the CPRD database (i.e., age, gender, previous stroke, smoking status, and eGFR) resulted in ICERs for sacubitril valsartan versus ACEi ranging between £18,142 and £18,432 per QALY gained, compared with ACEis. In an additional scenario, the model was calibrated to achieve a rate of all-cause hospitalisation and year 4 cumulative all-cause mortality which matched the CPRD population. This scenario resulted in an ICER of £12,595 per QALY gained. These analyses suggest that any differences between the PARADIGM-HF and the English HF population are unlikely to adversely affect the cost-effectiveness of sacubitril valsartan.

5.11.4 *What are the main strengths and weaknesses of the evaluation? How might these affect the interpretation of the results?*

Strengths

This economic evaluation is based on head-to-head data from PARADIGM-HF, the largest trial ever conducted in HF comparing sacubitril valsartan to the ACEi enalapril (both in combination with standard care), reflecting the NICE recommended first-line treatment and clinical practice in England. Additional strengths of the economic evaluation include the model structure and methods reflecting the clinical setting, the use of patient level data from PARADIGM-HF which allows for evaluating heterogeneity between patient characteristics, and the use of conservative assumptions.

The model structure and methods adopted for the economic evaluation are based on the clinical setting of HF, the implicit key clinical outcomes for HF (i.e. mortality, hospitalisation and HRQoL), and the available data (i.e. primarily PARADIGM-HF for the comparison of sacubitril valsartan with ACEi and the results of a NMA for the comparison with ARB).The methods are also consistent with a recent HTA for ivabradine (TA267) (34), but incorporate a novel approach to the prediction of HRQoL, in which EQ-5D is extrapolated based on time trends observed in PARADIGM-HF (see Section 5.4.9). We believe that this approach represents a clinically plausible scenario which reduces complexity and the necessity to map between disease-specific measures and EQ-5D. This approach also alleviates an issue observed on initial extrapolation of NYHA distributions from PARADIGM-HF, in which an increasingly high proportion of patients were predicted to fall in less severe NYHA classes over time. The current methodology, which extrapolates EQ-5D over time and captures an annual decrease in HRQoL, is considered to better reflect clinical practice (see Section 8.11). In addition, the regression models used in the economic evaluation to determine the impact of baseline characteristics on patient outcomes (Mortality - Table 54; hospitalisations – Table 55; HRQoL - Table 61) show that EQ-5D is a better predictor of severity of disease versus other covariates including NYHA.

Additional strengths of the evaluation are the use of patient-level data from PARADIGM-HF. The use of multivariable risk equations allows the evaluation to characterise

between-patient heterogeneity, reflecting the fact that the cost-effectiveness of sacubitril valsartan is determined by absolute benefit, which may be expected to differ between patients. Nevertheless, the results demonstrate low variation in estimated cost-effectiveness across subgroups and following changes to structural assumptions (Sections 5.9 and 5.7.6, respectively).

The model also adopts a number of conservative assumptions. The extrapolation of mortality assumes the most conservative distribution of those considered (Gompertz). The costs of hospitalisation are likely to be underestimated given the potential follow-up costs associated with many procedures and interventions. In addition, the base case results presented are based on all-cause mortality which provides a more conservative outcome compared with CV mortality (supplemented by non-CV mortality from life tables) which was used for ivabradine in TA267 (34).

Limitations

The main limitations of this analysis are the requirements to extrapolate beyond the follow-up for PARADIGM-HF, the uncertainty in the ARB comparison based on a NMA, and the generalisability of the PARADIGM-HF patient population to English clinical practices.

The extrapolation beyond the follow-up of PARADIGM-HF is a source of uncertainty which cannot readily be characterised by sensitivity analysis. This is particularly true for HRQoL, for which we are not aware of long-term projections in patients with HFrEF against which to validate our assumptions, though data from Sweden has suggested an annual decrease of 0.006 (vs 0.008 in this analysis) (287). These assumptions were therefore explored in scenario analysis and found to have only moderate effects on results.

The analysis makes some simplifying assumptions. It is assumed that all patients remain on therapy until death. This assumption is explored in scenario analysis, in which discontinuation is modelled using data from PARADIGM-HF. We observe that the model behaves relatively linearly: Increased discontinuation reduces costs and incremental QALYs approximately proportionately, leaving the ICER (relatively) unchanged.

Approximately 18% of discharged HF patients in English clinical practice receive an ARB (6). Direct data to inform a comparison of ARBs to sacubitril valsartan in the licensed population are not available. Therefore we conducted an NMA which shows that sacubitril valsartan improves mortality and hospitalisations for patients with HF compared with ARBs, and ACEis and ARBs have similar efficacy. In the economic evaluation, HRs for hospitalisation and mortality outcomes generated from the NMA were used to inform the clinical inputs for ARBs. The HRs for ARBs were associated with large credible intervals which highlights the substantial uncertainty in the NMA (see Section 4.10). However, as described in Table 1, the scope specifies ARBs as a comparator only for patients that do not tolerate ACEis and thus has been presented as a secondary comparison in this submission.

The issue of generalisability of the economic evaluation to clinical practice has been discussed in Section 5.11.3. Scenario analyses suggest that any differences between the PARADIGM-HF and the English HF population are unlikely to adversely affect the cost-effectiveness of sacubitril valsartan.

Finally, some model parameters (notably estimates of resource use associated with adverse events) are based on expert opinion rather than clinical data. In deterministic sensitivity analysis, all such inputs were observed to have extremely low influence on the conclusions of the analysis.

5.11.5 *What further analyses could be carried out to enhance the robustness or completeness of the results?*

The treatment effect for sacubitril valsartan is taken from PARADIGM-HF; when available, observational data sources will be able to determine the real-word efficacy and further improve the generalisability of the model results to English clinical practice.

6 Assessment of factors relevant to the NHS and other parties

Summary

- The estimated eligible patient population for sacubitril valsartan in England in 2016 is 222,727 patients with HFrEF.
- The expected uptake of sacubitril valsartan is [redacted] in 2016 rising to [redacted] by 2020.
- The key drivers of the budget impact analysis are the cost of sacubitril valsartan and savings incurred by reduction of hospitalisations leading to an estimated net budget impact of [redacted]million in 2016 increasing to [redacted] million in 2020.
- It is estimated that in 2020 alone, based on an uptake of [redacted]in the eligible HF population, sacubitril valsartan would prevent [redacted]_CV-related deaths and [redacted] hospitalisations.

6.1 *State how many patients are eligible for treatment in England. Present results for the full marketing authorisation/CE marking and for any subgroups considered. Also present results for the subsequent 5 years.*

The number of patients eligible for treatment with sacubitril valsartan is estimated based on the population of England and epidemiological data from published studies and an English HF CPRD analysis (See Table 102).

Table 102: Estimation of eligible patient population

	2016	2017	2018	2019	2020
Population of England (298)	54,872,953	55,202,373	55,527,390	55,835,285	56,134,779
Prevalence of HF England† (299)	0.74%	0.74%	0.74%	0.74%	0.74%
Number of prevalent pts with HF in England	406,809	409,251	411,661	413,943	416,164
Incidence of heart failure (HF) England (300)	0.05%	0.05%	0.05%	0.05%	0.05%
Number of incident pts with HF in England	29,138	29,312	29,485	29,649	29,808
Total number of prevalent and incident pts in England	435,947	438,564	441,146	443,592	445,971
Percentage of pts with HFrEF (6)	72%	72%	72%	72%	72%
Percentage of HF pts with NYHA II-IV (301)	89%	89%	89%	89%	89%
Percentage of HF pts with eGFR > 30 mL/min/1.73m^2 (302)	89%	89%	89%	89%	89%
Total estimated number of pts in England with HFrEF, NHYA II-IV and eGFR > 30 mL/min/1.73m	248,626	250,118	251,3591	252,986	254,343
Mortality risk per year (296)	10.42%	10.42%	10.42%	10.42%	10.42%
Net estimated number of pts with HF in England	222,772	224,064	225,384	226,633	227,849

† Number of patients with HF in England in 2014 (401,729) divided by number of people in England in 2014 (54,187,718) (299)
Abbreviations: eGFR, estimated glomerular filtration rate; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; NHYA, New York Heart Association class II to IV; pts, patients.

6.2 *Explain any assumption(s) that were made about current treatment options and uptake of technologies?*

Table 103 outlines the current treatment options for HFrEF. The current market share for these treatment options was sourced from an analysis of the HF population in England from the CPRD dataset (16). Sacubitril valsartan is expected to be used in combination with standard care (i.e. beta blockers and aldosterone antagonists) and replace current treatment options (i.e. ACEis and ARBs, also in combination with standard care). No additional therapies (over and above standard care) are expected to be used in combination with sacubitril valsartan. As a result, no incremental standard care costs associated with the use of sacubitril valsartan have been assumed in the budget impact analysis.

The average cost of ACEis and ARBs is based on the percentage use of different ACEis and ARBs according to prescription data (not HF-specific) (303) and the cost of each of these ACEis or ARBs used (274).

Additionally, Table 103 outlines the projected 5 year uptake of sacubitril valsartan in England. The uptake of sacubitril valsartan has been based on analogous newly

launched medicines including novel oral anticoagulants and a non-insulin dependent diabetes treatment (sitagliptin –first in class dipeptidyl peptidase-4 inhibitor).

Table 103: Market share for treatment options

Treatment	Current market share	Future market share				
		2016	2017	2018	2019	2020
Sacubitril valsartan	0.0%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ACEi	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ARB	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ACEi, Angiotensin converting enzyme inhibitor; ARB, Angiotensin II receptor blocker

6.3 *When relevant, explain any assumptions that were made about market share in England.*

See Table 103 (Section 6.2) for market share assumptions in England.

Current market share: In the CPRD analysis of HF in England (16) [redacted] patients received ACEi and [redacted] patients received ARBs and [redacted] patients received other treatments. A total of [redacted] of patients were receiving ACEi or ARB treatment. In the budget impact model, the remaining [redacted] (not on ACEi or ARB therapy) was re-distributed so that 100% of patients were receiving ACEis or ARBs according to the same ratio as identified in the CPRD analysis. This resulted in the assumption that [redacted] patients were receiving ACEis and [redacted] patients receiving ARBs (see Table 103).

Future market share: The displacement of ACEi and ARBs by sacubitril valsartan is assumed to be in the same ratio of current ACEi and ARB use (e.g. from Table 103, out of the 2.1% eligible patients anticipated to be on sacubitril valsartan in 2016, [redacted] of patients initiated were previously assumed to be on ACEis and [redacted] on ARBs).

The mortality rate used in the calculation of HFrEF population is sourced from a CPRD analysis of HF in England (296) and is assumed to be constant over time (see Table 102, Section 6.1). However, sacubitril valsartan is anticipated to reduce mortality based on the results shown in the PARADIGM-HF study (10); Using the estimates of mortality available from PARADIGM-HF, it is estimated that in 2020 alone, based on an estimated uptake of [redacted] treatment with sacubitril valsartan would prevent [redacted] CV-related deaths.

6.4 *In addition to technology costs, please consider other significant costs associated with treatment that may be of interest to commissioners (for example, administration costs, monitoring costs and the costs of managing adverse reactions).*

In addition to drug costs, other costs associated with treatment of HFrEF in the budget impact model are listed below:

Administration costs

When initiating sacubitril valsartan in RAAS-naïve patients, two visits, with either a GP (£35 per visit (13)), cardiologist (£130.86 per visit insert (14)) or HF specialist nurse (£33

per visit (13)) may be required to titrate patients from 50mg to 100mg and then from 100mg to the 200mg target dose. In patients previously treated with ACEi or ARB, only one titration visit will be required (to the target dose of 200mg) as patients would be initiated on 100mg. As part of current standard practice, initiation of ACEi or ARB treatment requires titration and therefore this cost has not been considered incremental for sacubitril valsartan over ACEi or ARB. This is aligned with the titration assumption in the cost-effectiveness model (See 'Initial costs associated with titrating sacubitril valsartan').

Monitoring costs

As discussed in Section 2.4.1, no additional tests or investigations are needed for sacubitril valsartan compared to displaced therapies.

Costs of managing adverse events

Costs of managing adverse events in the budget impact model have been based on the same sources and assumptions as the cost-effectiveness model (see Section 5.5.6 for further detail).

6.5 *State what unit costs were assumed and how they were calculated. If unit costs used in health economic modelling were not based on national reference costs or the payment-by-results tariff, explain how a cost for the activity was calculated?*

The unit costs were obtained from PSSRU and NHS National Schedule of Reference Costs (13, 14). In the budget impact analysis the same unit costs used in the cost-effectiveness model are applied. Please refer to Table 62, Table 63 and Table 69 for further detail.

6.6 *If there were any estimates of resource savings, explain what they were and when they are likely to be made*

The introduction of sacubitril valsartan into the market is projected to reduce the costs of hospitalisations. The PARADIGM-HF trial (see Section 4.7.1) demonstrated that compared with the evidence-based dose of enalapril, sacubitril valsartan significantly reduced the risk of hospitalisation for heart failure by 21% (P<0.001) as well as all-cause, CV and non-CV hospitalisation (see Table 17). Therefore, resource savings due to reduction in hospitalisation are expected from year 1 onwards [redacted] in 2016 increasing to [redacted]. In 2020 alone, based on an estimated uptake of [redacted] and data from PARADIGM-HF, sacubitril valsartan is estimated to prevent [redacted] hospitalisations.

Adverse event costs were considered for sacubitril valsartan, ACEi and ARB. Adverse event risks associated with sacubitril valsartan and enalapril were sourced from PARADIGM-HF based on the FAS population (see Section 4.7.1) and annualised rates calculated. Adverse event risk data for ARBs was considered to be equivalent to sacubitril valsartan based on known adverse events associated with ARBs (including valsartan). Adverse event selection was consistent with the methodology for the cost-effectiveness analysis (see Section 5.3.1 'Adverse events'). Introduction of sacubitril

valsartan is associated with a small cost reduction ([redacted] per year in 2016, increasing to [redacted] in 2020) by displacing ACEi and ARB use.

6.7 *State the estimated annual budget impact on the NHS in England*

The estimated annual budget impact for the NHS is shown in Table 104. This budget impact has been calculated based on the uptake of sacubitril valsartan and ACEi and ARBs (see Section 6.1), cost-savings due to hospitalisations (see Section 6.6) and minor cost-savings due to adverse events (see Section 6.6) for patients with HFrEF.

Table 104: Budget impact of sacubitril valsartan in the treatment of HFrEF in England

	2016	2017	2018	2019	2020
Patients treated with sacubitril valsartan, n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Annual net budget impact	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

6.8 *Identify any other opportunities for resource savings or redirection of resources that it has not been possible to quantify.*

Limited additional opportunities for resource savings or redirection of resources are expected. It is acknowledged that a large proportion of this population are elderly and past the age of employment. However, based on the age range of patients in PARADIGM-HF it is expected that a proportion of patients might still be in employment. [redacted]. As sacubitril valsartan reduces hospitalisation and reduces decline in HRQoL, there could be societal cost savings associated with sacubitril valsartan.

6.9 *Highlight the main limitations of the budget impact analysis.*

A few limitations have been identified with the budget impact analysis including:

- The calculation does not take into consideration discontinuation for any treatments while in PARADIGM-HF the discontinuation rate for sacubitril valsartan was 17.8% and enalapril was 19.8% over the 27 month median study follow-up. However, as the outcomes used in the model including hospitalisations and AEs are based on the PARADIGM-HF population and including the discontinuation would lead to reduced budget impact (reduced cost of sacubitril valsartan) this is expected to be a conservative budget impact analysis.
- The treatment of adverse events and the associated cost in the budget impact analysis is based on UK expert clinical opinion instead of evidence-based estimates. However this was the best available evidence. In addition, adverse events for ARBs have been assumed to be similar to sacubitril valsartan due to lack of data. This was based on the known adverse event profile of ARBs, the fact that sacubitril valsartan contains an ARB (valsartan) and the SmPC of valsartan (291). The estimated forecast for the uptake of sacubitril valsartan has

been based on analogues of recently launched NOACs and a non-insulin dependent diabetes treatment. No recent analogues are available in a directly comparable disease area.

- The prescription data for usage of individual ACEi and ARBs within each class are not specific to a population with HF and therefore may partially reflect the usage of individual ACEi/ARB in a separate CV disease area (e.g., hypertension). However, as ACEis and ARBs are generic and there are only minor differences in cost between medicines, this would be expected to have a minimal impact.

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Single Technology Appraisal (STA)

Sacubitril valsartan for treating heart failure with systolic dysfunction [ID822]

Dear [redacted]

The Evidence Review Group, BMJ Group, and the technical team at NICE have now had an opportunity to take a look at the submission received on 17 August by Novartis Pharmaceuticals. In general terms they felt that it is well presented and clear. However, the ERG and the NICE technical team would like further clarification relating to the clinical and cost effectiveness data.

Both the ERG and the technical team at NICE will be addressing these issues in their reports.

We request you to provide a written response to this letter to the Institute by **1pm**, **Friday 25 September**. Two versions of this written response should be submitted; one with academic/commercial in confidence information clearly marked and one from which this information is removed.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, and all information submitted under 'academic in confidence' in yellow.

If you present data that is not already referenced in the main body of your submission and that data is seen to be academic/commercial in confidence information, please complete the attached checklist for in confidence information.

Please do not 'embed' documents (i.e. PDFs, spreadsheets) within your response as this may result in your information being displaced or unreadable. Any supporting documents should be uploaded to NICE Docs/Appraisals via this link: <<Insert NICE DOCS LINK>>.

If you have any further queries on the technical issues raised in this letter then please contact Chris Chesters, Technical Lead (chris.chesters@nice.org.uk). Any procedural questions should be addressed to Lori Farrar, Project Manager (lori.farrar@nice.org.uk) in the first instance.

Yours sincerely

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Encl. checklist for in confidence information

Section A – clarification on clinical effectiveness data

A1. **Priority Question:** Please provide the patients' characteristics for the Western Europe region subgroup in the table below. Please also provide the standard deviation where appropriate.

Variable	Value
Mean age	
Female (%)	
Race - White	
Race - Black	
Race - Asian	
Race - Other	
NYHA class I	
NYHA class II	
NYHA class III	
NYHA class IV	
NYHA class III/IV	
LVEF %	
SBP mm HG	
Heart rate beats/min	
eGFR (mL/min/1.73m2)	
NT-proBNP (pg/mL)	
Sodium (mmol/L)	
Potassium (mmol/L)	
QRS duration (ms)	
BMI (kg/m2)	
Diabetes (%)	
Hypertension (%)	
Prior ACEi use (%)	
Prior ARB use (%)	
Beta blocker use (%)	
Mineralocorticoid receptor antagonist use (%)	
Digoxin use (%)	
Lipid lowering medication use (%)	
Allopurinol use (%)	
≤ 1 year since HF diagnosis (%)	

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1-5 years since HF diagnosis (%)	
>5 years since HF diagnosis (%)	
Ischaemic aetiology (%)	
Prior stroke (%)	
Prior atrial fibrillation/ flutter (%)	
Prior angina (%)	
Prior cancer (%)	
Current smoker (%)	
Prior HF hospitalisation (%)	
EQ-5D	

A2. **Priority Question:** Please provide Section 14 of the clinical study report (CSR) of the PARADIGM-HF trial.

A3. **Priority Question:** Please explain the difference in the patient numbers at baseline (the total study population and the number in each treatment group) between the PARADIGM-HF clinical study report (n=4209 for LCZ696 and n=4233 for enalapril; Table 11-3 page 97) and in the McMurray et al. (2014) study published in The New England Journal of Medicine (n=4187 for LCZ696 and n=4212 for enalapril; Table 1).

A4. Please provide the number of patients who did not tolerate enalapril 20 mg twice a day and sacubitril valsartan 200 mg twice a day during the run-in phase of the PARADIGM-HF study.

A5. Please supply the data files associated with each of the network meta-analyses so they can be replicated.

A6. Please give reasons why the following 2 studies were not considered for inclusion in the network meta-analysis:

1. The acute infarction ramipril efficacy (AIRE) study investigators (1993). The effect of ramipril on mortality and morbidity of survivors of acute myocardial infarction with clinical evidence of heart failure. Lancet; 342:821-28.
2. Lee et al. (2008). The comparative clinical effects of valsartan and ramipril in patients with heart failure. Korean Circulation Journal; 38:101-9.

A7. Please provide data for the baseline and post-intervention levels of serum potassium for participants in both arms of the PARADIGM-HF trial.

A8. Please clarify why region was used as a fixed-effect factor in the Cox's proportional hazard model in the statistical analysis of PARADIGM-HF.

A9. Please specify what the different clinical events included under CV hospitalisations and non-CV hospitalisations in the all-cause and cause-specific hospital admissions (full analysis set [FAS] analysis).

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Section B – clarification on cost effectiveness data

B1. **Priority question:** Please clarify if the baseline utility value of 0.81 used in the model ("Regression_Values" sheet, cell I47) is the correct value as the submission states that the baseline utility value at randomisation was 0.78. If the incorrect value has been used in the model, please clarify the outputs from the model run using the corrected baseline utility value of 0.78.

B2. **Priority question:** Please run the following scenario analyses (with any necessary corrections resulting from previous clarification questions [B1] incorporated into the model) and present total costs, total QALYs and ICERs for each relevant comparison:

- Base case analysis using the raw Kaplan Meier [KM] data to model the "within trial" period (as an alternative to using regression models) with:
    1) KM data used to model mortality, hospitalisation and quality of life (QoL) in the model simultaneously for the trial period (timeframe of the analysis = trial follow-up period)
    2) KM data used to model mortality, hospitalisation and QoL in the model simultaneously for the trial period and with extrapolated curves from the end of the trial period onwards (lifelong analysis)
    3) KM data used to model mortality and hospitalisation in the model simultaneously for the trial period, leaving the original QoL regression model unchanged (timeframe of the analysis = trial follow-up period)
    4) KM data used to model mortality and hospitalisation in the model simultaneously for the trial period and with extrapolated curves from the end of the trial period onwards (leaving the original QoL regression model unchanged).

B3. **Priority question:** The ERG has found the mortality in the model to be extremely insensitive to changes in the starting age of patients. For example when running the mean cohort model with a starting age of 82 years, the expected survival is 5.12 years and 5.58 years for sacubitril and enalapril, respectively. This compares with an expected survival of 6.89 years and 7.56 years in the base case mean cohort model for sacubitril and enalapril respectively, where the starting age in the model is 64 years. It seems implausible that starting the model nearly 20 years later decreases the expected survival by less than 2 years in both treatment arms. Please provide further rationale to explain the insensitivity to changes in starting age.

B4. **Priority question:** Please run the following scenario analyses (with any necessary corrections resulting from previous clarification questions B1 and B3 incorporated into the model) and present total costs, total QALYs and ICERs for each relevant comparison:

a) Subgroup analysis including the Western population only (please run the model with both the IPD and cohort level options and in the cohort level model please

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change all the relevant baseline covariates in the different models to reflect this specific population)

b) Subgroup analysis including only the patients diagnosed with heart failure with reduced ejection fraction (HFrEF) for less than 1 year (please run the model with both the IPD and cohort level options and in the cohort level model please change all the relevant baseline covariates in the different models to reflect this specific population)

c) Subgroup analysis including analysis a) and b) combined.

B5. **Priority question:** Regarding Table 56 (page 136 of the company submission):

a) Please clarify the use of the FAS population instead of the safety set for the purposes of modelling adverse events. The trial protocol specifies that "safety analyses will be performed based on the safety population" (Protocol for PARADIGM-HF, page 80).

b) Please provide a rationale for not including some of the hypotension, elevated serum creatinine and potassium events from the adverse event analysis (Table 3, McMurray et al. 2014 published in The New England Journal of Medicine). More specifically, the symptomatic with systolic blood pressure <90 mm Hg events, the ≥ 3.0 mg/dl serum creatinine events and the ≥ 6.0 mg/dl serum potassium events.

B6. **Priority question:** The adverse events analysis using the FAS population is not reported in the clinical study report (and only the Safety Set analysis is provided). Please provide the full analysis set of adverse events for the FAS population and explain the main differences in safety outcomes between the FAS and the safety set.

B7. **Priority question:** On page 142 of the company submission it is stated that "too few angioedema events were observed to make inference regarding the effects on HRQoL". However the costs of angioedema have been considered in the economic model. For the base case analysis, please include the impact of angioedema on HRQoL for the purposes of consistency.

B8. **Priority question:** The figures below report the mortality in the sacubitril valsartan and enalapril arms of the model respectively.

a) Please explain why the non-CV mortality is higher (in both arms of the model) when compared with UK life tables when it is reported in table 51, page 128 of the company submission that the 'exclusion of patients from the trial with presence of other diseases with life expectancy < 5 years may have led to lower rates of non-CV mortality'.

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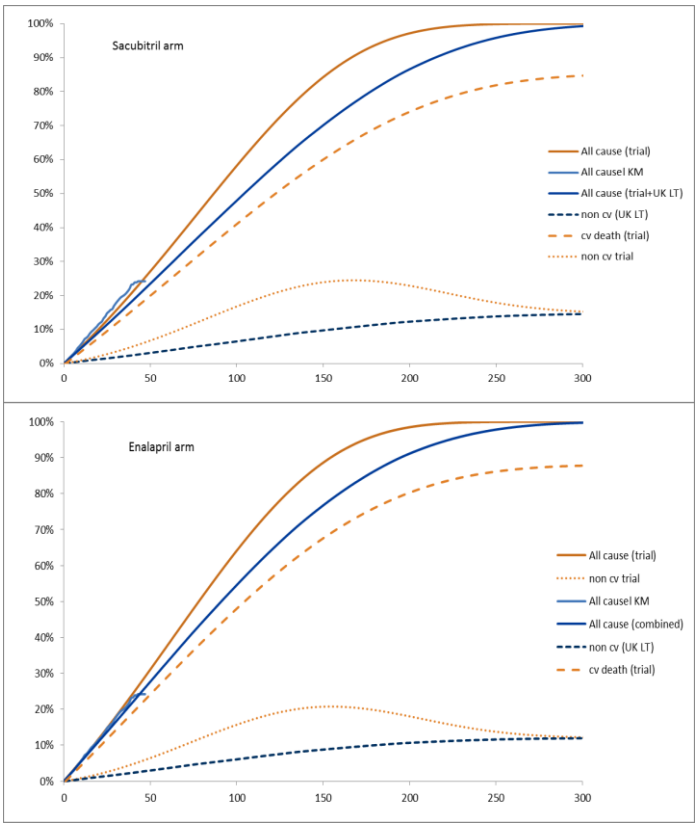
b) Please explain why the non-CV mortality is higher in the sacubitril valsartan arm of the model compared with the enalapril arm.



B9. **Priority question:** Please clarify any reasoning behind the decision not to include the New York Heart Association (NYHA) covariate in the hospitalisation model, as this was shown to be a prognostic factor of hospitalisations in the company's subgroup analysis.

B10. **Priority question:** Please report the duration of hospitalisation in the PARADIGM-HF trial, by treatment arm by time period. Please provide these data separately for cumulative hospitalisations, all CV hospitalisations and all other hospitalisations.

B11. **Priority question:** Page 182 of the company submission states:

'The mixed effects model of EQ-5D displays a small but statistically significant positive effect associated with sacubitril valsartan (0.011; p=0.001), beyond the benefit due to differences in hospitalisation and adverse events. This effect is thought to be due to improvements in symptoms in sacubitril valsartan patients.'

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For patients treated with sacubitril valsartan, please define any symptoms which may improve, but are not related to adverse events and hospitalisations.

B12. Priority question:

Please provide:

a) Table 14.1-2.1 (mentioned on pages 21 and 90 of the clinical study report for PARADIGM-HF but not reported within the document).
b) The on-treatment analysis of primary endpoint and its components (stated on page 50 of the company submission under the subheading 'Secondary analyses of the primary efficacy outcome') together with any Kaplan-Meier data available.
c) Table 14.2-3.2 (mentioned in the clinical study report of TITRATION but not reported in the document). Please also provide any additional data regarding the change from baseline in New York Heart Association (NYHA) class in ACEi/ARB-treatment naïve patients.
d) Listing 14.3-4.1.a which is mentioned in page 146 of the clinical study report for PARADIGM-HF but is not reported within the document.
e) KM data for CV death in the PARADIGM-HF trial.
f) KM data for CV death KM data for CV death in the PARADIGM-HF trial by time from diagnosis (i.e. less than 1 year, between 1 and 5 years and more than 5 years).

B13. Priority question: Please explain the discrepancy in values between the mean duration of follow-up during the double-blind period reported in page 21 of the PARADIGM-HF clinical study report and the mean duration of follow-up reported in Table 12-1 of the PARADIGM-HF clinical study report. Please do the same for the median duration of follow-up reported in page 90 and Table 12-1 of the PARADIGM-HF clinical study report. Please also clarify the mean duration of follow-up that was assumed in the model calculations when adjusting for variables monthly model cycles.

B14. Priority question: Please clarify whether other regression models (for example, using a logistic transformation) were considered to model quality of life (QoL).

B15. Please provide any rationale for the assumption that mild angioedema requires 2 cardiologist outpatient visits while severe angioedema does not require any cardiologist outpatient visits.

B16. Please explain why elevated serum creatinine, elevated serum potassium and severe angioedema were not included in the costs of hospitalisation.

B17. Please clarify what date visit 778 (end of study [EOS] point) took place, and what had been the follow-up period at that point.

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B18. Please clarify what results are available from the "predictive models of NYHA developed" (Appendix 8.12, page 141) as these were not included in the company submission.

B19. Please provide the model results including the initial set of covariates (before the backwards and forwards stepwise selection) and the results after the stepwise selection process.

B20. The ERG found some discrepancies between the values reported in the company submission and in the Excel model results. Please provide the correct values in the table below.

Outcomes/Analysis	Reference in the model	Company submission	Correct values
Total costs (alternative results vs ARBs)	'Reporting' C4:C5	p167 Table 86	
Total LYG (alternative results vs ARBs)	'Results' J8:L8	p167 Table 86	
Total QALYs (alternative results vs ARBs)	'Reporting' D4:D5	p167 Table 86	
Incremental costs(alternative results vs ARBs)	'Reporting' E5	p167 Table 86	
Incremental LYG(alternative results vs ARBs)	'Results' N8	p167 Table 86	
Incremental QALYs(alternative results vs ARBs)	'Reporting' F6	p167 Table 86	
ICER (per QALY gained) (alternative results vs ARBs)	'Reporting' G5	p167 Table 86	
Annual rate of decline in EQ-5D doubled	'Sensitivity Analysis' G54:K54	P189 Table 99	
No decline in EQ-5D over time	'Sensitivity Analysis' G55:K55	P189 Table 99	
No decline in EQ-5D after 5 years	'Sensitivity Analysis' G56:K56	P189 Table 99	
No decline in EQ-5D after 10 years	'Sensitivity Analysis' G57:K57	P189 Table 99	
Effect of sacubitril valsartan on EQ-5D (beyond differences in hospitalisation / adverse event rates) assumed to be zero	'Sensitivity Analysis' G58:K58	P189 Table 99	
Effect of sacubitril valsartan on hospitalisation rates assumed to apply to HF hospitalisation only	'Sensitivity Analysis' G59:K59	P189 Table 99	
Effect of hospitalisation on EQ-	'Sensitivity Analysis'	P189 Table 99	

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5D assumed to be zero	G61:K61		
Sacubitril valsartan treatment effects assumed to cease at year 5	'Sensitivity Analysis' G62:K62	P189 Table 99	
Sacubitril valsartan treatment effects assumed to cease at year 10	'Sensitivity Analysis' G63:K63	P189 Table 99	
Treatment discontinuation considered over lifetime time horizon	'Sensitivity Analysis' G64:K64	P189 Table 99	
Treatment discontinuation considered up to year 3	'Sensitivity Analysis' G65:K65	P189 Table 99	
Treatment discontinuation assumed to result in reduced therapy costs; efficacy estimates as in trial	'Sensitivity Analysis' G66:K66	P189 Table 99	

Section C:

NICE has noted there is a large volume of information marked as confidential in the company submission. A separate request will be sent to the company, however please consider lifting the confidentiality status of the data in the submission in advance of receiving a formal request.

Single Technology Appraisal (STA)

Sacubitril valsartan for treating heart failure with systolic dysfunction [ID822]

Dear [redacted]

The Evidence Review Group, BMJ Group, and the technical team at NICE have now had an opportunity to take a look at the submission received on 17 August by Novartis Pharmaceuticals. In general terms they felt that it is well presented and clear. However, the ERG and the NICE technical team would like further clarification relating to the clinical and cost effectiveness data.

Both the ERG and the technical team at NICE will be addressing these issues in their reports.

We request you to provide a written response to this letter to the Institute by **1pm**, **Friday 25 September**. Two versions of this written response should be submitted; one with academic/commercial in confidence information clearly marked and one from which this information is removed.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, and all information submitted under 'academic in confidence' in yellow.

If you present data that is not already referenced in the main body of your submission and that data is seen to be academic/commercial in confidence information, please complete the attached checklist for in confidence information.

Please do not 'embed' documents (i.e. PDFs, spreadsheets) within your response as this may result in your information being displaced or unreadable. Any supporting documents should be uploaded to NICE Docs/Appraisals via this link: <<Insert NICE DOCS LINK>>.

If you have any further queries on the technical issues raised in this letter then please contact Chris Chesters, Technical Lead (chris.chesters@nice.org.uk). Any procedural questions should be addressed to Lori Farrar, Project Manager (lori.farrar@nice.org.uk) in the first instance.

Yours sincerely

Dr Frances Sutcliffe
Associate Director – Appraisals
Centre for Health Technology Evaluation

Encl. checklist for in confidence information

Table of contents

Section A – clarification on clinical effectiveness data

A1. Priority Question: Please provide the patients' characteristics for the Western Europe region subgroup in the table below. Please also provide the standard deviation where appropriate.

Table 1: Characteristics of participants from the Western Europe region in PARADIGM HF across randomised groups (Randomised set)

Variable	Value	
	Sacubitril valsartan N=1,029	Enalapril N=1,028
Mean age, years (±SD)	[redacted]	[redacted]
Female, n (%)	[redacted]	[redacted]
Race – White, n (%)	[redacted]	[redacted]
Race – Black, n (%)	[redacted]	[redacted]
Race – Asian, n (%)	[redacted]	[redacted]
Race – Other, n (%)	[redacted]	[redacted]
NYHA class I, n (%)	[redacted]	[redacted]
NYHA class II, n (%)	[redacted]	[redacted]
NYHA class III, n (%)	[redacted]	[redacted]
NYHA class IV, n (%)	[redacted]	[redacted]
NYHA class III/IV, n (%)	[redacted]	[redacted]
LVEF %, mean (±SD)	[redacted]	[redacted]
SBP mm HG, mean (±SD)	[redacted]	[redacted]
Heart rate beats/min, mean (±SD)	[redacted]	[redacted]
eGFR (mL/min/1.73m2), mean (±SD)	[redacted]	[redacted]
Median NT-proBNP (IQR), pg/mL	[redacted]	[redacted]
Sodium (mmol/L) mean (±SD)	[redacted]	[redacted]
Potassium (mmol/L) mean (±SD)	[redacted]	[redacted]
QRS duration (ms)	[redacted]	[redacted]
BMI (kg/m2), mean (±SD)	[redacted]	[redacted]
Diabetes (%), n (%)	[redacted]	[redacted]
Hypertension, n (%)	[redacted]	[redacted]
Prior ACEi use, n (%)	[redacted]	[redacted]
Prior ARB use, n (%)	[redacted]	[redacted]
Beta blocker use, n (%)	[redacted]	[redacted]
Mineralocorticoid receptor antagonist use, n (%)	[redacted]	[redacted]
Digoxin use, n (%)	[redacted]	[redacted]
Lipid lowering medication use, n (%)	[redacted]	[redacted]

Allopurinol use, n (%)	[redacted]	[redacted]
≤ 1 year since HF diagnosis, n (%)	[redacted]	[redacted]
1-5 years since HF diagnosis, n (%)	[redacted]	[redacted]
>5 years since HF diagnosis, n (%)	[redacted]	[redacted]
Ischaemic aetiology, n (%)	[redacted]	[redacted]
Prior stroke, n (%)	[redacted]	[redacted]
Prior atrial fibrillation/flutter, n (%) Paroxysmal Permanent	[redacted] [redacted] [redacted]	[redacted] [redacted] [redacted]
Prior angina, n (%) † Stable angina pectoris Prior unstable angina	 [redacted] [redacted]	 [redacted] [redacted]
Prior cancer, n (%)	[redacted]	[redacted]
Current smoker, n (%)	[redacted]	[redacted]
Prior HF hospitalisation, n (%)	[redacted]	[redacted]
EQ-5D, mean (±SD)	[redacted]	[redacted]

† For completeness we included both as we were uncertain what was requested

A2. Priority Question: Please provide Section 14 of the clinical study report (CSR) of the PARADIGM-HF trial.

The data files have been uploaded on NICE docs. Please refer to the confidential files named: 'A2 Novartis_2014_CSR_PARADIGM-HF PART 1' and 'A2 Novartis_2014_CSR_PARADIGM-HF PART 2.

A3. Priority Question: Please explain the difference in the patient numbers at baseline (the total study population and the number in each treatment group) between the PARADIGM-HF clinical study report (n=4209 for LCZ696 and n=4233 for enalapril; Table 11-3 page 97) and in the McMurray et al. (2014) study published in The New England Journal of Medicine (n=4187 for LCZ696 and n=4212 for enalapril; Table 1).

The patient numbers described in the clinical study report (CSR) (Table 11-3 page 97) refer to the randomised set which consists of all patients who received a randomisation number, regardless of receiving trial medication.

The patient numbers referred to the in the McMurray study publication refers to the FAS (Full Analysis Set) which consists of all randomised patients with the exception of those patients who had been inadvertently randomised into the study, i.e., patients who had not qualified for randomisation and had not received study drug. Following the intent-to-treat principle, patients were analysed according to the treatment to which they were assigned at randomisation. Further exclusions from the FAS were only justified in exceptional circumstances (e.g., *serious* GCP violations). The determination of which patients were excluded from the FAS was made in a blinded manner before the database lock.

The difference between the two patient numbers (n=8,442 vs. n=8,339) is due to 43 patients being excluded from all efficacy analyses (See Flow diagram - Figure 4 of the manufacturer submission, (1)). Six of these patients failed the sacubitril valsartan run-in period, but were randomised erroneously and never received study medication, i.e., they were misrandomised; reasons for run-in failure of these patients were hyperkalaemia (n=2), renal dysfunction (n=1), hypotension and other AE (n=1), abnormal laboratory value (n=1), and protocol deviation (n=1). Thirty seven patients were prospectively excluded because they were randomised at sites that were later closed due to serious GCP violations discovered prior to database lock, and as a result, the efficacy data for the 37 patients randomised at these sites were excluded from the FAS, but their safety data were included in the safety analyses.

1. McMurray JJ, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure. N Engl J Med. 2014 Sep 11;371(11):993-1004.

A4. Please provide the number of patients who did not tolerate enalapril 20 mg twice a day and sacubitril valsartan 200 mg twice a day during the run-in phase of the PARADIGM-HF study.

Please note the enalapril dose during the run in phase was 10 mg twice daily.

10,513 patients entered the enalapril run-in phase and 1,102 patients (10.47%) failed this run-in period. 9,419 patients then entered the sacubitril valsartan run-in phase and 982 patients (9.33%) failed this run-in phase. [redacted] In addition, the number of patients who discontinued due to other reasons is included in the table. Please note – deaths could be a potential marker for tolerability.

Table 2: Reasons for treatment discontinuation during run-in period (enrolled set)

	Enalapril run-in N=10,513 n (%)	**Sacubitril valsartan run-in N=9,419 n (%)**
Primary reason for premature discontinuation - Tolerability	[redacted]	[redacted]
AEs	[redacted]	[redacted]
Cough	[redacted]	[redacted]
Hyperkalaemia	[redacted]	[redacted]
Hypotension	[redacted]	[redacted]
Renal dysfunction	[redacted]	[redacted]
Other	[redacted]	[redacted]
Abnormal laboratory values	[redacted]	[redacted]
Abnormal test procedure result(s)	[redacted]	[redacted]
Primary reason for premature discontinuation - Other†	[redacted]	[redacted]
Death*	[redacted]	[redacted]
Premature discontinuation for any reason	[redacted]	[redacted]

[redacted]

A5. Please supply the data files associated with each of the network meta-analyses so they can be replicated.

The data files have been uploaded on NICE docs which includes a short description how to run these in R. Please refer to the confidential file named ‘A5 NMA model codes and data sets’.

A6. Please give reasons why the following 2 studies were not considered for inclusion in the network meta-analysis:

Both studies were excluded based on the PICOS criteria used for the SR (see Table 7 of manufacturer submission):

1. The acute infarction ramipril efficacy (AIRE) study investigators (1993). The effect of ramipril on mortality and morbidity of survivors of acute myocardial infarction with clinical evidence of heart failure. Lancet; 342:821-28.

This study was excluded on the basis of the patient population: The SR PICOS criteria specified 'Adult patients with chronic HFrEF (defined by LVEF below 40-45% or simply reported as "reduced")'. This article does not state whether the ejection fraction is reduced in the study population. A recent Cochrane systematic review (2) also excluded this trial despite broader patient population inclusion criteria (all patients with CHF were included). They do not specify why it was excluded however they refer to the study in the text as a post-MI study so it was likely excluded from the Cochrane SR on the basis of patient population as well.

2. Lee et al. (2008). The comparative clinical effects of valsartan and ramipril in patients with heart failure. Korean Circulation Journal; 38:101-9.

The SR PICOS criteria excluded studies where 100% of the patient population included was non-North American or non-European.

2. Heran BS, Musini VM, Bassett K, Taylor RS, Wright JM. Angiotensin receptor blockers for heart failure. In: The Cochrane C, editor. Cochrane Database of Systematic Reviews. Chichester, UK: John Wiley & Sons, Ltd; 2012.

A7. Please provide data for the baseline and post-intervention levels of serum potassium for participants in both arms of the PARADIGM-HF trial.

This data has been uploaded into NICE docs. Please refer to the confidential file named ‘A7 Table 1 14.3.1-1.17 Change for patients serum potassium 5.5molL 6 molL 6.5 mmolL safety set.

Shifts in serum potassium levels according to pre-defined categories of ≥ 5.5 mmol/L, > 6 mmol/L, and > 6.5 mmol/L are presented in Table 14.3.1-1.17 (uploaded into NICE docs). Most patients in both treatment groups (>97%) had baseline serum potassium levels that were lower than the thresholds of ≥ 5.5 mmol/L, > 6 mmol/L, and > 6.5 mmol/L. Post-randomisation, the proportion of patients with newly occurring serum potassium levels meeting these threshold criteria (i.e., shift from absent to present) was consistently lower in the sacubitril valsartan group compared with the enalapril group: 19.57% vs. 21.12% with ≥ 5.5 mmol/L; 4.33% vs. 5.54% with > 6 mmol/L; and 1.36% vs. 1.77% with > 6.5 mmol/L, respectively.

A8. Please clarify why region was used as a fixed-effect factor in the Cox's proportional hazard model in the statistical analysis of PARADIGM-HF.

It was decided to include region as a fixed-effect factor in the pre-specified Cox's proportional hazard model because of the expected large variation of the rate of hospitalisations for heart failure (a component of the primary endpoint in PARADIGM-HF) among regions (3).

Including important prognostic factors in the model is expected to improve efficiency in the treatment comparison. Conversely, ignoring important covariates in a Cox-regression model could bias the treatment effect towards no effect and therefore reduce the power of the statistical test (4).

3. Blair JE, Zannad F, Konstam MA, Cook T, Traver B, Burnett JC Jr, Grinfeld L, Krasa H, Maggioni AP, Orlandi C, Swedberg K, Udelson JE, Zimmer C, Gheorghiade M; EVEREST Investigators. Continental differences in clinical characteristics, management, and outcomes in patients hospitalized with worsening heart failure results from the EVEREST (Efficacy of Vasopressin Antagonism in Heart Failure: Outcome Study with Tolvaptan) program. J Am Coll Cardiol. 2008;52:1640–1648.
4. Struthers CA and Kalbfleisch. Misspecified proportional hazard models. Biometrika 1986 73(2):363-369; doi:10.1093/biomet/73.2.363

A9. Please specify what the different clinical events included under CV hospitalisations and non-CV hospitalisations in the all-cause and cause-specific hospital admissions (full analysis set [FAS] analysis).

Please refer to the confidential file named ‘A9 Section 12.4 Prefer term for distinguishing CV hospitalisation and non CV hospitalisation’. This is extracted from the detailed statistical methodology document (Submission Confidential reference pack: Novartis. A multicenter, randomized, double-blind, parallel group, active-controlled study to evaluate the efficacy and safety of LCZ696 compared to enalapril on morbidity and mortality in patients with chronic heart failure and reduced ejection fraction RAP Module 3 – Detailed Statistical Methodology. Data on file. 2012).

Section B – clarification on cost effectiveness data

B1. Priority question: Please clarify if the baseline utility value of 0.81 used in the model ("Regression_Values" sheet, cell I47) is the correct value as the submission states that the baseline utility value at randomisation was 0.78. If the incorrect value has been used in the model, please clarify the outputs from the model run using the corrected baseline utility value of 0.78.

The ERG is correct that the baseline utility value of 0.81 used in the model is erroneous; the value on the 'Regression_Values' sheet should be 0.7798.

- This is the mean value for the 8,271 available EQ-5D scores at baseline, and is used to centre baseline EQ-5D on its mean value in the regression equations.
- Please note that the mean baseline EQ-5D value of 0.7803 presented on the 'Population' sheet of the model is the average baseline EQ-5D for the 8,399 patients in the PARADIGM-HF full analysis set (FAS), including imputed data for the 128 patients with missing EQ-5D at baseline, and therefore differs slightly.
- For patients with missing EQ-5D data, this was imputed using the region-specific mean. This approach was preferred over, for example, multiple imputation because such methods do not respect the independence of baseline variables from randomisation; it is therefore preferable to impute missing baseline deterministically using other baseline data (5,6)
- The baseline EQ-5D value from the trial is 0.7798 (See Figure 1), however, the imputed baseline EQ-5D value (0.7803) is required for the model to be able to run the patient level data analysis (Excel model - Sheet 'PLD_PARADIGM' average of BI31-849).

Figure 1: Baseline EQ-5D (UK index)

In a cross-check of the inputs with mean values on the 'Regression_Values' sheet, we noted that mean QRS duration is also incorrect at the fourth decimal place

- The correct value is 117.3589
- Updating mean baseline QRS duration, prior to updating mean baseline EQ-5D, changes the ICER by less than £1

The mean baseline EQ-5D value and mean baseline QRS duration on the 'Regression_Values' sheet have now been corrected; a comparison between the model presented in the submission to NICE and the corrected model is presented in Table 3.

- The change to the ICER is minimal, providing a marginally lower cost per QALY gained.

All further analyses use the corrected model, unless otherwise specified.

Table 3: Comparison between model presented in NICE submission and corrected model

		Model presented in NICE submission	Corrected model	% change
Total costs	**ACEi**	£13,286	£13,287	0.01%
	Sacubitril valsartan	£20,734	£20,801	0.32%
Total life-years	**ACEi**	6.03	6.08	0.83%
	Sacubitril valsartan	6.51	6.56	0.77%
Incremental cost per life-year gained		£15,536	£15,618	0.53%
Total QALYs	**ACEi**	4.46	4.60	3.14%
	Sacubitril valsartan	4.87	5.02	3.08%
Incremental cost per QALY		£18,187	£17,939	-1.36%

Abbreviations: ACEi, angiotensin-converting-enzyme inhibitor; QALYs, quality adjusted life years

5. White IR, Royston P, Wood AM. Multiple imputation using chained equations: Issues and guidance for practice. Stat Med. 2011 Feb 20;30(4):377-99.
6. White IR, Thompson SG. Adjusting for partially missing baseline measurements in randomized trials. Stat Med. 2005 Apr 15;24(7):993-1007.

B2. Priority question: Please run the following scenario analyses (with any necessary corrections resulting from previous clarification questions [B1] incorporated into the model) and present total costs, total QALYs and ICERs for each relevant comparison:

- Base case analysis using the raw Kaplan Meier [KM] data to model the "within trial" period (as an alternative to using regression models) with:
    1) KM data used to model mortality, hospitalisation and quality of life (QoL) in the model simultaneously for the trial period (timeframe of the analysis = trial follow-up period)
    2) KM data used to model mortality, hospitalisation and QoL in the model simultaneously for the trial period and with extrapolated curves from the end of the trial period onwards (lifelong analysis)
    3) KM data used to model mortality and hospitalisation in the model simultaneously for the trial period, leaving the original QoL regression model unchanged (timeframe of the analysis = trial follow-up period)
    4) KM data used to model mortality and hospitalisation in the model simultaneously for the trial period and with extrapolated curves from the end of the trial period onwards (leaving the original QoL regression model unchanged).

All analyses use the all-cause Kaplan-Meier survival for years 0-3 of the PARADIGM-HF study, and the unadjusted estimated rate of all-cause hospitalisation (0.383 and 0.439 for sacubitril valsartan and enalapril, respectively). Modelling time horizon to the trial follow-up duration is not considered an adequate timeframe to model the costs and benefits associated with a lifelong treatment for a chronic condition.

All analyses were performed using the mean cohort-level approach to evaluation, as this is consistent with the cohort-level approach to the construction of Kaplan-Meier curves for survival, average hospitalisation rates and average EQ-5D at each visit.

Questions 1) and 2) additionally use EQ-5D data presented in Table 4 to estimate changes from baseline EQ-5D by arm.

Table 4: Between-treatment analysis of the change from baseline in EQ-5D index score by treatment group (FAS)

	Sacubitril valsartan			Enalapril			Sacubitril valsartan vs. enalapril			
Month	**n**	**LSM of CFB**	**SE**	**n**	**LSM of CFB**	**SE**	**LSM difference**	**ll**	**ul**	**p-value**
4	[redacted]									
8	[redacted]									
12	[redacted]									
24	[redacted]									
36	[redacted]									

Abbreviations: CFB, change from baseline; CI, confidence interval; ll, lower limit; SE, standard error; ul, upper limit.
p-values are two-sided
Visit 9 = 4 mo, Visit 10 = 8 mo, Visit 11 = 1 yr, Visit 14 = 2 yr, Visit 17 = 3 yr
Mean difference of difference CFB= Mean difference of [CFB (sacubitril valsartan) - CFB (Enalapril)].
The analysis is performed with a repeated measures mixed-effects model including treatment, region, visit, and treatment-by-visit interaction as fixed effect factors and baseline EQ-5D value as a covariate, with a common unstructured covariance for each treatment group.

Four alternative scenarios were considered to extrapolate QoL data beyond month 36 in answer to Question 2):

- Scenario 1 – the average rate of change in months 0-36 in both model arms is applied beyond month 36.
- Scenario 2 – the average rate of change in months 0-36 in the ACEi arm is applied beyond month 36; the difference between the two model arms at month 36 is applied to inform EQ-5D in the sacubitril valsartan arm.
- Scenario 3 – the average rate of change in months 0-36 in the ACEi arm is applied beyond month 36; the average difference between the two model arms over the 36 months from the trial is applied to inform EQ-5D in the sacubitril valsartan arm.
- Scenario 4 – the average rate of change in months 0-36 in the ACEi arm is applied beyond month 36; EQ-5D in the sacubitril valsartan arm is assumed to be the same as in the ACEi arm beyond month 36.

The alternative scenarios for the first ten years of the model are presented graphically in Figure 2.

Figure 2: Alternative scenarios for Q2 (Years 0-10)

Abbreviations: ACEi, angiotensin-converting-enzyme inhibitor

Table 5: Results for B2 (using corrected model; all analyses run using cohort-level approach)

Question	Time horizon	Mortality	QoL†	Total costs		Total QALYs		ICER
				ACEi	Sacubitril valsartan	ACEi	Sacubitril valsartan	
NA	3 years	As base-case	As base-case	£5,479	£8,130	1.97	2.03	£43,320
1)	3 years	Kaplan-Meier	Table 4	£5,524	£8,131	1.93	2.00	£36,434
NA	Lifetime	As base-case	As base-case	£12,738	£20,149	4.45	4.88	£17,383*
2)	Lifetime	Kaplan-Meier	Scenario 1	£12,755	£20,030	4.26	4.87	£11,905
2)	Lifetime	Kaplan-Meier	Scenario 2	£12,755	£20,030	4.26	4.74	£15,083
2)	Lifetime	Kaplan-Meier	Scenario 3	£12,755	£20,030	4.26	4.70	£16,616
2)	Lifetime	Kaplan-Meier	Scenario 4	£12,755	£20,030	4.26	4.64	£18,905
3)	3 years	Kaplan-Meier	As base-case	£5,524	£8,131	1.93	2.00	£39,222
4)	Lifetime	Kaplan-Meier	As base-case	£12,755	£20,030	4.34	4.78	£16,754

Abbreviations: ACEi, angiotensin-converting-enzyme inhibitor; ICER, incremental cost-effectiveness ratio; NA, not applicable; QALYs, quality-adjusted life-year; QoL, quality of life.

† Scenario 1 – the average rate of change in months 0-36 in both model arms is applied beyond month 36; scenario 2 – the average rate of change in months 0-36 in the ACEi arm is applied beyond month 36 - the difference between the two model arms at month 36 is applied to inform EQ-5D in the sacubitril valsartan arm; scenario 3 – the average rate of change in months 0-36 in the ACEi arm is applied beyond month 36 - the average difference between the two model arms from the trial is applied to inform EQ-5D in the sacubitril valsartan arm; scenario 4 – the average rate of change in months 0-36 in the ACEi arm is applied beyond month 36- EQ-5D in the sacubitril valsartan arm is assumed to be the same as in the ACEi arm beyond month 36.

* Note: this is the base case ICER using the mean cohort level approach and therefore slightly differs from the ICER presented in question B1 which is the ICER based on the patient level analysis (£17,939).

B3. Priority question: The ERG has found the mortality in the model to be extremely insensitive to changes in the starting age of patients. For example when running the mean cohort model with a starting age of 82 years, the expected survival is 5.12 years and 5.58 years for sacubitril and enalapril, respectively. This compares with an expected survival of 6.89 years and 7.56 years in the base case mean cohort model for sacubitril and enalapril respectively, where the starting age in the model is 64 years. It seems implausible that starting the model nearly 20 years later decreases the expected survival by less than 2 years in both treatment arms. Please provide further rationale to explain the insensitivity to changes in starting age.

Age is not a determinant for outcome in heart failure which was shown in the subgroup analysis in PARADIGM-HF (7) and the consideration of age alone ignores other important clinical prognostic factors of mortality such as time since diagnosis of heart failure or diabetes.

Unfortunately, we are unable to exactly replicate the ERG results for the mean cohort model run with a starting age of 82 years. Potential approaches to running the mean cohort model with a starting age of 82 and resulting expected survival are presented in Table 6, and are similar to those reported by the ERG.
Please note that the analyses in Table 6 use the model settings from the Excel model submitted to NICE, and for consistency with the question do not correct for the updated baseline EQ-5D or QRS duration used on the 'Regression_Values' sheet (Question B1).

Table 6: Expected survival (using uncorrected model as sent to NICE)

Scenario	Expected survival (years)		% Change from base-case		Change from base-case (years)		Incremental sacubitril valsartan vs. ACEi (years)
	ACEi	sacubitril valsartan	ACEi	sacubitril valsartan	ACEi	sacubitril valsartan	
No adjustment	6.89	7.56	-	-	-	-	0.67
Selecting the 'User-defined patient' option and entering a mean age of 82	4.89	5.43	29%	21%	-2.00	-1.46	0.54
Filtering the patient-level data to include only patients aged >78 (n = 745, mean age = 81.92)†	5.12	5.68	26%	18%	-1.77	-1.21	0.56

Abbreviations: ACEi, angiotensin-converting-enzyme inhibitor.
† Example was chosen as mean patient age is approximately 82 yrs

In PARADIGM-HF, only 341 patients (i.e. 4%) were aged 82 or older at baseline; we therefore acknowledge that predictions of mortality for patients at or above this age are subject to greater uncertainty than for patients with ages closer to the mean baseline age in PARADIGM-HF.

However, we note that life expectancy for 82 year-old males and females in England and Wales is 7.2 years and 8.45 years, respectively (8); given the prevalence of chronic conditions in such age groups, survival estimates of approximately 5 years in a population with HFrEF appear plausible.

- Survival in patients with HF broadly aligns with average survival in patients with HF as reported in the literature; expected survival of 50% at 5 years with average age of patients at diagnosis 78 years (9).
- Life expectancy in the general population for males and females aged 64 years is 19 and 22 years, respectively (8). Conversely, model predicted survival in the PARADIGM-HF population is 7.24 years (in the ACEi arm; corrected model). Whilst life expectancy varies substantially between 64 and 82 years old in members of the general population, we would not expect to observe such magnitudes of difference in individuals with HFrEF, as consideration of age alone ignores other important clinical prognostic factors of mortality such as time since diagnosis of heart failure or diabetes (though these factors may be correlated with age), see Table 7.

Table 7: Expected survival for selected subgroups (using corrected model)

Subgroup	Expected survival (years)		Incremental sacubitril valsartan vs. ACEi (years)
	ACEi	sacubitril valsartan	
FAS	7.24	7.90	0.66
Age ≥ 75 years	5.96	6.55	0.59
Age < 75 years	7.53	8.21	0.68
Diabetes	6.60	7.23	0.63
No diabetes	7.57	8.25	0.68
≤ 1 year from diagnosis of HF	8.20	8.91	0.71
1-5 years from diagnosis of HF	6.92	7.57	0.65
> 5 years from diagnosis of HF	6.70	7.33	0.63

Abbreviations: ACEi, angiotensin-converting-enzyme inhibitor; FAS, full analysis set; HF, heart failure; NT-proBNP, N-terminal pro b-type natriuretic peptide.

- Jhund et. al. examine the efficacy and safety of sacubitril valsartan according to age in PARADIGM-HF (10). The authors examined the pre-specified efficacy and safety outcomes according to age category (years): <55 (n=1624), 55–64 (n=2655), 65–74 (n=2557), and ≥75 (n=1563).
- Jhund et al demonstrated that the HR for sacubitril valsartan compared to enalapril was consistent across the spectrum of age for the primary endpoint (CV death or hospitalization for heart failure, (p-value for interaction=0.94)) and all-cause mortality, (p-value for interaction=0.99).
- The rate of death from any cause was relatively high in the youngest patients (aged <55 years). In the remaining age categories, the rate of death increased with increasing age. The relationship was also generally flat indicating that the magnitude of the effect of sacubitril valsartan on each outcome was similar across the spectrum of age. This finding was also observed even after adjusting for differences in baseline characteristics. No interaction was found between treatment and sex or between treatment, age, and sex. Please see Figure 2 in Jhund et al (10)
- These findings demonstrate that mortality is non-linear with respect to age in PARADIGM-HF. The regression models in the economic model attempt to characterise this non-linearity using a quadratic relationship.

7. McMurray JJ, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure. N Engl J Med. 2014 Sep 11;371(11):993-1004.
8. Office for National Statistics. National Life Tables, England & Wales 2011-13. 2014 [updated 2014 24 October 2013; cited 27th June 2014]; Available from: http://www.ons.gov.uk/ons/rel/lifetables/national-life-tables/2011-2013/rft-ew.xls.
9. American Heart Association. 2013 ACCF/AHA Guideline for the Management of Heart Failure. Available at: http://circ.ahajournals.org/content/128/16/e240.extract (Accessed June 2015). 2013.
10. Jhund PS, Fu M, Bayram E, Chen C-H, Negrusz-Kawecka M, Rosenthal A, et al. Efficacy and safety of LCZ696 (sacubitril-valsartan) according to age: insights from PARADIGM-HF. Eur Heart J. 2015 2015/07/31/:ehv330.

B4. Priority question: Please run the following scenario analyses (with any necessary corrections resulting from previous clarification questions B1 and B3 incorporated into the model) and present total costs, total QALYs and ICERs for each relevant comparison:

a) Subgroup analysis including the Western population only (please run the model with both the IPD and cohort level options and in the cohort level model please change all the relevant baseline covariates in the different models to reflect this specific population)
b) Subgroup analysis including only the patients diagnosed with heart failure with reduced ejection fraction (HFrEF) for less than 1 year (please run the model with both the IPD and cohort level options and in the cohort level model please change all the relevant baseline covariates in the different models to reflect this specific population)
c) Subgroup analysis including analysis a) and b) combined.

Regression models for all-cause mortality, hospitalisation and EQ-5D were derived using only data from patients belonging to the relevant subgroup. This data has been uploaded into NICE docs; please refer to 'B4c Subgroup Models'. Baseline covariates in the statistical models were not subject to re-selection (See Page 132 of the manufacturer submission) and hence the same covariates as used in the base-case analyses were used.

Please note that the regression models were estimated including the trial-wide treatment effect of sacubitril valsartan over enalapril. Additional analyses were also run substituting the overall trial-wide treatment effects with subgroup-specific treatment effects in the regression models.

We believe using the trial-wide treatment effect is the appropriate approach because:

- In the primary analysis of PARADIGM-HF presented by McMurray et al (11), tests of interaction identified no differences in treatment effect between subgroups for sacubitril valsartan and ACEi (enalapril), although a nominally significant interaction was observed between NYHA class at randomisation and the effect of treatment on the primary composite endpoint (p=0.03).[1] Without evidence of heterogeneity between subgroups, it is appropriate to apply the overall result to each subgroup.
- The subgroup analysis presented in the manufacturer's submission also assumes a common trial-wide treatment effect based on this rationale.
- The subgroup for patients in Western Europe and duration of heart failure ≤ 1 year in particular is composed of a limited number of subjects (n=509). Resulting estimates of treatment effects should therefore be considered unreliable and exploratory only.

Results were run for each subgroup by incorporating the relevant regression models, and filtering the population on the 'PLD_PARADIGM' sheet to only include individuals from the relevant subgroup

[1] Though when considering all-cause mortality, a significant interaction was observed for diabetes status at baseline (p=[redacted]; see Table 111 of Appendix)

- For the IPD model run, filtering patients means that costs and outcomes are only averaged across the patients belonging to that subgroup
- For the mean cohort model run, filtering patients means that baseline characteristics reflect the average characteristics of patients belonging to the relevant subgroup

Table 8 and Table 9 present results based on the cohort level and IPD model respectively assuming the overall trial-wide treatment effects using the all-cause mortality approach and are consistent with the primary analysis.
Table 11 and Table 12 presents results based on the cohort level and IPD model respectively assuming the overall trial-wide treatment effects using the CV mortality approach and are slightly higher but consistent with the primary analysis.

Table 8: Results of subgroup analyses for the mean cohort model, using regression models for subgroups but treatment effects from the FAS – all-cause mortality

Mean Cohort		FAS	Western Europe	Time since diagnosis < 1 year	Western Europe & time since diagnosis < 1 year
Total costs	**ACEi**	£12,738	£14,505	£16,896	£20,222
	Sacubitril valsartan	£20,149	£21,142	£27,867	£31,913
Total QALYs	**ACEi**	4.45	4.20	6.76	7.32
	Sacubitril valsartan	4.88	4.53	7.48	7.92
Incremental cost per QALY		£17,383	£20,517	£15,193	£19,736

Abbreviations: ACEi, angiotensin-converting-enzyme inhibitor; FAS, full-analysis set; QALYs, quality-adjusted life years

Table 9: Results of subgroup analyses for the IPD, using regression models for subgroups but treatment effects from the FAS – all-cause mortality

Individual patient data		FAS	Western Europe	Time since diagnosis < 1 year	Western Europe & time since diagnosis < 1 year
Total costs	**ACEi**	£13,287	£14,867	£17,595	£21,136
	Sacubitril valsartan	£20,801	£21,572	£28,490	£32,656
Total QALYs	**ACEi**	4.60	4.30	6.94	7.39
	Sacubitril valsartan	5.02	4.62	7.59	7.92
Incremental cost per QALY		£17,939	£21,221	£16,520	£21,688

Abbreviations: ACEi, angiotensin-converting-enzyme inhibitor; FAS, full-analysis set; IPD, individual patient data; QALYs, quality-adjusted life years

Table 10: Results of subgroup analyses for the mean cohort model, using regression models for subgroups but treatment effects from the FAS – CV mortality

Individual patient data		FAS	Western Europe	Time since diagnosis < 1 year	Western Europe & time since diagnosis < 1 year
Total costs	**ACEi**	£14,824	£17,111	£20,200	£20,970
	Sacubitril valsartan	£23,871	£25,262	£32,626	£32,901
Total QALYs	**ACEi**	5.13	4.86	8.08	7.57
	Sacubitril valsartan	5.71	5.28	8.76	8.14
Incremental cost per QALY		£15,529	£19,053	£18,353	£20,949

Abbreviations: ACEi, angiotensin-converting-enzyme inhibitor; FAS, full-analysis set; QALYs, quality-adjusted life years

Table 11: Results of subgroup analyses for the IPD, using regression models for subgroups but treatment effects from the FAS – CV mortality

Individual patient data		FAS	Western Europe	Time since diagnosis < 1 year	Western Europe & time since diagnosis < 1 year
Total costs	**ACEi**	£14,814	£17,036	£19,003	£20,360
	Sacubitril valsartan	£23,458	£24,903	£30,284	£31,146
Total QALYs	**ACEi**	5.08	4.80	7.45	7.06
	Sacubitril valsartan	5.60	5.19	8.04	7.55
Incremental cost per QALY		£16,678	£20,350	£19,052	£22,436

Abbreviations: ACEi, angiotensin-converting-enzyme inhibitor; FAS, full-analysis set; IPD, individual patient data; QALYs, quality-adjusted life years

Results for the mean cohort model runs (Table 12 and Table 14 for all-cause and CV mortality respectively) and IPD model runs (Table 13 and Table 15 for all cause and CV mortality respectively) including subgroup-specific treatment effects are presented below. Using the IPD approach for all-cause mortality, ICERs vary between £11,932 for the population with ≤ 1 year since diagnosis of HF, to dominated for the combined Western Europe (and others) and ≤ 1 year since diagnosis of HF population. This variation is driven primarily by the differences in treatment effect estimated in the regression models. The variation in direction of the ICER (Western Europe ICER increases vs. FAS, while ICER decreases for ≤1 year since diagnosis vs FAS) implies that the combination subgroup does not provide credible internal consistency. This, in addition to the rationale described above regarding the use of the trial-wide treatment effect, implies that this data should be interpreted with caution. In addition, the ICER results for all-cause mortality are inconsistent with results for the CV mortality approach therefore implying that the subgroup-specific treatment effects approach should be interpreted carefully and considered unreliable and exploratory only.

Table 12: Results of subgroup analyses for the mean cohort model using regression models for subgroups and subgroup-specific treatment effect – all-cause mortality

Mean cohort		FAS	Western Europe	Time since diagnosis ≤ 1 year	Western Europe & time since diagnosis ≤ 1 year
Total costs	ACEi	£12,738	£14,505	£15,963	£20,222
	Sacubitril valsartan	£20,149	£20,136	£27,434	£27,252
Total QALYs	ACEi	4.45	4.20	7.22	7.32
	Sacubitril valsartan	4.88	4.37	8.18	7.20
Incremental cost per QALY		£17,383	£32,924	£11,932	Dominated

Abbreviations: ACEi, angiotensin-converting-enzyme inhibitor; FAS, full-analysis set; QALYs, quality-adjusted life years

Table 13: Results of subgroup analyses for the IPD model using regression models for subgroups and subgroup-specific treatment effect – all-cause mortality

Individual patient data		FAS	Western Europe	Time since diagnosis ≤ 1 year	Western Europe & time since diagnosis ≤ 1 year
Total costs	ACEi	£13,287	£13,725	£16,476	£21,136
	Sacubitril valsartan	£20,801	£19,031	£27,755	£28,153
Total QALYs	ACEi	4.60	3.94	7.36	7.39
	Sacubitril valsartan	5.02	4.10	8.23	7.31
Incremental cost per QALY		£17,939	£33,123	£12,957	Dominated

Abbreviations: ACEi, angiotensin-converting-enzyme inhibitor; FAS, full-analysis set; IPD, individual patient data; QALYs, quality-adjusted life years

Table 14: Results of subgroup analyses for the mean cohort model using regression models for subgroups and subgroup-specific treatment effect – CV mortality

Mean cohort		FAS	Western Europe	Time since diagnosis ≤ 1 year	Western Europe & time since diagnosis ≤ 1 year
Total costs	ACEi	£14,824	£17,111	£20,200	£20,970
	Sacubitril valsartan	£23,871	£24,482	£32,240	£30,814
Total QALYs	ACEi	5.13	4.86	8.08	7.57
	Sacubitril valsartan	5.71	5.19	8.90	8.08
Incremental cost per QALY		£15,529	£21,963	£14,828	£19,440

Abbreviations: ACEi, angiotensin-converting-enzyme inhibitor; FAS, full-analysis set; QALYs, quality-adjusted life years

Table 15: Results of subgroup analyses for the IPD model using regression models for subgroups and subgroup-specific treatment effect – CV mortality

Mean cohort		FAS	Western Europe	Time since diagnosis ≤ 1 year	Western Europe & time since diagnosis ≤ 1 year
Total costs	**ACEi**	£14,814	£17,036	£19,003	£20,360
	Sacubitril valsartan	£23,458	£24,162	£29,894	£29,161
Total QALYs	**ACEi**	5.08	4.80	7.45	7.06
	Sacubitril valsartan	5.60	5.11	8.16	7.50
Incremental cost per QALY		£16,678	£23,284	£15,308	£20,023

Abbreviations: ACEi, angiotensin-converting-enzyme inhibitor; FAS, full-analysis set; IPD, individual patient data; QALYs, quality-adjusted life years

11. McMurray JJ, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure. N Engl J Med. 2014 Sep 11;371(11):993-1004.

B5. Priority question: Regarding Table 56 (page 136 of the company submission):

a) Please clarify the use of the FAS population instead of the safety set for the purposes of modelling adverse events. The trial protocol specifies that "safety analyses will be performed based on the safety population" (Protocol for PARADIGM-HF, page 80).

Adverse event rates derived from the FAS population were used in the model in order to ensure consistency with the modelling of clinical and QoL outcomes (mortality, hospitalisation and EQ-5D) which were also based on the FAS population.
There are no substantial differences between the percentage of adverse events in the FAS and safety set populations (See Question B6).

b) Please provide a rationale for not including some of the hypotension, elevated serum creatinine and potassium events from the adverse event analysis (Table 3, McMurray et al. 2014 published in The New England Journal of Medicine). More specifically, the symptomatic with systolic blood pressure <90 mm Hg events, the ≥ 3.0 mg/dl serum creatinine events and the ≥ 6.0 mg/dl serum potassium events.

The examples provided above are subgroups of the overall adverse event rates and therefore are double counted in the table. I.e., 388 patients treated with enalapril had symptomatic hypotension of which 59 patients also had a systolic blood pressure below 90 mm Hg (See Table 16 – replicate of Table 3 from McMurray). Therefore, all adverse events from this table have been included in the model.

Table 16: Adverse events during randomized treatment (FAS)

Event (n, (%))	Sacubitril valsartan n=4187	Enalapril n=4212	P-value
Hypotension			
Symptomatic	588 (14.0)	388 (9.2)	<0.001
Symptomatic with systolic blood pressure <90 mm Hg	112 (2.7)	59 (1.4)	<0.001
Elevated serum creatinine			
≥2.5 mg/dl	139 (3.3)	188 (4.5)	0.007
≥3.0 mg/dl	63 (1.5)	83 (2.0)	0.10
Elevated potassium			
>5.5 mmol/litre	674 (16.1)	727 (17.3)	0.15
>6.0 mmol/litre	181 (4.3)	236 (5.6)	0.007
Cough	474 (11.3)	601 (14.3)	<0.001
Angioedema			
No treatment or use of antihistamines only	10 (0.2)	5 (0.1)	0.19
Use of catecholamines or glucocorticoids without hospitalisation	6 (0.1)	4 (0.1)	0.52
Hospitalisation without airway compromise	3 (0.1)	1 (<0.1)	0.31
Airway compromise	0	0	-

B6. Priority question: The adverse events analysis using the FAS population is not reported in the clinical study report (and only the Safety Set analysis is provided). Please provide the full analysis set of adverse events for the FAS population and explain the main differences in safety outcomes between the FAS and the safety set.

After the run-in period, a total of 8442 patients were randomized to either sacubitril valsartan or enalapril during the double-blind phase in a 1:1 ratio. Of those 8442 patients, 8432 were exposed to double-blind study medication (4203 patients exposed to sacubitril valsartan and 4229 patients exposed to enalapril) which formed the Safety Set. Ten patients (including the 6 misrandomised patients - See Question A3) did not receive study medication and were excluded from the safety set.

The full analysis set (FAS) population includes 8,399 patients (sacubitril valsartan n=4,187; enalapril n=4,212) which is 33 patients less than the Safety Set. The difference between the FAS and the randomised set is described in Question A3.

- Table 17 presents adverse events in the double-blind trial period of PARADIGM-HF for the FAS population – this table is a replica of Table 41 in the manufacturer's submission dossier which present the Safety Set population.
- Table 18 presents the most common adverse events (≥2% of patients in any group) during the double-blind period by preferred term and treatment group for the FAS population – this table is a replica of Table 42 in the manufacturer's submission dossier which present the safety set population.

There are no substantial differences between the percentage of adverse events in the FAS and safety set populations. In Table 18 which presents the adverse events with a frequency above 2% for the FAS, the largest difference between the adverse events reported from the safety set (see manufacturer's submission - Table 41) and the FAS presented here is less than or equal to 0.1% for both treatment groups.

Table 17: Summary of adverse events in the double-blind trial period of PARADIGM-HF (FAS)

Adverse events (FAS)	Sacubitril valsartan n=4,185 n (%)	Enalapril n=4,210 n (%)
≥1 adverse event	3,405 (81.36)	3,487 (82.83)
≥1 treatment related adverse event	901 (21.53)	969 (23.02)
Hypotension	428 (10.23	291 (6.91)
Hyperkalaemia	191 (4.56)	235 (5.58)
Renal impairment	112 (2.68)	178 (4.23)
Cough	64 (1.53)	161 (3.82)
≥1 serious adverse event	1,930 (46.1)	2,135 (50.7)
Cardiac failure	587 (14.03)	647 (15.37)
Pneumonia	155 (3.70)	179 (4.25)
Cardiac failure chronic	112 (2.68)	135 (3.21)
Cardiac failure congestive	112 (2.68)	139 (3.30)
AF	108 (2.58)	113 (2.68)
Cardiac death	85 (2.03)	114 (2.71)
≥1 treatment related serious adverse event	110 (2.63)	173 (4.11)
Cardiac disorders	38 (0.91)	58 (1.38)
Cardiac failure	19 (0.45)	26 (0.62)
Discontinuation due to adverse events	449 (10.7)	515 (12.2)
Cardiac failure leading to discontinuation	63 (1.51)	65 (1.54)
Deaths	727 (17.3)	846 (20.1)

Abbreviations: AF, atrial fibrillation; FAS, full analysis set

Table 18: Most common adverse events (≥2% of patients in any group) during the double-blind period by preferred term and treatment group (FAS)

Adverse events	Sacubitril valsartan n=4,185 n (%)	Enalapril n=4,210 n (%)
Hypotension	737 (17.61)[†]	504 (11.97)
Cardiac failure	727 (17.37)	829 (19.68)
Hyperkalaemia	486 (11.61)	590 (14.01)
Renal impairment	420 (10.04)	483 (11.47)
Cough	368 (8.79)	533 (12.60)
Dizziness	264 (6.31)	206 (4.89)
Atrial fibrillation	251 (6.00)	236 (5.61)
Pneumonia	227 (5.42)	234 (5.56)
Oedema peripheral	215 (5.14)	212 (5.04)
Dyspnoea	213 (5.09)	306 (7.27)
Nasopharyngitis	202 (4.83)	172 (4.09)
Upper respiratory tract infection	203 (4.85)	201 (4.77)
Urinary tract infection	198 (4.73)	192 (4.56)
Diarrhoea	193 (4.61)	189 (4.49)
Bronchitis	183 (4.37)	223 (5.30)
Angina pectoris	171 (4.09)	170 (4.04)
Anaemia	165 (3.94)	200 (4.75)
Back pain	162 (3.87)	138 (3.28)
Influenza	159 (3.80)	132 (3.14)
Hypokalaemia	139 (3.32)	107 (2.54)
Cardiac failure chronic	135 (3.23)	155 (3.68)
Cardiac failure congestive	133 (3.18)	166 (3.94)
Arthralgia	126 (3.01)	119 (2.83)
Hypertension	125 (2.99)	193 (4.58)
Fatigue	125 (2.99)	129 (3.06)
Diabetes mellitus	123 (2.94)	134 (3.18)
Gout	121 (2.89)	120 (2.85)
Renal failure	112 (2.68)	142 (3.37)
Hyperuricaemia	105 (2.51)	147 (3.49)
Ventricular tachycardia	108 (2.58)	137 (3.25)
Non cardiac chest pain	104 (2.49)	122 (2.90)
Headache	102 (2.44)	106 (2.52)
Renal failure acute	95 (2.27)	93 (2.21)
Syncope	93 (2.22)	114 (2.71)
COPD	93 (2.22)	105 (2.49)
Insomnia	91 (2.17)	91 (2.16)
Pain in extremity	91 (2.17)	99 (2.35)

Asthenia	88 (2.10)	78 (1.85)
Nausea	87 (2.08)	100 (2.38)
Cardiac death	86 (2.05)	114 (2.71)
Constipation	86 (2.05)	124 (2.95)
Pyrexia	78 (1.86)	85 (2.02)
Cardiac failure acute	72 (1.71)	100 (2.38)

Abbreviations: COPD, chronic obstructive pulmonary disease

B7. Priority question: On page 142 of the company submission it is stated that "too few angioedema events were observed to make inference regarding the effects on HRQoL". However the costs of angioedema have been considered in the economic model. For the base case analysis, please include the impact of angioedema on HRQoL for the purposes of consistency.

The total number of angioedema events that did not require hospitalisation during randomised treatment was 25 (12).[2]

A hypothetical extreme scenario was explored in which a utility decrement of 1.0 was applied for the model cycle in which an angioedema event occurred.

- The results for this scenario are presented alongside the base-case results in Table 19.
- Even in this extreme scenario, differences in the number of QALYs as compared with the base-case model are not observable at the second decimal place.
- This scenario is associated with a change in the ICER of 0.1% vs. the base-case.
- It is considered that including the effect of angioedema on EQ-5D explicitly would therefore have a negligible impact on the ICER.

Table 19: Results for base-case model based on IPD, and hypothetical extreme scenario in which a utility decrement of 1 is applied for angioedema events (using corrected model)

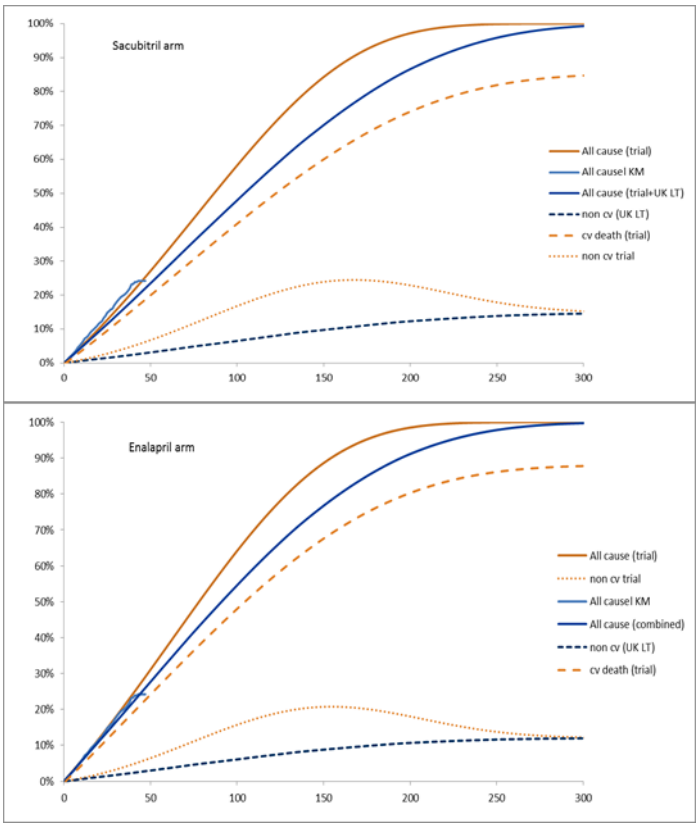
		Base-case model	Scenario in which utility decrement of 1 is applied for the model cycle in which an angioedema event occurs
Total costs	**ACEi**	£13,287	£13,287
	Sacubitril valsartan	£20,801	£20,801
Total QALYs	**ACEi**	4.5976	4.5972
	Sacubitril valsartan	5.0164	5.0156
Incremental cost per QALY		£17,939	£17,957

Abbreviations: ACEi, angiotensin-converting-enzyme inhibitor; IPD, individual patient data; QALY, quality-adjusted life years

12. McMurray JJ, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure. N Engl J Med. 2014 Sep 11;371(11):993-1004.

[2] Hospitalisation is already included within the statistical model of EQ-5D

B8. Priority question: The figures below report the mortality in the sacubitril valsartan and enalapril arms of the model respectively.



a) Please explain why the non-CV mortality is higher (in both arms of the model) when compared with UK life tables when it is reported in table 51, page 128 of the company submission that the 'exclusion of patients from the trial with presence of other diseases with life expectancy < 5 years may have led to lower rates of non-CV mortality'.

The statement 'exclusion of patients from the trial with presence of other diseases with life expectancy < 5 years may have led to lower rates of non-CV mortality' referred to the fact that non-CV mortality in the PARADIGM-HF trial is expected to be lower than non-CV mortality in the real-world HF population (due to the selection criteria specified above).
However, the ERG have correctly recognised that the use of UK life tables in the CV mortality approach has resulted in lower non-CV mortality than the non-CV mortality observed in the trial. As such, the use of life tables may not adequately address this limitation of the all-cause mortality approach (specified in Table 51) as the life tables appear to underestimate non-CV mortality compared with the trial data. For this reason, the electronic model includes functionality (see cell F83 in the 'Mortality' sheet) to include an optional standardised mortality ratio (SMR) applicable to non-CV mortality when the CV mortality approach is selected. In addition, it should be noted that the deaths in the study are adjudicated while miscoding in life tables is very likely, hence, the comparison between these two datasets should be interpreted carefully.

No reliable estimates of non-CV mortality are available in HF patients; this was highlighted in Table 51 as a limitation to the CV mortality approach using life tables.

The risk of all-cause death is higher in patients with HF compared to the general population. As shown in PARADIGM-HF, the proportion of these deaths for the HF population due to CV causes is substantially greater than non-CV causes. While, for the general population this is the opposite (see life tables in rows 81:191 of the 'Mortality' sheet in the model). Despite this, the risk of non-CV death is expected to be higher in the real world HF population compared to the general population as the HF population is more likely to be at risk for other diseases/ contraindications, e.g., renal failure, due to underlying disease and/or treatments.

b) Please explain why the non-CV mortality is higher in the sacubitril valsartan arm of the model compared with the enalapril arm.

The results of PARADIGM-HF showed that there was a slightly higher, yet non-significant proportion of non-CV deaths in the sacubitril valsartan arm (16.81%) compared to the enalapril arm (13.14%). This could be related to the statistically significant reduction in CV deaths in the sacubitril valsartan arm compared to enalapril (which may result in a slightly increased number of patients dying from non-CV causes in sacubitril valsartan). However the increase in non-CV deaths is not proportional to the reduction in CV deaths for sacubitril valsartan compared to enalapril, which is demonstrated by the statistically significant reduction in all-cause mortality for sacubitril valsartan compared to enalapril.

In the context of the base-case approach used in the Excel model, using all-cause mortality, the proportion deaths attributable to CV causes is assumed for simplicity to be constant, but different, in both model arms (78% and 83% in sacubitril valsartan and ACEi arms, respectively). This is based on the PARADIGM-HF trial where, by end of study, 78% (558/711) and 83% (693/835) of all deaths were contributable to CV causes for sacubitril valsartan and enalapril, respectively. This endpoint was included in model results for information and model validation only, and these inputs and assumptions do not affect other model outcomes. At the lifetime time horizon, when ~100% of patients have died, this results in approximately 22% and 17% of deaths being attributable to non-CV mortality in sacubitril valsartan and ACEi arms, respectively. [3]

[3] Please note – the non-CV mortality data in the model and the non- CV mortality results from the PARADIGM-HF trial are different. This is due to the fact that in the model, patients who died of unknown causes were included in the non-CV deaths for simplicity.

B9. Priority question: Please clarify any reasoning behind the decision not to include the New York Heart Association (NYHA) covariate in the hospitalisation model, as this was shown to be a prognostic factor of hospitalisations in the company's subgroup analysis.

There was a nominally significant interaction between NYHA class (I/II vs III/IV) and the effect of treatment on time to first all-cause hospitalisation (p=0.0946; Figure 3). Negative binomial models of all-cause hospitalisation including NYHA, treatment and region as fixed effects also demonstrated increased incidence of hospitalisation with higher NYHA classification at randomisation (p<0.001; Figure 4). The inclusion of an interaction term between NYHA class (I/II vs III/IV) and treatment was nominally significant (p=0.0886; Figure 5). However, after inclusion of the additional clinical variables considered for stepwise selection, NYHA (fitted as a main effect) was no longer found to be a significant predictor (p=0.452; Figure 6)

We believe that reason for this change is that the effect of worsening symptoms on hospitalisation is better captured by alternative variables including EQ-5D; such variables were instead selected by the stepwise procedure over NYHA.
Indeed, exclusion of both EQ-5D and NT-proBNP led to a highly significant effect for NYHA in a model containing all remaining clinical variables considered for stepwise selection (p=0.009; Figure 5). Using the more refined classification of NYHA (i.e. including four levels – I, II, III or IV) in the above models made no difference to the statistical inference.

Figure 3: Cox PH model of time to 1st all-cause hospitalisation. Interaction test for NYHA subgroup membership in time to first all-cause hospitalisation.

Figure 4: Negative binomial model of all-cause hospitalisation. Model of NYHA as only clinical prognostic factor

Figure 5: Negative binomial model of all-cause hospitalisation. Model of NYHA as only clinical prognostic factor, including an interaction with treatment.

Figure 6: Negative binomial model of all-cause hospitalisation. Full model including all clinical variables.

Figure 7: Negative binomial model of all-cause hospitalisation. Full model excluding EQ-5D and NT-proBNP.

B10. **Priority question:** Please report the duration of hospitalisation in the PARADIGM-HF trial, by treatment arm by time period. Please provide these data separately for cumulative hospitalisations, all CV hospitalisations and all other hospitalisations.

These data has been uploaded into NICE docs. Please refer to the confidential file named 'B10 Analyses of the number of days in hospital for All-cause, CV, and non-CV hospitalization during double-blind period by treatment group (FAS)'

B11. **Priority question:** Page 182 of the company submission states:

> 'The mixed effects model of EQ-5D displays a small but statistically significant positive effect associated with sacubitril valsartan (0.011; p=0.001), beyond the benefit due to differences in hospitalisation and adverse events. This effect is thought to be due to improvements in symptoms in sacubitril valsartan patients.'
>
> For patients treated with sacubitril valsartan, please define any symptoms which may improve, but are not related to adverse events and hospitalisations.

In PARADIGM-HF the KCCQ clinical summary score from baseline to Month 8 was measured as a secondary endpoint (See Company Submission section 4.1 page 60 and 61). This clinical summary score of the KCCQ questionnaire measures physical limitation and HF symptoms. The specific symptoms measured by this questionnaire are shortness of breath, fatigue, and, swelling in feet, ankles, and/or legs and determines stability, frequency and burden of symptoms.

In PARADIGM-HF, patients experienced increased HF symptoms and physical limitation (based on a reduced KCCQ clinical summary score); however, with sacubitril valsartan the worsening in symptoms was significantly less than with enalapril. In addition, improvement in NYHA class was more likely for patients treated with sacubitril valsartan compared with enalapril.

Figure 8 presents the change from baseline over time for the total symptom score of the KCCQ (data extracted from CSR Table 14.2-3.20). Hence, sacubitril valsartan improves the following symptoms associated with heart failure: shortness of breath, fatigue, and, swelling in feet, ankles, and/or legs.

Figure 8: Change from baseline over time for the total symptom score of the KCCQ

Abbreviations: CFB, change from baseline; KCCQ, Kansas City Cardiomyopathy Questionnaire; SE, standard error

B12. **Priority question:** Please provide:

a) Table 14.1-2.1 (mentioned on pages 21 and 90 of the clinical study report for PARADIGM-HF but not reported within the document).

These data has been uploaded into NICE docs. Please refer to the confidential file named 'B12a Table 14.1-2.1 Duration of study follow-up for double-blind period, by treatment group Randomized set'.

b) The on-treatment analysis of primary endpoint and its components (stated on page 50 of the company submission under the subheading 'Secondary analyses of the primary efficacy outcome') together with any Kaplan-Meier data available.

These data has been uploaded into NICE docs. Please refer to the confidential file named 'B12b Table 14.2-1.3 On-treatment analysis of primary endpoint and its component'.

c) Table 14.2-3.2 (mentioned in the clinical study report of TITRATION but not reported in the document). Please also provide any additional data regarding the change from baseline in New York Heart Association (NYHA) class in ACEi/ARB-treatment naïve patients.

These data has been uploaded into NICE docs. Please refer to the confidential files named

- 'B12c Table 14.2-3.2 Between-treatment analysis of change from baseline NYHA Full analysis set'.
- B12c Table 14.2-3.2.N1 Between-treatment summary of CFB FAS (ACEi/ARB naïve patients, Study CLCZ696B2228)

d) Listing 14.3-4.1.a which is mentioned in page 146 of the clinical study report for PARADIGM-HF but is not reported within the document.

These data has been uploaded into NICE docs. Please refer to the confidential file named 'B12d Listing 14.3-4.1.a Listing of reasons for permanent treatment discontinuation for run-in failure patient, by treatment group Enrolled set'.

e) KM data for CV death in the PARADIGM-HF trial.

These data has been uploaded into NICE docs. Please refer to the confidential file named 'B12e Table 14.2-2.9 Kaplan-Meier table of the cumulative event rate for confirmed cardiovascular death by treatment group Full analysis set'.

f) KM data for CV death KM data for CV death in the PARADIGM-HF trial by time from diagnosis (i.e. less than 1 year, between 1 and 5 years and more than 5 years).

These data have been uploaded on NICE docs. Please refer to the confidential file named 'B12f KM data for CV death PARADIGM-HF trial by time from diagnosis'.

B13. **Priority question:** Please explain the discrepancy in values between the mean duration of follow-up during the double-blind period reported in page 21 of the PARADIGM-HF clinical study report and the mean duration of follow-up reported in Table 12-1 of the PARADIGM-HF clinical study report. Please do the same for the median duration of follow-up reported in page 90 and Table 12-1 of the PARADIGM-HF clinical study report. Please also clarify the mean duration of follow-up that was assumed in the model calculations when adjusting for variables monthly model cycles.

The values reported on page 21 and page 90 of the PARADIGM-HF clinical study report are the values for the median duration of follow up for the randomised set. The values reported in Table 12-1 of the PARADIGM-HF clinical study report are the mean and median duration of follow-up for the safety set.

The difference between the randomised set and the safety set is described in the answer to question A3 and B6.

All major analyses used within the economic model are based on patient-level data and therefore do not require assumptions regarding the mean duration of follow-up. Adverse event rates were calculated based on total exposure time in each arm of PARADIGM-HF; 9,308 and 9,235 years in the sacubitril valsartan and enalapril arms, respectively (Table 14.2-3.5 in the CSR). In order to convert rates (of mortality, hospitalisation, AEs etc.) to monthly probabilities, a cycle length of 365.25/12=30.4375 days is assumed.

B14. **Priority question:** Please clarify whether other regression models (for example, using a logistic transformation) were considered to model quality of life (QoL).

In addition to the models estimated to examine the time trend in QoL, an ordinary least squares regression was considered in order to test the consistency of the mixed model outcomes. No transformations of the dependent variable were considered.
Mixed regression models have been used previously to model health-related quality of life (QoL) in heart failure and other cardiovascular conditions, with no transformations reported (13-15). In addition, the ivabradine manufacturer submission to NICE used a mixed regression model, with no transformations reported (16), and the ERG considered this to be clinically plausible (17).

13. Flynn KE, Lin L, Moe GW, Howlett JG, Fine LJ, Spertus JA, et al. Relationships between changes in patient-reported health status and functional capacity in outpatients with heart failure. Am Heart J. 2012 Jan;163(1):88-94 e3.
14. Lewis EF, Li Y, Pfeffer MA, Solomon SD, Weinfurt KP, Velazquez EJ, et al. Impact of cardiovascular events on change in quality of life and utilities in patients after myocardial infarction: a VALIANT study (valsartan in acute myocardial infarction). JACC Heart Fail. 2014 Apr;2(2):159-65.
15. Li Y, Neilson MP, Whellan DJ, Schulman KA, Levy WC, Reed SD. Associations between Seattle Heart Failure Model scores and health utilities: findings from HF-ACTION. J Card Fail. 2013 May;19(5):311-6.
16. Servier Laboratories Ltd. Ivabradine for the treatment of chronic heart failure. Specification for manufacturer/sponsor submission of evidence. Available at: https://www.nice.org.uk/guidance/ta267/documents/heart-failure-chronic-ivabradine-servier-laboratories-ltd2 last accessed 16 February 2015. 2012.
17. BMJ Technology Assessment Group. Ivabradine for the treatment of chronic heart failure (STA report). Available at: http://www.nice.org.uk/guidance/ta267/documents/heart-failure-chronic-ivabradine-evidence-review-group-report2 (last accessed: 15/01/15). 2012.

B15. Please provide any rationale for the assumption that mild angioedema requires 2 cardiologist outpatient visits while severe angioedema does not require any cardiologist outpatient visits.

The rationale for the assumption regarding mild and severe angioedema is based on heart failure clinical expert opinion received at a Novartis advisory board (See Appendix 14: Advisory board 2 content in main submission document). This has also been verified with individual heart failure healthcare professionals.

UK clinical experts advised that patients with milder angioedema would require 2 outpatient visits in addition to treatment with antihistamines and those patients with more severe angioedema would require an ER visit and a follow-up GP visit in addition to treatment with glucocorticoids.

B16. Please explain why elevated serum creatinine, elevated serum potassium and severe angioedema were not included in the costs of hospitalisation.

Items included in the costing of hospitalisation were based on all diagnoses with >30 reported cases in PARADIGM-HF. The costs of hospitalised angioedema were therefore not used to inform the estimate of the average cost of a hospitalisation, but would be expected to have negligible impact on this average cost. Non-hospitalised AEs were costed according to clinical expert opinion.

B17. Please clarify what date visit 778 (end of study [EOS] point) took place, and what had been the follow-up period at that point.

This data has been uploaded into NICE docs. Please refer to the confidential file named ‘B17 Table 14.1-2.1.N1 Duration of study follow-up for double-blind period for all patients alive at EOS visit 778, by treatment group Randomized set’.

B18. Please clarify what results are available from the "predictive models of NYHA developed" (Appendix 8.12, page 141) as these were not included in the company submission.

A fully functional cost-effectiveness model using a predictive model of NYHA class is available. As in TA267, the NYHA distribution was assumed to remain constant after the trial period. This assumption was required to avoid implausible distributions of NYHA occurring over time. A comparison between the base-case results for the model presented in the NICE submission and the base-case results for the model initially developed based on NYHA classes is presented in Table 20.

Both models have been updated with the corrected baseline EQ-5D score and QRS duration identified in Question B1. The results demonstrate that the approach adopted in our submitted model is comparatively conservative, resulting in a lower number of total and incremental QALYs, though differences are modest.

Table 20: Comparison of base-case results in model presented in NICE submission, and model initially developed based on NYHA class (both models updated with corrected baseline EQ-5D score)

		Model presented in NICE submission	Initial NYHA-based model
Total costs	**ACEi**	£13,287	£13,287
	Sacubitril valsartan	£20,801	£20,801
Total QALYs	**ACEi**	4.60	4.76
	Sacubitril valsartan	5.02	5.22
Incremental cost per QALY		£17,939	£16,443

Abbreviations: ACEi, angiotensin-converting-enzyme inhibitor; NYHA, New York heart association

B19. Please provide the model results including the initial set of covariates (before the backwards and forwards stepwise selection) and the results after the stepwise selection process.

Results for all-cause mortality, all-cause hospitalisation and EQ-5D are presented below. Please note that Stata's mixed command does not support stepwise selection, and therefore non-statistically significant covariates were removed manually.

Figure 9: All-cause mortality. Gompertz regression model. 'Saturated model' containing all variables considered for selection.

Gompertz regression -- log relative-hazard form

No. of subjects = 8,399 Number of obs = 8,399
No. of failures = 1,546
Time at risk = 6772604
LR chi2(41) = 608.48
Log likelihood = -5130.4871 Prob > chi2 = 0.0000

_t	Haz. Ratio	Std. Err.	z	P>|z|	[95% Conf.	Interval]
LCZ696	.858784	.0439545	-2.97	0.003	.7768148	.9494026
female	.6825627	.0478741	-5.44	0.000	.5948951	.7831496
DBT_FLG2	1.21888	.067767	3.56	0.000	1.09304	1.359208
AF_FLG1	.9469499	.0568808	-0.91	0.364	.841778	1.065262
HYP_FLG1	.9728498	.0619329	-0.43	0.665	.858731	1.102134
ACE_FLG1	.7096435	.2279051	-1.07	0.286	.378158	1.331703
ARB_FLG1	.7695363	.2467035	-0.82	0.414	.41053	1.442492
AD2_FLG2	.9880839	.0536738	-0.22	0.825	.8882916	1.099087
DGX_FLG2	1.103424	.0638979	1.70	0.089	.9850317	1.236045
LIP_FLG2	.9042808	.0512392	-1.78	0.076	.8092296	1.010497
BTA_FLG2	.7505802	.0662386	-3.25	0.001	.6313624	.8923096
STK_FLG1	1.183583	.0982591	2.03	0.042	1.00585	1.39272
CURSMK1C	1.049338	.078158	0.65	0.518	.9068074	1.21427
ICH_FLG1	1.181147	.0703049	2.80	0.005	1.051086	1.327301
allopurinol	.9371592	.1083505	-0.56	0.575	.7471382	1.175509
PHH_FLG1	1.150878	.0641248	2.52	0.012	1.031816	1.28368
cancer	.9480536	.1199731	-0.42	0.673	.7398031	1.214926
angina	.9237807	.3800334	-0.19	0.847	.4124713	2.068921
bbranchblock	1.023209	.1710645	0.14	0.891	.7373211	1.419946
race_cat2	1.370739	.1796759	2.41	0.016	1.06018	1.77227
race_cat3	1.944129	.558922	2.31	0.021	1.106652	3.415379
race_cat4	1.079647	.1197453	0.69	0.490	.8687075	1.341806
region_cat2	1.575511	.2073456	3.45	0.001	1.217304	2.039126
region_cat3	1.13045	.1287124	1.08	0.282	.9043445	1.413086
region_cat4	1.378722	.162537	2.72	0.006	1.094281	1.737099
region_cat5	.7826474	.2376442	-0.81	0.420	.4316245	1.419143
NYH_B2_cat2	1.118929	.1596361	0.79	0.431	.845985	1.479934
NYH_B2_cat3	1.373517	.2074581	2.10	0.036	1.021568	1.846719
NYH_B2_cat4	1.189328	.3685852	0.56	0.576	.6478962	2.183222
HF_FLG1_cat2	1.202312	.0811098	2.73	0.006	1.053402	1.372274
HF_FLG1_cat3	1.309982	.0958152	3.69	0.000	1.135028	1.511904
AGE1N_c	1.009136	.0029194	3.14	0.002	1.003431	1.014875
ln_egfr_c	.77106	.0750565	-2.67	0.008	.6371337	.9331377
EJF_B1_c	.9879192	.0042241	-2.84	0.004	.9796748	.9962331
ln_ntbnp_c	1.475851	.041625	13.80	0.000	1.396482	1.559732
SBP_B2_c	.9975484	.0018265	-1.34	0.180	.9939749	1.001135
HR_B2_c	1.005692	.0021903	2.61	0.009	1.001408	1.009994
sodium_c	.9698075	.0086691	-3.43	0.001	.9529644	.9869484
QRS_B2_c	1.001766	.0006082	2.91	0.004	1.000575	1.002959
BMI_B2_c	.9957554	.005772	-0.73	0.463	.9845065	1.007133
baseeq5d_GB_c	.5719011	.0665224	-4.80	0.000	.4553139	.7183414
_cons	.0001547	.0000597	-22.75	0.000	.0000727	.0003294
/gamma	.0003648	.0000813	4.49	0.000	.0002055	.0005241

Figure 10: All-cause mortality. Backwards stepwise selection procedure output.

```
. //Backwards stepwise selction
. stepwise, pr(.1): streg ${binbase} ${categories} ${contbase_c} baseeq5d_GB_c, d(gomp)
                    begin with full model
p = 0.8908 >= 0.1000  removing bbranchblock
p = 0.8460 >= 0.1000  removing angina
p = 0.8286 >= 0.1000  removing AD2_FLG2
p = 0.6769 >= 0.1000  removing cancer
p = 0.6600 >= 0.1000  removing HYP_FLG1
p = 0.5660 >= 0.1000  removing NYH_B2_cat4
p = 0.5550 >= 0.1000  removing allopurinol
p = 0.5420 >= 0.1000  removing NYH_B2_cat2
p = 0.4955 >= 0.1000  removing CURSMK1C
p = 0.4739 >= 0.1000  removing race_cat4
p = 0.4290 >= 0.1000  removing region_cat5
p = 0.4203 >= 0.1000  removing BMI_B2_c
p = 0.4088 >= 0.1000  removing ARB_FLG1
p = 0.2643 >= 0.1000  removing AF_FLG1
p = 0.1934 >= 0.1000  removing ACE_FLG1
p = 0.1734 >= 0.1000  removing SBP_B2_c
p = 0.1855 >= 0.1000  removing region_cat3
p = 0.1112 >= 0.1000  removing DGX_FLG2

Gompertz regression -- log relative-hazard form

No. of subjects =        8,399                 Number of obs    =       8,399
No. of failures =        1,546
Time at risk    =      6772604
                                               LR chi2(23)      =      594.94
Log likelihood  =   -5137.2545                 Prob > chi2      =      0.0000
```

_t	Haz. Ratio	Std. Err.	z	P>|z|	[95% Conf.	Interval]
LCZ696	.8580987	.0438557	-2.99	0.003	.7763079	.9485068
female	.6850644	.0476072	-5.44	0.000	.5978315	.7850259
DBT_FLG2	1.202428	.0649531	3.41	0.001	1.08163	1.336718
NYH_B2_cat3	1.237756	.075173	3.51	0.000	1.098851	1.39422
HR_B2_c	1.005673	.0021633	2.63	0.009	1.001442	1.009922
EJF_B1_c	.9864896	.0040974	-3.27	0.001	.9784914	.9945531
HF_FLG1_cat3	1.312813	.0946718	3.77	0.000	1.139776	1.51212
QRS_B2_c	1.001781	.0005897	3.02	0.003	1.000626	1.002938
region_cat4	1.243366	.0903061	3.00	0.003	1.07839	1.43358
LIP_FLG2	.9008678	.0507584	-1.85	0.064	.8066796	1.006053
BTA_FLG2	.7366398	.0647175	-3.48	0.001	.6201159	.8750592
STK_FLG1	1.180206	.0976316	2.00	0.045	1.003559	1.387947
ln_egfr_c	.7895725	.0754266	-2.47	0.013	.6547539	.9521512
ICH_FLG1	1.178111	.0692167	2.79	0.005	1.049969	1.321893
ln_ntbnp_c	1.483549	.0404529	14.47	0.000	1.406344	1.564992
PHH_FLG1	1.147292	.0632726	2.49	0.013	1.029747	1.278254
sodium_c	.9701816	.0085245	-3.45	0.001	.9536168	.9870341
HF_FLG1_cat2	1.208465	.081156	2.82	0.005	1.059426	1.378471
baseeq5d_GB_c	.5719038	.0654812	-4.88	0.000	.4569441	.7157854
race_cat2	1.291003	.158019	2.09	0.037	1.015641	1.641023
race_cat3	1.506215	.1255364	4.91	0.000	1.279214	1.773499
AGE1N_c	1.008668	.0027138	3.21	0.001	1.003363	1.014001
region_cat2	1.573732	.1243007	5.74	0.000	1.348028	1.837227
_cons	.0001364	.0000179	-67.83	0.000	.0001055	.0001764
/gamma	.0003607	.000081	4.45	0.000	.0002019	.0005194

Figure 11: All-cause hospitalisation. Negative binomial regression model. 'Saturated model' containing all variables considered for selection.

Negative binomial regression — Number of obs = 8,399
LR chi2(42) = 952.15
Dispersion = mean — Prob > chi2 = 0.0000
Log likelihood = -10713.802 — Pseudo R2 = 0.0425

tn_hos	IRR	Std. Err.	z	P>|z|	[95% Conf.	Interval]
age2	1.000452	.0001075	4.21	0.000	1.000241	1.000663
LCZ696	.8375473	.0318236	-4.67	0.000	.7774401	.9023017
female	.7424431	.036656	-6.03	0.000	.6739653	.8178786
DBT_FLG2	1.388328	.0576978	7.89	0.000	1.279726	1.506147
AF_FLG1	1.097453	.0481221	2.12	0.034	1.007075	1.195942
HYP_FLG1	1.063657	.0512206	1.28	0.200	.9678585	1.168938
ACE_FLG1	.8112173	.1810801	-0.94	0.349	.5237594	1.256443
ARB_FLG1	.9027258	.200579	-0.46	0.645	.5840166	1.395361
AD2_FLG2	.9561659	.0384651	-1.11	0.265	.8836712	1.034608
DGX_FLG2	.9903755	.0446108	-0.21	0.830	.9066885	1.081787
LIP_FLG2	1.076909	.0465501	1.71	0.087	.9894304	1.172122
BTA_FLG2	.7216943	.0523939	-4.49	0.000	.6259754	.8320496
STK_FLG1	1.155332	.0751725	2.22	0.026	1.017004	1.312475
CURSMK1C	1.242876	.0671441	4.02	0.000	1.118003	1.381695
ICH_FLG1	1.090579	.0488431	1.94	0.053	.9989291	1.190637
allopurinol	1.117183	.0937527	1.32	0.187	.9477476	1.316911
PHH_FLG1	1.384896	.0569513	7.92	0.000	1.277654	1.501141
cancer	1.174207	.1030782	1.83	0.067	.9886023	1.394658
angina	1.464437	.3960592	1.41	0.158	.8619099	2.488166
bbranchblock	1.186768	.1446781	1.40	0.160	.9345367	1.507076
race_cat2	1.16765	.1118695	1.62	0.106	.9677463	1.408848
race_cat3	1.074652	.2558351	0.30	0.762	.6739504	1.713593
race_cat4	.9244216	.0797077	-0.91	0.362	.7806848	1.094623
region_cat2	.7668151	.0742378	-2.74	0.006	.6342831	.9270394
region_cat3	1.072342	.0824828	0.91	0.364	.9222748	1.246828
region_cat4	.7714565	.0630176	-3.18	0.001	.6573243	.9054056
region_cat5	.7060825	.1753605	-1.40	0.161	.4339639	1.148834
NYH_B2_cat2	1.033549	.1001495	0.34	0.733	.8547728	1.249716
NYH_B2_cat3	1.073242	.1127204	0.67	0.501	.8735704	1.318553
NYH_B2_cat4	.9327653	.2213462	-0.29	0.769	.5858431	1.485126
HF_FLG1_cat2	1.290582	.0634964	5.18	0.000	1.171943	1.42123
HF_FLG1_cat3	1.474187	.0775341	7.38	0.000	1.329793	1.63426
AGE1N_c	.9478166	.0127481	-3.98	0.000	.9231572	.9731348
ln_egfr_c	.6245131	.0458255	-6.42	0.000	.5408566	.7211091
EJF_B1_c	.9993518	.0032515	-0.20	0.842	.9929993	1.005745
ln_ntbnp_c	1.257089	.0266364	10.80	0.000	1.205951	1.310394
SBP_B2_c	.9981944	.0013241	-1.36	0.173	.9956025	1.000793
HR_B2_c	1.006618	.0016337	4.06	0.000	1.003421	1.009825
sodium_c	.9783525	.0065241	-3.28	0.001	.9656488	.9912234
QRS_B2_c	1.002969	.0005832	5.10	0.000	1.001826	1.004112
BMI_B2_c	1.001224	.00398	0.31	0.758	.993454	1.009055
baseeq5d_GB_c	.6278423	.0579605	-5.04	0.000	.5239264	.752369
_cons	.0587583	.031136	-5.35	0.000	.0207978	.1660049
ln(exposure)	1	(exposure)				
/lnalpha	.4215878	.0360481			.3509348	.4922409
alpha	1.52438	.0549511			1.420395	1.635978

LR test of alpha=0: chibar2(01) = 3291.41 — Prob >= chibar2 = 0.000

Figure 12: All-cause hospitalisation. Backwards stepwise selection procedure output.

```
. stepwise, pr(.1): nbreg tn_hos age2 ${binbase} ${categories} ${contbase_c} baseeq5d_GB_c, irr exp(exposure)
                    begin with full model
p = 0.8420 >= 0.1000  removing EJF_B1_c
p = 0.8391 >= 0.1000  removing DGX_FLG2
p = 0.7637 >= 0.1000  removing NYH_B2_cat4
p = 0.7609 >= 0.1000  removing race_cat3
p = 0.7651 >= 0.1000  removing BMI_B2_c
p = 0.6361 >= 0.1000  removing ARB_FLG1
p = 0.6188 >= 0.1000  removing NYH_B2_cat2
p = 0.3724 >= 0.1000  removing region_cat3
p = 0.3567 >= 0.1000  removing NYH_B2_cat3
p = 0.3546 >= 0.1000  removing race_cat4
p = 0.3501 >= 0.1000  removing AD2_FLG2
p = 0.2242 >= 0.1000  removing SBP_B2_c
p = 0.3217 >= 0.1000  removing HYP_FLG1
p = 0.1626 >= 0.1000  removing bbranchblock
p = 0.1672 >= 0.1000  removing allopurinol
p = 0.1470 >= 0.1000  removing angina

Negative binomial regression                    Number of obs     =      8,399
                                                LR chi2(26)       =     939.41
Dispersion     = mean                           Prob > chi2       =     0.0000
Log likelihood =  -10720.17                     Pseudo R2         =     0.0420

------------------------------------------------------------------------------
       tn_hos |        IRR   Std. Err.      z    P>|z|     [95% Conf. Interval]
--------------+---------------------------------------------------------------
         age2 |   1.000447   .0001069     4.18   0.000     1.000237    1.000656
       LCZ696 |    .841642   .0319153    -4.55   0.000     .7813571     .906578
       female |   .7396104   .0364323    -6.12   0.000     .6715431     .814577
     DBT_FLG2 |   1.394076   .0561436     8.25   0.000     1.288267    1.508575
      AF_FLG1 |   1.104142    .046051     2.38   0.018     1.017475    1.198192
     QRS_B2_c |   1.003075   .0005712     5.39   0.000     1.001956    1.004195
     ACE_FLG1 |   .8978809   .0419561    -2.31   0.021     .8193017    .9839965
 HF_FLG1_cat2 |    1.29887   .0637572     5.33   0.000     1.179732    1.430041
 HF_FLG1_cat3 |   1.487526   .0773095     7.64   0.000     1.343464    1.647036
      HR_B2_c |   1.006874   .0016245     4.25   0.000     1.003696    1.010063
     LIP_FLG2 |   1.078108    .046264     1.75   0.080     .9911411    1.172707
     BTA_FLG2 |   .7206981   .0521705    -4.52   0.000     .6253682    .8305598
     STK_FLG1 |   1.153904   .0749476     2.20   0.028     1.015975    1.310558
     CURSMK1C |   1.235902   .0665619     3.93   0.000     1.112093    1.373496
      ICH_FLG1 |   1.095452     .04867     2.05   0.040     1.004096     1.19512
   ln_ntbnp_c |   1.254709   .0254217    11.20   0.000      1.20586    1.305537
     PHH_FLG1 |   1.388424   .0563336     8.09   0.000     1.282288    1.503345
       cancer |   1.174194   .1027595     1.83   0.067     .9891159    1.393904
   region_cat5 |   .7106503   .0449117    -5.40   0.000     .6278584    .8043595
    ln_egfr_c |   .6133355    .044476    -6.74   0.000     .5320755    .7070058
    race_cat2 |    1.17878   .1072479     1.81   0.071     .9862536    1.408889
     sodium_c |   .9791702   .0064377    -3.20   0.001     .9666335    .9918695
      AGE1N_c |   .9486107   .0126958    -3.94   0.000     .9240509    .9738233
   region_cat2 |   .6877742   .0430454    -5.98   0.000      .608376    .7775345
baseeq5d_GB_c |   .6168977   .0551412    -5.40   0.000     .5177603    .7350172
   region_cat4 |   .7282468   .0359551    -6.42   0.000     .6610783    .8022398
         _cons |   .0607291    .028394    -5.99   0.000     .0242893    .1518372
 ln(exposure) |          1  (exposure)
--------------+---------------------------------------------------------------
      /lnalpha |   .4250948   .0360052                      .3545259    .4956636
--------------+---------------------------------------------------------------
         alpha |   1.529735   .0550784                      1.425505    1.641587
------------------------------------------------------------------------------
LR test of alpha=0: chibar2(01) =  3310.19                Prob >= chibar2 = 0.000
```

Figure 13: EQ-5D. Mixed model. 'Saturated model' containing all variables considered for selection.

```
. mixed eq5d baseeq5d_c i.(${binbase} ${catbase}) ${contbase_c} i.achosp0to30 i.achosp30to90 cough hypotension _t|| SID1A: if VIS1N!=5

Performing EM optimization:

Performing gradient-based optimization:

Iteration 0:   log likelihood =  12111.484
Iteration 1:   log likelihood =  12111.484

Computing standard errors:

Mixed-effects ML regression                     Number of obs     =     34,208
Group variable: SID1A                           Number of groups  =      7,908

                                                Obs per group:
                                                              min =          1
                                                              avg =        4.3
                                                              max =          7

                                                Wald chi2(46)     =    7131.09
Log likelihood =  12111.484                     Prob > chi2       =     0.0000
```

eq5d	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
baseeq5d_c	.4886673	.0079704	61.31	0.000	.4730456	.504289
1.LCZ696	.0105168	.0031719	3.32	0.001	.0043	.0167337
female						
female	-.031202	.0040092	-7.78	0.000	-.0390599	-.023344
1.DBT_FLG2	-.0144657	.0035394	-4.09	0.000	-.0214027	-.0075286
1.AF_FLG1	-.004414	.0037827	-1.17	0.243	-.011828	.0030001
1.HYP_FLG1	.001774	.0039437	0.45	0.653	-.0059555	.0095035
1.ACE_FLG1	-.0102751	.0184073	-0.56	0.577	-.0463528	.0258025
1.ARB_FLG1	-.0115082	.0183196	-0.63	0.530	-.047414	.0243975
1.AD2_FLG2	.0006093	.0033733	0.18	0.857	-.0060022	.0072208
1.DGX_FLG2	.0033031	.0037673	0.88	0.381	-.0040807	.0106868
1.LIP_FLG2	.0015212	.0035698	0.43	0.670	-.0054755	.0085178
1.BTA_FLG2	.00935	.0063897	1.46	0.143	-.0031736	.0218736
1.STK_FLG1	-.0117543	.005748	-2.04	0.041	-.0230203	-.0004883
1.CURSMK1C	-.0128162	.0046383	-2.76	0.006	-.0219071	-.0037254
1.ICH_FLG1	-.0075755	.003709	-2.04	0.041	-.0148451	-.000306
1.allopurinol	.00502	.0074977	0.67	0.503	-.0096751	.0197152
1.PHH_FLG1	-.0017024	.0033637	-0.51	0.613	-.0082951	.0048903
1.cancer	-.0081046	.0077672	-1.04	0.297	-.0233281	.0071188
1.angina	-.019278	.0243215	-0.79	0.428	-.0669473	.0283913
1.bbranchblock	.0032438	.0106943	0.30	0.762	-.0177167	.0242042
race						
Black	.0071022	.0080792	0.88	0.379	-.0087327	.022937
Asian	-.0203348	.0202259	-1.01	0.315	-.0599769	.0193072
Other	-.0012348	.0069508	-0.18	0.859	-.0148582	.0123886
region						
Latin America	.04243	.0082566	5.14	0.000	.0262475	.0586126
Western Europe	.0145137	.0069876	2.08	0.038	.0008182	.0282092
Central Europe	.0022435	.0072867	0.31	0.758	-.0120382	.0165251
Asia-Pacific	.0632037	.0211748	2.98	0.003	.0217019	.1047056
NYH_B2						
II	-.0079042	.0076671	-1.03	0.303	-.0229313	.007123
III	-.0493423	.0084763	-5.82	0.000	-.0659556	-.032729
IV	-.0889326	.0206162	-4.31	0.000	-.1293396	-.0485257
HF_FLG1						
2	-.0166334	.003944	-4.22	0.000	-.0243634	-.0089033
3	-.0228722	.0043489	-5.26	0.000	-.0313958	-.0143486
AGE1N_c	-.0007071	.0001796	-3.94	0.000	-.0010591	-.000355
ln_egfr_c	-.0024225	.0062198	-0.39	0.697	-.0146132	.0097681
EJF_B1_c	-.0003826	.0002806	-1.36	0.173	-.0009325	.0001674
ln_ntbnp_c	-.0096198	.0017992	-5.35	0.000	-.0131462	-.0060933
SBP_B2_c	.0000588	.0001128	0.52	0.602	-.0001623	.0002799
HR_B2_c	-.0002641	.00014	-1.89	0.059	-.0005385	.0000103
sodium_c	.0010438	.0005776	1.81	0.071	-.0000882	.0021758
QRS_B2_c	-.0000222	.0000476	-0.47	0.641	-.0001154	.000071
BMI_B2_c	-.0019479	.0003411	-5.71	0.000	-.0026165	-.0012794
1.achosp0to30	-.1046419	.0057213	-18.29	0.000	-.1158553	-.0934284
1.achosp30to90	-.0537626	.0043431	-12.38	0.000	-.0622748	-.0452503
cough	-.0279855	.0065378	-4.28	0.000	-.0407994	-.0151716
hypotension	-.0290059	.0063141	-4.59	0.000	-.0413814	-.0166305
_t	-.0078448	.0009214	-8.51	0.000	-.0096506	-.0060389
_cons	.8207699	.0225453	36.41	0.000	.7765818	.8649579

Random-effects Parameters	Estimate	Std. Err.	[95% Conf.	Interval]
SID1A: Identity				
var(_cons)	.0144068	.000323	.0137873	.015054
var(Residual)	.0211416	.0001852	.0207818	.0215076

LR test vs. linear model: chibar2(01) = 6669.96 Prob >= chibar2 = 0.0000

B20. The ERG found some discrepancies between the values reported in the company submission and in the Excel model results. Please provide the correct values in the table below.

Please note that the data in Table 21 use the model settings from the Excel model submitted to NICE, and for consistency with the question do not correct for the updated baseline EQ-5D and QRS value used on the 'Regression_Values' sheet (Question B1).

Table 21: Corrected values for discrepancies between results in Excel model and manufacturer's submission.

Outcomes/Analysis	Reference in the model	Company submission	Correct values
The correct values are presented in p167 Table 86. The discrepancy in the values between Table 86 and the 'Reporting' and 'Results' sheets is due to the hazard ratio for CV mortality in ARB vs. ACEi comparison ('ARB_comparison' sheet, cell G12) was not set at the default value (1.033) from the NMA (see Table 29 of manufacturer submission). If this hazard ratio is manually entered in the cell specified above, and the CV mortality scenario selected, the model results will then match with those outlined in Table 86 of the manufacturer submission.			
Total costs (alternative results vs ARBs)	'Reporting' C4:C5	p167 Table 86	£13,837
Total LYG (alternative results vs ARBs)	'Results' J8:L8	p167 Table 86	6.63
Total QALYs (alternative results vs ARBs)	'Reporting' D4:D5	p167 Table 86	4.87
Incremental costs(alternative results vs ARBs)	'Reporting' E5	p167 Table 86	£9,569
Incremental LYG(alternative results vs ARBs)	'Results' N8	p167 Table 86	0.71
Incremental QALYs(alternative results vs ARBs)	'Reporting' F6	p167 Table 86	0.57
ICER (per QALY gained) (alternative results vs ARBs)	'Reporting' G5	p167 Table 86	£16,817
The QALYs in Table 99 of the submission were misaligned (i.e. QALY result in row 10 should have been in row 9 of the table, etc.) The correct values are specified in the model 'Sensitivity Analysis' sheet. The ICERs specified in the submission are correct.			
Annual rate of decline in EQ-5D doubled	'Sensitivity Analysis' G54:K54	P189 Table 99	QALYs: Sacubitril valsartan: 4.61 ACEi:4.23
No decline in EQ-5D over time	'Sensitivity Analysis' G55:K55	P189 Table 99	QALYs: Sacubitril valsartan: 5.13 ACEi:4.69
No decline in EQ-5D after 5 years	'Sensitivity Analysis' G56:K56	P189 Table 99	QALYs: Sacubitril valsartan: 4.96 ACEi:4.53
No decline in EQ-5D after 10 years	'Sensitivity Analysis' G57:K57	P189 Table 99	QALYs: Sacubitril valsartan: 4.89 ACEi:4.48
Effect of sacubitril valsartan on EQ-5D (beyond differences in hospitalisation / adverse event rates) assumed to be zero	'Sensitivity Analysis' G58:K58	P189 Table 99	QALYs: Sacubitril valsartan: 4.80 ACEi:4.46
Effect of sacubitril valsartan on	'Sensitivity Analysis'	P189 Table 99	QALYs:

hospitalisation rates assumed to apply to HF hospitalisation only	G59:K59		Sacubitril valsartan: 4.87 ACEi:4.46
Effect of hospitalisation on EQ-5D assumed to be zero	'Sensitivity Analysis' G61:K61	P189 Table 99	QALYs: Sacubitril valsartan: 4.90 ACEi:4.49
Sacubitril valsartan treatment effects assumed to cease at year 5	'Sensitivity Analysis' G62:K62	P189 Table 99	QALYs: Sacubitril valsartan: 4.69 ACEi:4.46
Sacubitril valsartan treatment effects assumed to cease at year 10	'Sensitivity Analysis' G63:K63	P189 Table 99	QALYs: Sacubitril valsartan: 4.81 ACEi:4.46
Treatment discontinuation considered over lifetime time horizon	'Sensitivity Analysis' G64:K64	P189 Table 99	QALYs: Sacubitril valsartan: 4.75 ACEi:4.46
Treatment discontinuation considered up to year 3	'Sensitivity Analysis' G65:K65	P189 Table 99	QALYs: Sacubitril valsartan: 4.80 ACEi:4.46
Treatment discontinuation assumed to result in reduced therapy costs; efficacy estimates as in trial	'Sensitivity Analysis' G66:K66	P189 Table 99	QALYs: Sacubitril valsartan: 4.87 ACEi:4.46

Section C:

NICE has noted there is a large volume of information marked as confidential in the company submission. A separate request will be sent to the company, however please consider lifting the confidentiality status of the data in the submission in advance of receiving a formal request.

We appreciate that there are substantial data currently marked as academic or commercial-in-confidence, however we feel this is necessary to maintain the confidentiality of unpublished data and data that is currently commercially sensitive data. The following text explains the rationale for the confidentiality status of data included in our submission. As outlined below, the availability of the list price prior to release of draft guidance by NICE will enable a significant amount of the CiC mark up to be removed.

Academic in confidence

- Unpublished clinical trial data (PARADIGM-HF and TITRATION) is marked academic-in-confidence to prevent plagiarism of study protocols and unpublished results
- Unpublished research performed by Novartis including the ASSESS study and SR and NMA, CPRD analysis (publication aimed for Q2 2016 , Q4 2015, and Q4 2015 respectively)

Commercial in confidence

- CHMP/Marketing authorisation indication and dates are subject to change
- EAMS is now been published and the CiC has been removed
- Market share and patient treated data is commercially sensitive until 5 years post TAG
- List price is commercially sensitive and is anticipated to be available in Q4 2015; Novartis will remove all CiC mark-up for costs and QALYs at this stage, prior to release of draft guidance by NICE.

Additional confidential reference uploaded to NICE docs

- A2 Novartis_2014_CSR_PARADIGM-HF PART 1
- A2 Novartis 2014 CSR PARADIGM-HF PART 2
- A5 NMA model codes and data sets
- A7 Table 1 14.3.1-1.17 Change for patients serum potassium 5.5molL 6 molL 6.5 mmolL safety set.
- A9 Section 12.4 Prefer term for distinguishing CV hospitalisation and non CV hospitalisation
- B4c Subgroup models
- B10 Analyses of the number of days in hospital for All-cause, CV, and non-CV hospitalization during double-blind period by treatment group (FAS))
- B12a Table 14.1-2.1 Duration of study follow-up for double-blind period, by treatment group Randomized set
- B12b Table 14.2-1.3 On-treatment analysis of primary endpoint and its component'
- B12c Table 14.2-3.2 Between-treatment analysis of change from baseline NYHA Full analysis set'.
- B12c Table 14.2-3.2.N1 Between-treatment summary of CFB NYHA FAS ACEi/ARB naïve patients
- B12d Listing 14.3-4.1.a Listing of reasons for permanent treatment discontinuation for run-in failure patient, by treatment group Enrolled set'.
- B12e Table 14.2-2.9 Kaplan-Meier table of the cumulative event rate for confirmed cardiovascular death by treatment group Full analysis set'.
- B12f KM data for CV death PARADIGM-HF trial by time from diagnosis'.
- B17 Table 14.1-2.1.N1 Duration of study follow-up for double-blind period for all patients alive at EOS visit 778, by treatment group Randomized set

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Sacubitril Valsartan for Heart Failure with Systolic Dysfunction

[ID822]

Novartis Pharmaceuticals UK Ltd

Addendum – update to cost-effectiveness results (Section 5.7-5.10 of company submission)

[29 September 2015]

File name	Version	Contains confidential information	Date
Company submission STA - Addendum	2.0	Yes	27 November 2015

Contents

List of Tables

List of Figures

Introduction

This addendum was developed following two errors in the Excel model submitted by Novartis Pharmaceuticals Ltd identified in the ERG clarification letter entitled 'ID822 Sacubitril CHF NICE Clarification letter to PM for Company [noACIC]'.

Specifically, the errors were identified in the response to Question B1 'Please clarify if the baseline utility value of 0.81 used in the model ("Regression_Values" sheet, cell I47) is the correct value as the submission states that the baseline utility value at randomisation was 0.78. If the incorrect value has been used in the model, please clarify the outputs from the model run using the corrected baseline utility value of 0.78.'

The errors identified were in the 'Regression_Values' sheet of the Excel model submitted and were as follows:

- Cell I47 - The baseline utility value of 0.81 should be 0.7798.
- Cell I27 - The mean QRS duration value of 117.3592 should be 117.3589

Running the model using these corrected values leads to a change in all model results presented in the original company submission.

This addendum presents the cost-effectiveness model results using the correct baseline utility and mean QRS duration value. The structure of this addendum follows the results sections from Section 5.7 to 5.10 of the company submission.

In addition, an overview section has been included that shows the difference between the cost per QALY gained results presented in the company submission versus this addendum.

1 Base case results

1.1.1 *Base case incremental cost effectiveness analysis results – all-cause mortality*

1.1.1.1 Base case results – primary comparison versus ACEi

Table 1: Base case results vs. ACEi (Table 72 in submission)

Technologies	Total			Incremental			ICER (£) vs. ACEi
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	
ACEi	£13,287	6.08	4.60	-	-	-	-
Sacubitril valsartan	£20,801	6.56	5.02	£7,514	0.48	0.42	£17,939

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

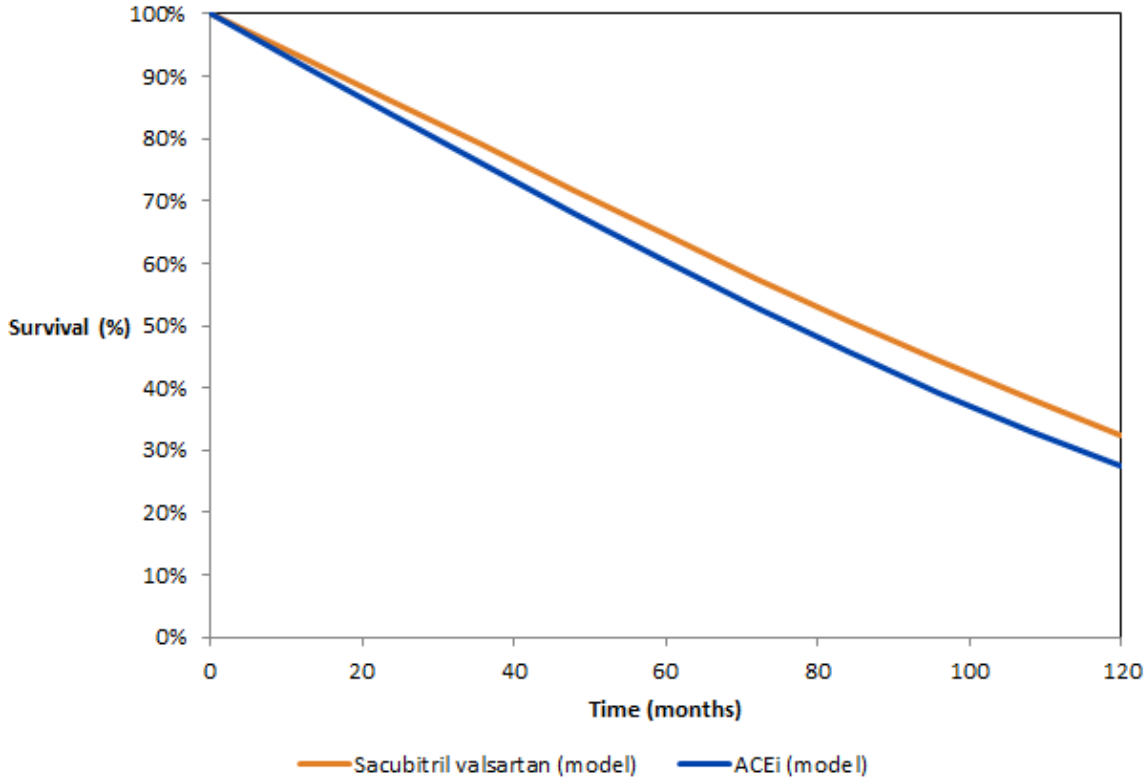
Clinical outcomes

Table 2: Mortality outcomes (Table 73 in submission)

Component	ACEi	Sacubitril valsartan	Incremental†
CV mortality (%) at year 2	13%	11%	-2%
CV mortality (%) at year 5	33%	28%	-5%
CV mortality (%) at year 10	60%	53%	-7%
All-cause mortality (%) at year 2	16%	14%	-2%
All-cause mortality (%) at year 5	40%	35%	-4%
All-cause mortality (%) at year 10	72%	68%	-5%
Expected survival (years)	7.24	7.90	0.66

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; CV, cardiovascular.
†Values shown in the 'Incremental' column are absolute differences (i.e. differences in percentage points) and not relative percentage changes.

Figure 1: Visual representation of the model mortality outcomes (Figure 30 in submission)



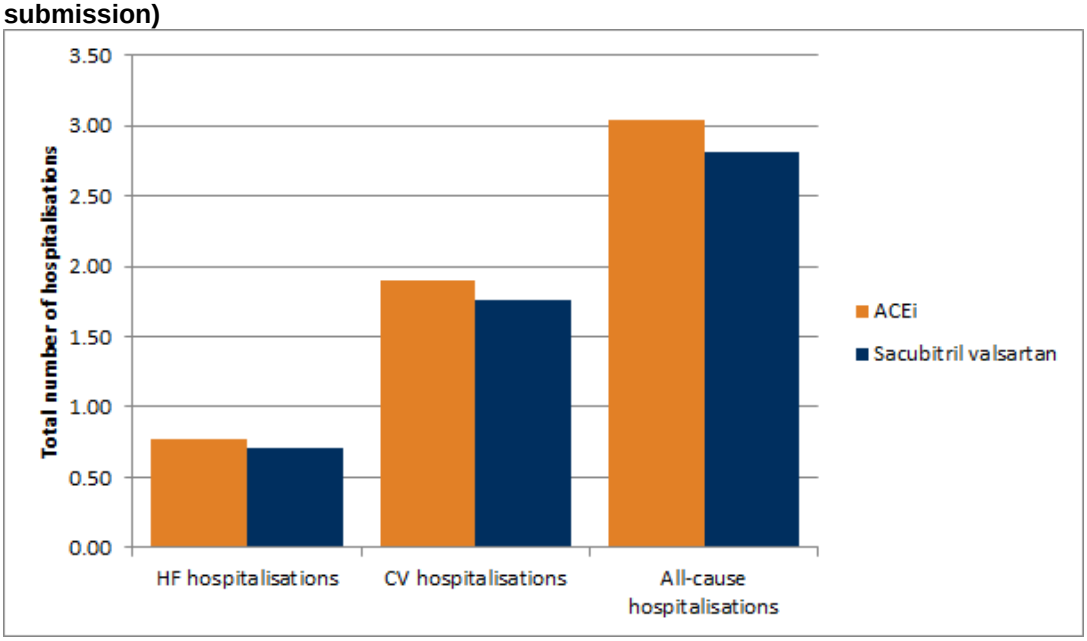
Abbreviations: ACEi, angiotensin-converting enzyme inhibitor;

Table 3: Hospitalisation outcomes (Table 74 in submission)

Component	ACEi	Sacubitril valsartan	Incremental
HF hospitalisations	0.77	0.71	-0.06
CV hospitalisations	1.90	1.76	-0.14
All-cause hospitalisations	3.04	2.81	-0.22
No. of hospitalisations per year	0.42	0.36	-0.06

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; CV, cardiovascular; HF, heart failure.

Figure 2: Visual representation of the model hospitalisation outcomes (Figure 31 in submission)



Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; CV, cardiovascular; HF, heart failure.

1.1.1.2 Base case results - secondary comparison versus ARBs

Table 4: Summary of incremental cost-effectiveness vs. ARB (Table 75 in submission)

Technologies	Total			Incremental			ICER (£) vs. ARB
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	
ARB	£12,288	5.94	4.50	-	-	-	-
Sacubitril valsartan	£20,801	6.56	5.02	£8,513	0.62	0.52	£16,481

Abbreviations: ARB, angiotensin receptor blocker; ICER, incremental cost-effectiveness ratio; LYG, Life Years Gained; QALYs, Quality Adjusted Life Years

Clinical outcomes

Table 5: Mortality outcomes for comparison vs. ARB (Table 76 in submission)

Component	ARB	Sacubitril valsartan	Incremental†
CV mortality (%) at year 2	14%	11%	-3%
CV mortality (%) at year 5	34%	28%	-6%
CV mortality (%) at year 10	61%	53%	-8%
All-cause mortality (%) at year 2	17%	14%	-3%
All-cause mortality (%) at year 5	41%	35%	-6%
All-cause mortality (%) at year 10	74%	68%	-6%
Expected survival (years)	7.05	7.90	0.85

Abbreviations: ARB, angiotensin receptor blocker; CV, cardiovascular.
†Values shown in the 'Incremental' column are absolute differences (i.e. differences in percentage points) and not relative percentage changes.

Table 6: Hospitalisation outcomes for comparison vs. ARB (Table 77 in submission)

Component	ARB	Sacubitril valsartan	Incremental
HF hospitalisations	0.68	0.71	0.04
CV hospitalisations	1.66	1.76	0.09
All-cause hospitalisations	2.67	2.81	0.15
No. of hospitalisations per year	0.38	0.36	-0.02

Abbreviations: ARB, angiotensin receptor blocker; CV, cardiovascular; HF, heart failure.
Note: Hospitalisations are lower in the ARB arm compared to sacubitril valsartan as this is based on 'lifetime' hospitalisations and patients on ARB have a lower life expectancy. Number of hospitalisation per year is reduced with sacubitril valsartan as was shown in the NMA.

1.1.2 *For the outcomes highlighted in the decision problem (see section 3), provide the corresponding outcomes from the model and compare them with clinically important outcomes such as those reported in clinical trials, as suggested in the table below. Discuss reasons for any differences between the modelled results in the cost-effectiveness analysis and the observed results in the clinical trials (for example, adjustment for crossover*

Mortality

Table 7: Predicted vs. observed survival for sacubitril valsartan (Table 78 in submission)

Month	Predicted survival from model (Sacubitril valsartan)	Observed survival from PARADIGM-HF (Sacubitril valsartan)
0	100%	100%
3	98%	98%
6	97%	97%
9	95%	95%
12	93%	93%
15	91%	91%
18	90%	90%
21	88%	88%
24	86%	86%
27	84%	84%
30	82%	82%
33	81%	81%
36	79%	79%

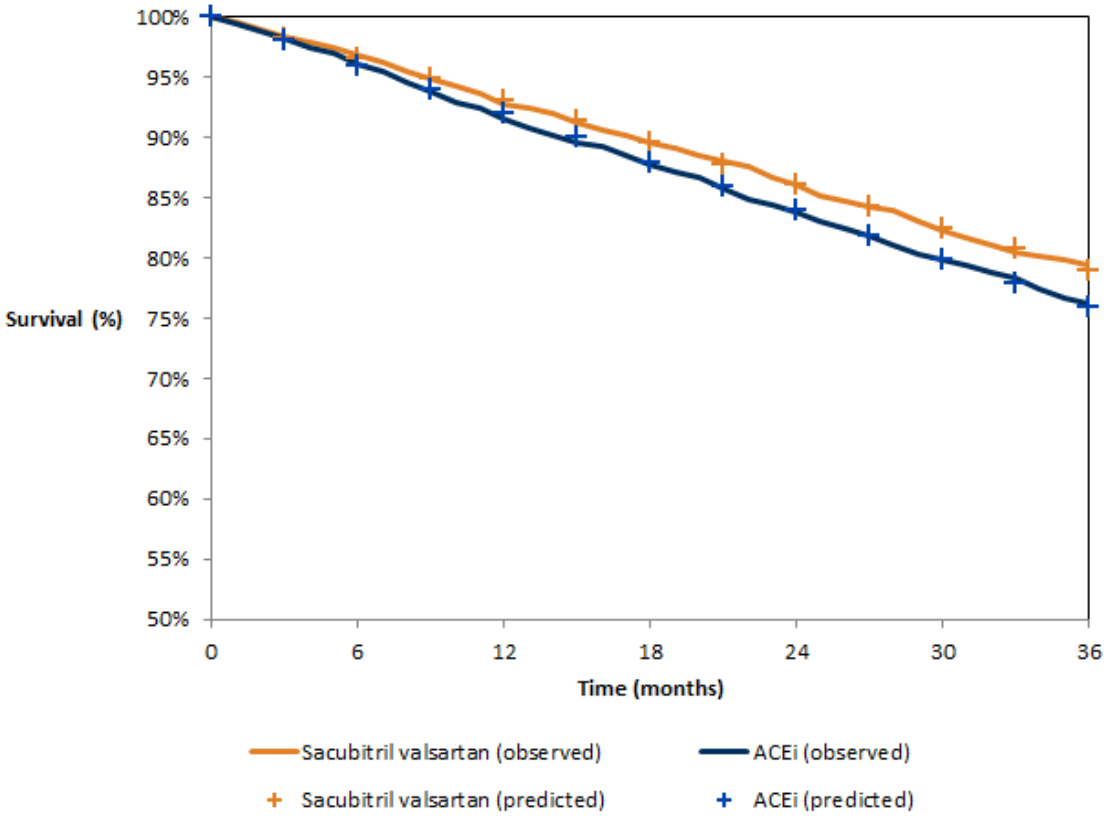
Table 8: Predicted vs. observed survival for ACEi (Table 79 in submission)

Month	Predicted survival from model (ACEi)	Observed survival from PARADIGM-HF (ACEi)
0	100%	100%
3	98%	98%
6	96%	96%
9	94%	94%
12	92%	92%
15	90%	90%
18	88%	88%

21	86%	86%
24	84%	84%
27	82%	82%
30	80%	80%
33	78%	78%
36	76%	76%

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor

Figure 3: Predicted vs. observed survival for sacubitril valsartan and ACEi (Figure 32 in submission)



Abbreviations: ACEi, angiotensin-converting enzyme inhibitor.

Hospitalisation

Table 9: Summary of model results compared with clinical data (Table 80 in submission)

Outcome	PARADIGM-HF clinical trial result		Model result
	Unadjusted estimated rate	Estimated rate from NB model†	
Annual hospitalisation rate (Sacubitril valsartan)	0.38	0.42	0.42
Annual hospitalisation rate (ACEi)	0.44	0.50	0.50

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; NB, negative binomial.
† Negative binomial (NB) regression model, adjusted for treatment and region. Log(follow-up duration) is the offset variable.

1.1.3 *Provide (if appropriate) the proportion of the cohort in the health state over time (Markov trace) for each state, supplying 1 for each comparator*

Table 10: Proportion of cohort in alive health state (Table 81 in submission)

Year	% in Alive health state	
	Sacubitril valsartan	ACEi
0	100%	100%
1	93%	92%
2	86%	84%
3	79%	76%
4	72%	68%
5	65%	60%
6	58%	53%
7	51%	46%
8	44%	39%
9	38%	33%
10	32%	28%
11	27%	22%
12	22%	18%
13	18%	14%
14	14%	11%
15	11%	8%

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor

1.1.4 *Provide details of how the model assumes QALYs accrued over time*

Table 11: QALYs accrued over time, sacubitril valsartan (Table 82 in submission)

Year	QALYs	Hospitalisation decrements	AE decrements	Total
1	0.7542	-0.0065	-0.0006	0.7471
2	0.6710	-0.0052	-0.0005	0.6653
3	0.5925	-0.0042	-0.0004	0.5879
4	0.5189	-0.0033	-0.0003	0.5153
5	0.4504	-0.0025	-0.0003	0.4476
6	0.3872	-0.0020	-0.0002	0.385
7	0.3295	-0.0015	-0.0002	0.3278
8	0.2771	-0.0011	-0.0001	0.2759
9	0.2303	-0.0008	-0.0001	0.2294
10	0.1889	-0.0006	-0.0001	0.1882
11	0.1528	-0.0004	-0.0001	0.1523
12	0.1217	-0.0003	0.0000	0.1214
13	0.0954	-0.0002	0.0000	0.0952
14	0.0735	-0.0001	0.0000	0.0734
15	0.0556	-0.0001	0.0000	0.0555

Abbreviations: AE, adverse event; QALY, quality-adjusted life year.

Table 12: QALYs accrued over time, ACEi (Table 83 in submission)

Year	QALYs	Hospitalisation decrements	AE decrements	Total
1	0.7399	-0.0076	-0.0005	0.7318
2	0.6502	-0.0059	-0.0004	0.6439
3	0.5667	-0.0046	-0.0003	0.5618
4	0.4895	-0.0035	-0.0003	0.4857
5	0.4188	-0.0027	-0.0002	0.4159
6	0.3545	-0.0020	-0.0002	0.3523
7	0.2966	-0.0015	-0.0001	0.2950
8	0.2452	-0.0011	-0.0001	0.2440
9	0.2000	-0.0007	-0.0001	0.1992
10	0.1609	-0.0005	-0.0001	0.1603
11	0.1274	-0.0004	0.0000	0.1270
12	0.0993	-0.0002	0.0000	0.0991
13	0.0761	-0.0002	0.0000	0.0759
14	0.0572	-0.0001	0.0000	0.0571
15	0.0421	-0.0001	0.0000	0.0420

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; AE, adverse event; QALY, quality-adjusted life year.

1.1.5 *Provide details of the disaggregated QALYs and costs by health state, and of resource use predicted by the model in the base case incremental cost effectiveness analysis by category of cost*

Table 13: Base case results – disaggregated costs for ACEi comparison (lifetime time horizon) (Table 84 in submission)

Component	ACEi	Sacubitril valsartan	Incremental
Primary therapy	£153	£7,838	£7,685
Background therapy	£544	£587	£43
Hospitalisation	£7,440	£6,819	-£621
HF management	£5,058	£5,458	£400
Adverse events	£92	£98	£6
Total costs	**£13,287**	**£20,801**	**£7,514**

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; HF, heart failure.

1.1.6 *Alternative analysis – CV mortality approach*

1.1.6.1 Alternative results vs ACEi

Table 14: Summary of incremental cost-effectiveness vs. ACEi – alternative analysis (Table 85 in submission)

Technologies	Total			Incremental			ICER (£)
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	vs. ACEi
ACEi	£14,814	6.78	5.08	-	-	-	-
Sacubitril valsartan	£23,458	7.40	5.60	£8,644	0.62	0.52	£16,678

Abbreviations: ACEi, angiotensin converting enzyme inhibitor; ICER, incremental cost-effectiveness ratio; LYG, life adjusted years; QALYs; quality adjusted life years.

1.1.7 *Alternative results vs ARBs*

Table 15: Summary of incremental cost-effectiveness vs. ARB – alternative analysis (Table 86 in submission)

Technologies	Total			Incremental			ICER (£)
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	vs. ARB
ARB	£13,835	6.69	5.02	-	-	-	-
Sacubitril valsartan	£23,458	7.40	5.60	£9,623	0.71	0.58	£16,569

Abbreviations: ARB, angiotensin receptor blocker; Inc, incremental; ICER, incremental cost-effectiveness ratio LYG, life adjusted years; QALYs; quality adjusted life years

2 Sensitivity analyses

2.1 *Probabilistic sensitivity analysis*

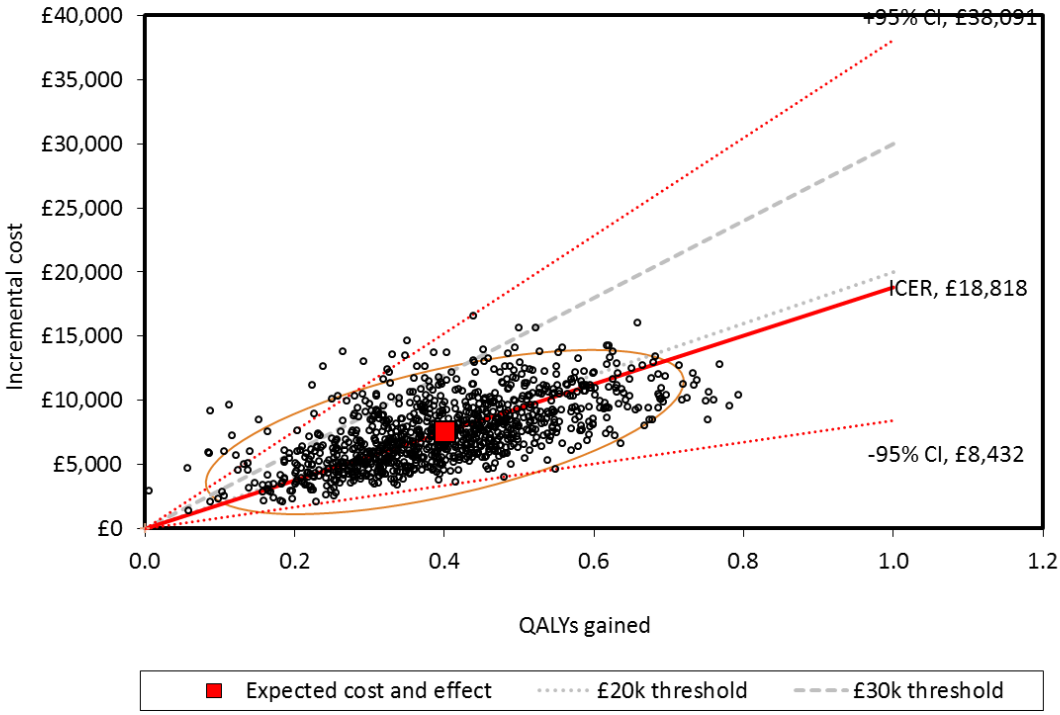
2.1.1 *Present the incremental cost effectiveness results of a probabilistic sensitivity analysis (including 95% confidence intervals).*

2.1.1.1 Primary comparison vs ACEi

The results of 1,000 simulations were plotted on the CEP (Figure 4), and the CEAC was calculated (Figure 5). It is noted that all simulation results lie in the north-east quadrant of the cost-effectiveness plane, i.e. sacubitril valsartan is always more expensive and more effective than ACEi. The probabilistic ICER is £18,818 (95% CI: £8,432, £38,091).

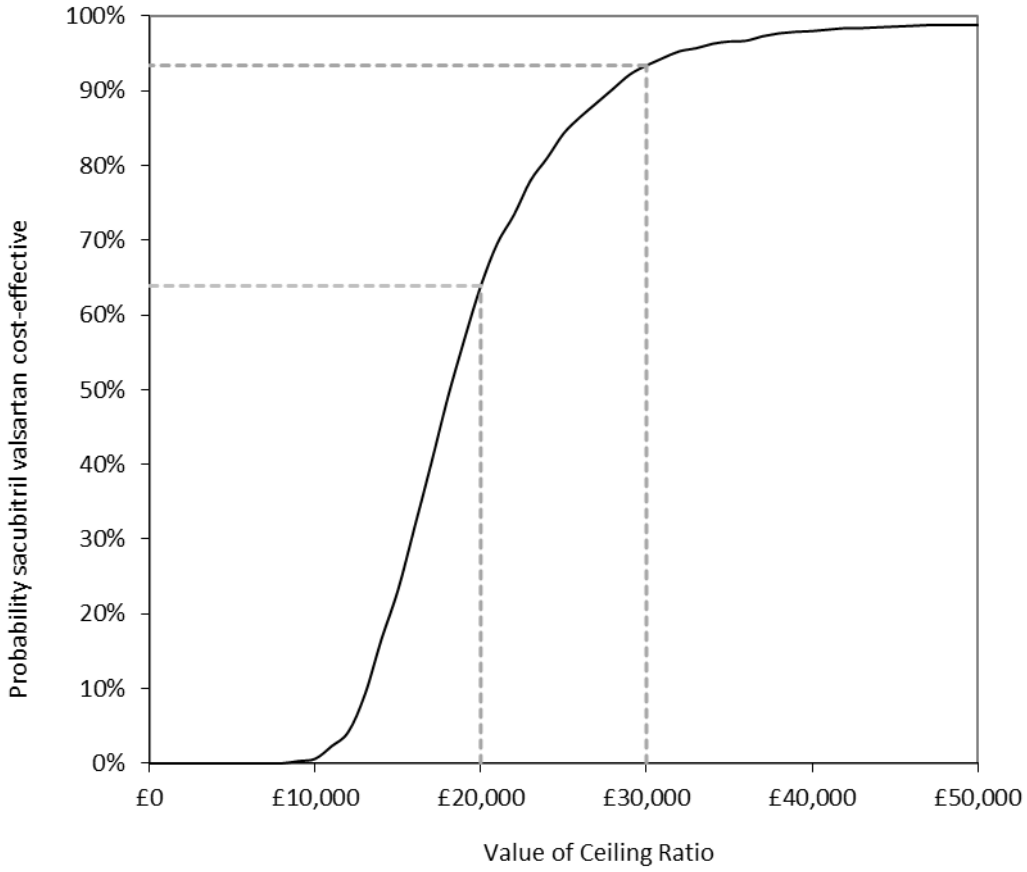
The CEAC (Figure 5) presents the probability that sacubitril valsartan is a cost-effective treatment option at various values of the ceiling ratio, or various willingness-to-pay thresholds. The probabilities of sacubitril valsartan being cost-effective at the lifetime time horizon at thresholds of £20,000 and £30,000 are 64% and 93%, respectively.

Figure 4: Cost-effectiveness plane and 95% confidence ellipse – ACEi comparison (Figure 33 in submission)



Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; CI, confidence interval; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year.

Figure 5: Cost-effectiveness acceptability curve – ACEi comparison (Figure 34 in submission)

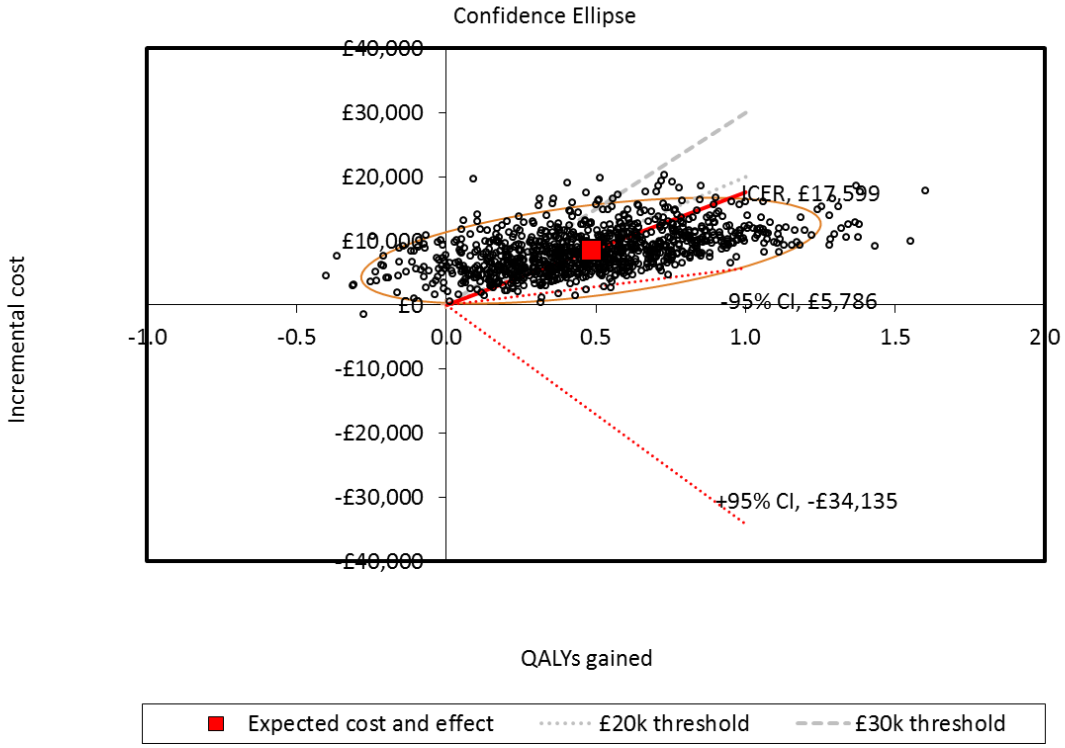


Abbreviations: ACEi, angiotensin-converting enzyme inhibitor.

2.1.1.2 Secondary comparison vs ARBs

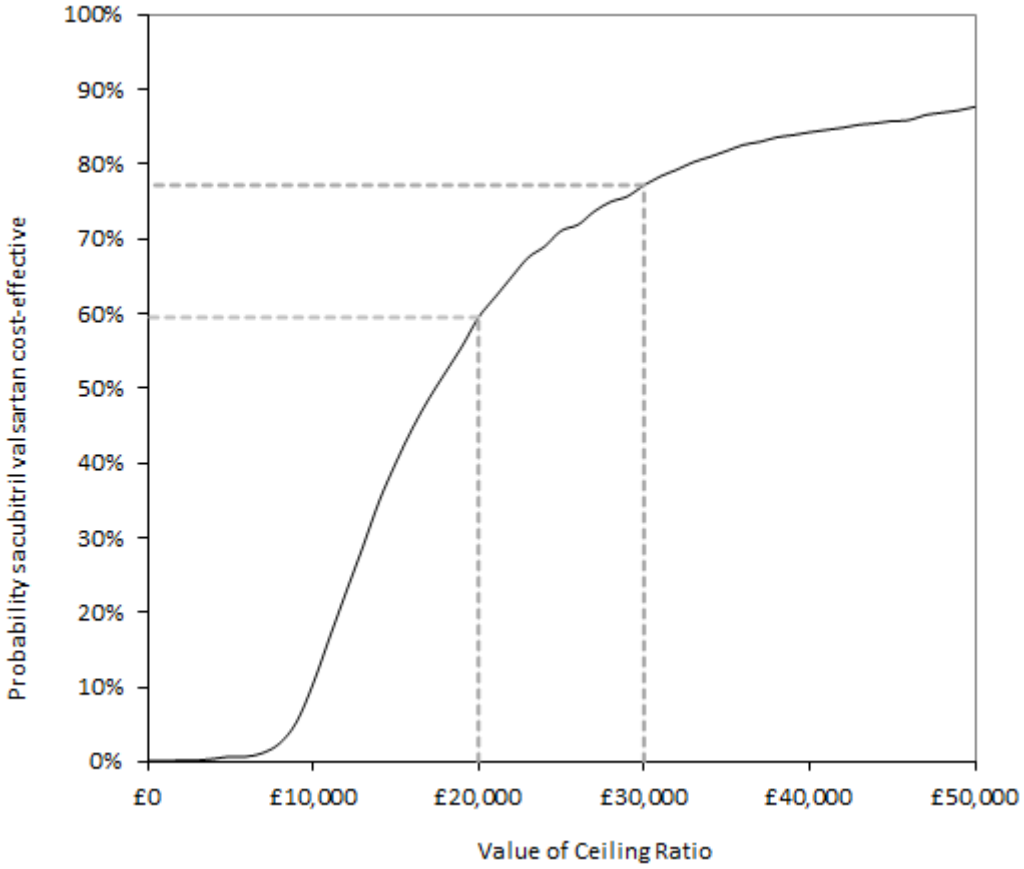
The results of 1,000 simulations were plotted on the CEP (Figure 6), and the CEAC was calculated (Figure 7). The comparison against ARBs is subject to greater uncertainty than the comparison against ACEis, driven by uncertainty in the results of the NMA. The probabilistic ICER is £17,599. The 95% CIs for the probabilistic ICER were undefined because the lower limit lies in the north-east quadrant and the upper limit lies in the north-west quadrant of the CEP (See Figure 6). The probabilities of sacubitril valsartan being cost-effective at the lifetime time horizon at thresholds of £20,000 and £30,000 are 60% and 77%, respectively.

Figure 6: Cost-effectiveness plane and 95% confidence ellipse – ARB comparison (Figure 35 in submission)



Abbreviations: ARB, angiotensin II receptor blocker; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year.

Figure 7: Cost-effectiveness acceptability curve – ARB comparison (Figure 36 in submission)



Abbreviations: ARB, angiotensin II receptor blocker.

2.2 *Deterministic sensitivity analysis*

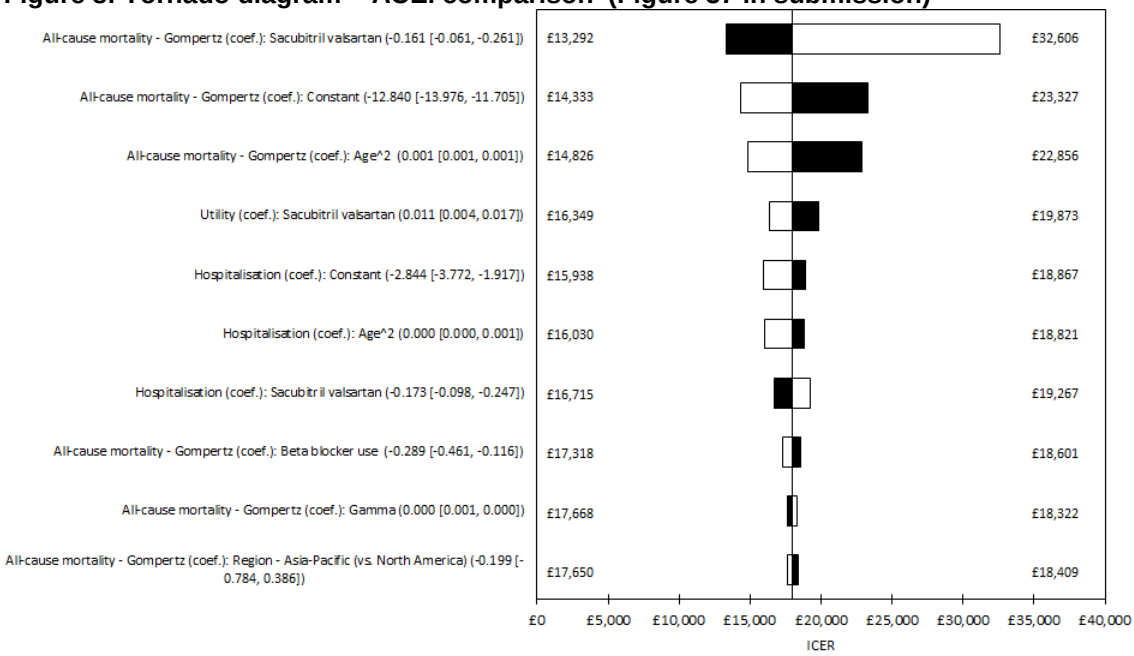
2.2.1 *Present the results of deterministic sensitivity analysis. Consider the use of tornado diagrams.*

Table 16: Deterministic sensitivity analysis using patient-level analysis – ACEi comparison (Table 87 in submission)

Parameter	Mean (range varied between)	ICER with low value	ICER with high value
All-cause mortality - Gompertz (coef.): sacubitril valsartan	-0.161 (-0.061, -0.261)	£13,292	£32,606
All-cause mortality - Gompertz (coef.): Constant	-12.840 (-13.976, -11.705)	£23,327	£14,333
All-cause mortality - Gompertz (coef.): Age^2*	0.0009 (0.0006, 0.0011)	£22,856	£14,826
Utility (coef.): Sacubitril valsartan	0.011 (0.004, 0.017)	£19,873	£16,349
Hospitalisation (coef.): Constant	-2.844 (-3.772, -1.917)	£18,867	£15,938
Hospitalisation (coef.): Age^2*	0.0005 (0.0002, 0.0007)	£18,821	£16,030
Hospitalisation (coef.): Sacubitril valsartan	-0.173 (-0.098, -0.247)	£16,715	£19,267
All-cause mortality - Gompertz (coef.): BB use	-0.289 (-0.461, -0.116)	£18,601	£17,318
All-cause mortality - Gompertz (coef.): Gamma	0.00037 (0.00021, 0.00053)	£17,668	£18,322

* Age exhibited a non-linear effect, and therefore a quadratic transformation was included.
Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; BB, beta blocker; coef., coefficient; ICER, incremental cost-effectiveness ratio.

Figure 8: Tornado diagram – ACEi comparison† (Figure 37 in submission)



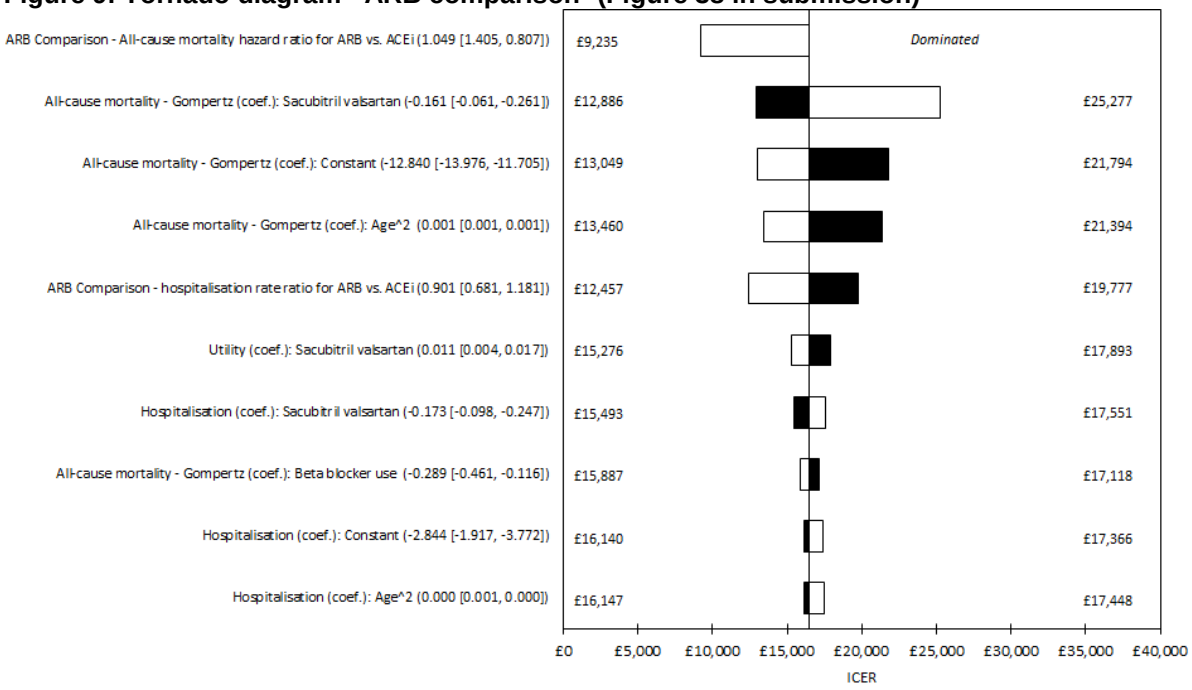
† Black shading is used to signify where the low value of the parameter has been used; white shading is used to signify where the high value of the parameter has been used
Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; coef, coefficient. ICER, incremental cost-effectiveness ratio.

Table 17: Deterministic sensitivity analysis using patient-level analysis – ARB comparison (Table 88 in submission)

Parameter	Mean (range varied between)	ICER with low value	ICER with high value
ARB Comparison - All-cause mortality hazard ratio for ARB vs. ACEi	1.049 (0.807, 1.405)	Dominated	£9,235
All-cause mortality - Gompertz (coef.): sacubitril valsartan	-0.161 (-0.061, -0.261)	£12,886	£25,277
All-cause mortality - Gompertz (coef.): Constant	-12.840 (-13.976, -11.705)	£21,794	£13,049
All-cause mortality - Gompertz (coef.): Age^2*	0.0009 (0.0006, 0.0011)	£21,394	£13,460
ARB Comparison - hospitalisation rate ratio for ARB vs. ACEi	0.901 (0.681, 1.181)	£19,777	£12,457
Utility (coef.): sacubitril valsartan	0.011 (0.004, 0.017)	£17,893	£15,276
Hospitalisation (coef.): sacubitril valsartan	-0.173 (-0.098, -0.247)	£15,493	£17,551
All-cause mortality - Gompertz (coef.): BB use	-0.289 (-0.461, -0.116)	£17,118	£15,887
Hospitalisation (coef.): Constant	-2.844 (-1.917, -3.772)	£16,140	£17,366
Hospitalisation (coef.): Age^2*	0.0005 (0.0002, 0.0007)	£16,147	£17,448

* Age exhibited a non-linear effect, and therefore a quadratic transformation was included.
Abbreviation: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BB, beta blocker; coef., coefficient; ICER, incremental cost-effectiveness ratio.

Figure 9: Tornado diagram –ARB comparison† (Figure 38 in submission)



†Black shading is used to signify where the low value of the parameter has been used; white shading is used to signify where the high value of the parameter has been used
Abbreviations: ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; coef., coefficient; ICER, incremental cost-effectiveness ratio.

2.3 *Scenario analysis*

2.3.1 *CPRD analysis*

Table 18: Reweighted base-case vs results using age and gender only (Table 92 in submission)

Therapy	Total costs	Total QALYs	Inc costs	Inc QALYs	ICER
ACEi	£13,079	4.01	--	--	
Sacubitril valsartan	£19,916	4.39	£6,837	0.38	£17,877

Abbreviations: ACEi, angiotensin-converting-enzyme inhibitor; CPRD, Clinical Practice Research Datalink; QALYs, quality-adjusted life-years; ICER, incremental cost-effectiveness ratio; Inc, incremental.

Table 19: Reweighted results using all variables available in CPRD (Table 93 in submission)

Therapy	Total costs	Total QALYs	Inc costs	Inc QALYs	ICER
ACEi	£12,724	4.09	--	--	--
Sacubitril valsartan	£19,885	4.47	£7,161	0.39	£18,167

Abbreviations: ACEi, angiotensin-converting-enzyme inhibitor; CPRD, Clinical Practice Research Datalink; QALYs, quality-adjusted life-years; ICER, incremental cost-effectiveness ratio; Inc, incremental.

[redacted]. The results of the calibrated analysis (Table 20) show improved cost-effectiveness of sacubitril valsartan (compared to the base case analysis using the mean patient characteristics approach in Table 21), driven principally by greater cost-savings achieved through reduced hospitalisations.

Table 20: Results following calibration of model using outcomes from CPRD analysis (mean patient characteristics approach) (Table 94 in submission)

Therapy	Total costs*	Total QALYs	Inc costs	Inc QALYs	ICER
ACEi	£28,962	3.41	--	--	--
Sacubitril valsartan	£33,676	3.80	£4,714	0.38	£12,358

Abbreviations: ACEi, angiotensin-converting-enzyme inhibitor; QALYs, quality-adjusted life-years; ICER, incremental cost-effectiveness ratio; Inc, incremental.

[redacted]

Table 21: Base case results using mean patient characteristics approach (Table 95 in submission)

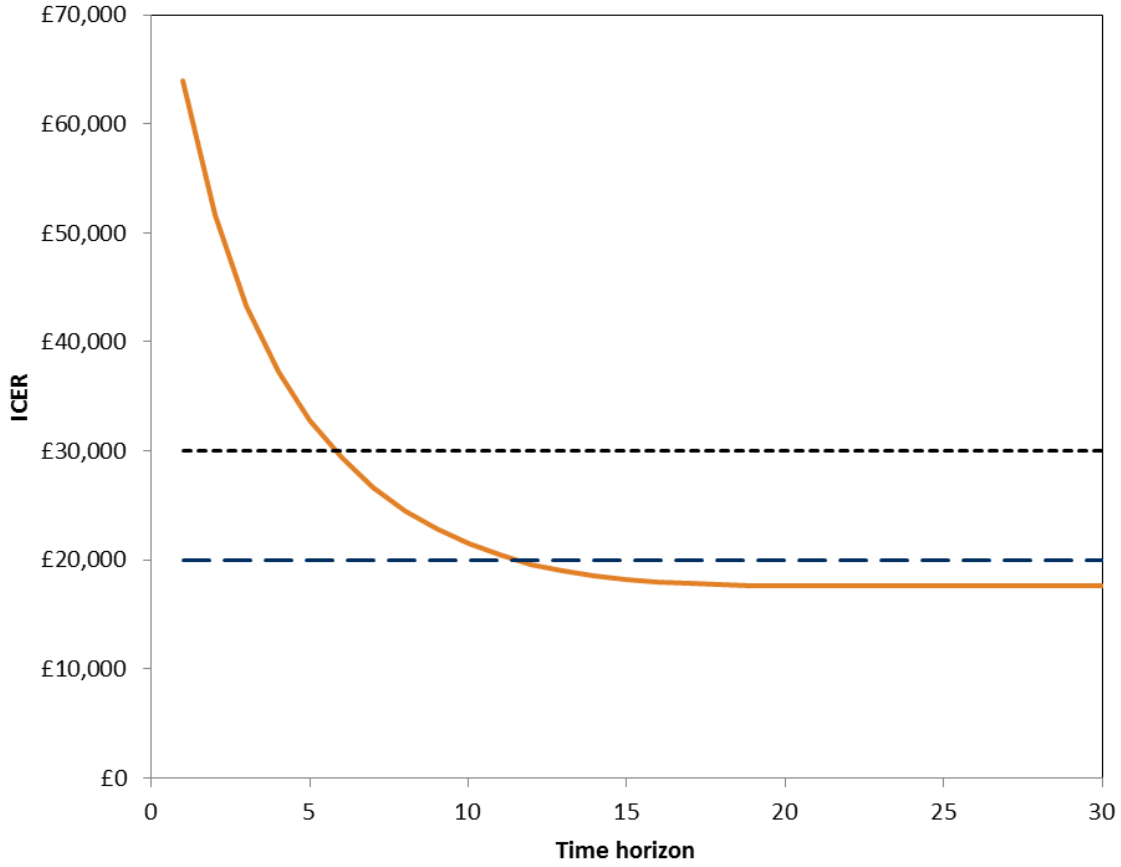
Therapy	Total costs	Total QALYs	Inc costs	Inc QALYs	ICER
ACEi	£12,738	4.45	--	--	--
Sacubitril valsartan	£20,149	4.88	£7,411	0.43	£17,383

Abbreviations: ACEi, angiotensin-converting-enzyme inhibitor; QALYs, quality-adjusted life-years; ICER, incremental cost-effectiveness ratio; Inc, incremental.

2.3.2 *Other scenario analyses*

2.3.2.1 Present the results of scenario analysis. Include details of structural sensitivity analysis.

Figure 10: ICER over a varying time horizon (Figure 42 in submission)



Abbreviations: ICER, incremental cost-effectiveness ratio.

Table 22: Results of scenario analyses (Table 99 in submission)

Scenario name	Sacubitril valsartan		ACEi		ICER	% change from base case
	Costs	QALYs	Costs	QALYs		
Base case analysis	£20,801	5.02	£13,287	4.60	£17,939	–
Discount rates altered to reflect historic NICE discount rates of 6% for costs and 1.5% for outcomes	£18,581	5.54	£11,977	5.05	£13,390	-25%
Weibull distribution used in all-cause mortality model	£27,080	6.40	£17,009	5.81	£17,135	-4%
Exponential distribution used in model of all-cause mortality	£29,714	6.95	£18,709	6.33	£17,698	-1%
Annual rate of decline in EQ-5D halved	£20,801	5.15	£13,287	4.71	£17,236	-4%
Annual rate of decline in EQ-5D doubled	£20,801	4.75	£13,287	4.37	£19,535	9%
No decline in EQ-5D over time	£20,801	5.28	£13,287	4.83	£16,588	-8%
No decline in EQ-5D after 5 years	£20,801	5.11	£13,287	4.67	£17,238	-4%
No decline in EQ-5D after 10 years	£20,801	5.04	£13,287	4.61	£17,688	-1%
Effect of sacubitril valsartan on EQ-5D (beyond differences in hospitalisation / adverse event rates) assumed to be zero	£20,801	4.95	£13,287	4.60	£21,516	20%
Effect of sacubitril valsartan on hospitalisation rates assumed to apply to HF hospitalisation only	£21,556	5.01	£13,287	4.60	£19,895	11%
Effect of sacubitril valsartan on hospitalisation rates assumed to apply to CV hospitalisation only	£21,217	5.01	£13,287	4.60	£19,013	6%
Effect of hospitalisation on EQ-5D assumed to be zero	£20,801	5.05	£13,287	4.63	£18,032	1%
Sacubitril valsartan treatment effects assumed to cease at year 5	£20,521	4.82	£13,287	4.60	£31,808	77%
Sacubitril valsartan treatment effects assumed to cease at year 10	£20,677	4.95	£13,287	4.60	£20,941	17%
Treatment discontinuation considered over lifetime time horizon	£18,623	4.89	£13,293	4.60	£18,150	1%
Treatment discontinuation considered up to year 3	£19,548	4.95	£13,290	4.60	£17,932	0%
Treatment discontinuation assumed to result in reduced therapy costs; efficacy estimates as in trial	£18,660	5.02	£13,293	4.60	£12,814	-29%
Hospitalisation costs doubled	£27,620	5.02	£20,726	4.60	£16,458	-8%
Hospitalisation costs halved	£17,391	5.02	£9,567	4.60	£18,680	4%
Proportions of hospitalisation types derived using Western Europe population	£21,503	5.02	£14,053	4.60	£17,787	-1%
All adverse event rates set to zero	£20,703	5.02	£13,195	4.60	£17,909	0%
Primary therapies costed assuming target doses from PARADIGM-HF	£20,801	5.02	£13,296	4.60	£17,918	0%
Cost of ramipril applied to ACEi arm	£20,801	5.02	£13,330	4.60	£17,835	-1%
Cost of titration included	£21,062	5.02	£13,287	4.60	£18,564	3%
Increased risk of hospitalisation over time	£28,500	4.99	£21,193	4.57	£17,443	-3%

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; CV, cardiovascular; HF, heart failure; HRQoL, health-related quality of life; ICER, incremental cost-effectiveness ratio; NICE, National Institute of Health and Care Excellence; QALY, quality-adjusted life-year;

3 Subgroup analysis

3.1 *If subgroup analyses were done, please present the results in tables similar to those in section 5.7.*

Table 23: Subgroup analyses (Table 100 in submission)

#	Subgroup	Δ Costs	Δ QALYs	ICER	% change from base case
1	Full analysis set	£7,514	0.42	£17,939	0%
2	Baseline age < 65 years	£7,932	0.44	£18,189	1%
3	Baseline age ≥ 65 years	£7,079	0.40	£17,657	-3%
4	Baseline age < 75 years	£7,789	0.43	£18,137	3%
5	Baseline age ≥ 75 years	£6,312	0.37	£16,944	-7%
6	Region - North America	£7,453	0.41	£18,119	7%
7	Region - Latin America	£7,020	0.42	£16,619	-8%
8	Region - Western Europe	£7,930	0.44	£18,173	9%
9	Region - Central Europe	£7,511	0.39	£19,208	6%
10	Region - Asia-Pacific	£7,447	0.45	£16,651	-13%
11	Baseline NYHA class I/ II	£7,842	0.44	£17,709	6%
12	Baseline NYHA III/ IV	£6,516	0.35	£18,836	6%
13	Baseline LVEF ≤ median	£7,140	0.41	£17,235	-8%
14	Baseline LVEF > median	£7,948	0.42	£18,738	9%
15	Baseline SBP ≤ median	£7,427	0.42	£17,563	-6%
16	Baseline SBP > median	£7,619	0.41	£18,404	5%
17	Baseline eGFR < 60	£6,746	0.39	£17,175	-7%
18	Baseline eGFR ≥ 60	£7,954	0.43	£18,336	7%
19	Baseline NT-proBNP ≤ median	£8,748	0.46	£19,203	5%
20	Baseline NT-proBNP > median	£6,184	0.38	£16,304	-15%
21	Diabetes at baseline	£6,835	0.39	£17,344	6%
22	No diabetes at baseline	£7,874	0.43	£18,227	5%
23	Hypertension at baseline	£7,432	0.41	£18,114	-1%
24	No hypertension at baseline	£7,713	0.44	£17,546	-3%
25	Prior use of ACEi	£7,555	0.42	£18,030	3%
26	Prior use of ARB	£7,369	0.42	£17,620	-2%
27	Use of BB at baseline	£7,603	0.42	£18,051	2%
28	No use of BB at baseline	£6,328	0.39	£16,321	-10%
29	Use of AA at baseline	£7,415	0.42	£17,852	9%
30	No use of AA at baseline	£7,638	0.42	£18,047	1%
31	≤ 1 year since diagnosis of HF	£8,486	0.46	£18,606	3%
32	1-5 years since diagnosis of HF	£7,253	0.41	£17,764	-5%
33	> 5 years since diagnosis of HF	£6,905	0.40	£17,427	-2%
34	Ischaemic aetiology	£7,282	0.41	£17,885	3%
35	Non-ischaemic aetiology	£7,862	0.44	£18,014	1%
36	Prior AF at baseline	£7,141	0.40	£17,911	-1%
37	No prior AF at baseline	£7,731	0.43	£17,954	0%

#	Subgroup	Δ Costs	Δ QALYs	ICER	% change from base case
38	Prior HF hospitalisation	£7,220	0.41	£17,609	-2%
39	No prior HF hospitalisation	£8,011	0.43	£18,466	5%

Abbreviations: AA, aldosterone antagonists; ACEi, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin receptor blocker; BB, beta blocker; eGFR, estimated glomerular filtration rate; HF, heart failure; ICER, incremental cost-effectiveness ratio; LVEF, left ventricular ejection fraction; NT-proBNP, N terminal pro-brain natriuretic peptide; NYHA, New York Heart Association; QALYs, quality-adjusted life years; SBP, systolic blood pressure.

4 External validity

4.1 *External validity against ivabradine model*

Outcomes from the economic model were compared against the most comparable model identified by the systematic literature review, the model of ivabradine used in TA267 (see Table 24). Minimal differences exist between the results of the ACEi arm in the updated model presented in the addendum and the original model submitted.

Table 24: Comparison of comparator arms in ivabradine and present economic models (Table 101 in submission)

Technologies	Standard care ivabradine model‡	ACEi arm in sacubitril valsartan model	Absolute difference	Relative difference
Technology cost†	£642	£697	£55	9%
Follow-up costs	£1,803	£5,058	£3,255	180%
Hospitalisation	£7,001	£7,440	£439	6%
Total costs	**£9,446**	**£13,287**	**£3,841**	**41%**
QALYs	3.99	4.60	0.61	15%
Life-years	5.61	6.08	0.47	8%
Survival Year 5	59%	60%	1%	1%
Survival Year 10	22%	28%	6%	27%

† Therapy titration and drug costs; ‡ As reported in manufacturer submission to NICE (34)
Abbreviations: ACEi, angiotensin converting enzyme inhibitor; QALY, quality-adjusted life year.

5 Overview of cost per QALY gained results between company submission and addendum

Component	Company STA submission	Company STA addendum	Incre-mental
Base case results – primary comparison versus ACEi	£18.187	£17,939	-1.36%
Base case results - secondary comparison versus ARBs	£16,753	£16,481	-1.62%
Alternative analysis – CV mortality approach versus ACEi	£16,894	£16,678	-1.28%
Alternative analysis – CV mortality approach versus ARBs	£16,817£	£16,569	-1.47%
Scenario analysis			
Discount rates altered to reflect historic NICE discount rates of 6% for costs and 1.5% for outcomes	£13,604	£13,390	-1.57%
Weibull distribution used in all-cause mortality model	£17,368	£17,135	-1.34%
Exponential distribution used in model of all-cause mortality	£17,923	£17,698	-1.26%
Annual rate of decline in EQ-5D halved	£17,466	£17,236	-1.32%
Annual rate of decline in EQ-5D doubled	£19,826	£19,535	-1.47%
No decline in EQ-5D over time	£16,799	£16,588	-1.26%
No decline in EQ-5D after 5 years	£17,473	£17,238	-1.34%
No decline in EQ-5D after 10 years	£17,934	£17,688	-1.37%
Effect of sacubitril valsartan on EQ-5D (beyond differences in hospitalisation / adverse event rates) assumed to be zero	£21,877	£21,516	-1.65%
Effect of sacubitril valsartan on hospitalisation rates assumed to apply to HF hospitalisation only	£20,203	£19,895	-1.52%
Effect of sacubitril valsartan on hospitalisation rates assumed to apply to CV hospitalisation only	£19,294	£19,013	-1.46%
Effect of hospitalisation on EQ-5D assumed to be zero	£18,284	£18,032	-1.38%
Sacubitril valsartan treatment effects assumed to cease at year 5	£32,020	£31,808	-0.66%
Sacubitril valsartan treatment effects assumed to cease at year 10	£21,159	£20,941	-1.03%
Treatment discontinuation considered over lifetime time horizon	£18,348	£18,150	-1.08%
Treatment discontinuation considered up to year 3	£18,156	£17,932	-1.23%
Treatment discontinuation assumed to result in reduced therapy costs; efficacy estimates as in trial	£12,926	£12,814	-0.87%
Hospitalisation costs doubled	£16,669	£16,458	-1.27%
Hospitalisation costs halved	£18,946	£18,680	-1.40%
Proportions of hospitalisation types derived using Western Europe population	£18,031	£17,787	-1.35%
All adverse event rates set to zero	£18,157	£17,909	-1.37%
Primary therapies costed assuming target doses from PARADIGM-HF	£18,166	£17,918	-1.37%
Cost of ramipril applied to ACEi arm	£18,081	£17,835	-1.36%
Cost of titration included	£18,827	£18,564	-1.40%
Increased risk of hospitalisation over time	£17,960	£17,443	-2.88%
Reweighting CPRD (age and gender only)	£18,142	£17,877	-1.46%
Reweighting CPRD (all variables)	£18,432	£18,167	-1.44%
Calibration of model using CPRD outcomes	£12,595	£12,358	-1.88%
Subgroups			
Baseline age < 65 years	£18,434	£18,189	-1.33%
Baseline age ≥ 65 years	£17,909	£17,657	-1.41%
Baseline age < 75 years	£18,384	£18,137	-1.34%
Baseline age ≥ 75 years	£17,195	£16,944	-1.46%
Region - North America	£18,374	£18,119	-1.39%
Region - Latin America	£16,839	£16,619	-1.31%
Region - Western Europe	£18,415	£18,173	-1.31%
Region - Central Europe	£19,502	£19,208	-1.51%
Region - Asia-Pacific	£16,860	£16,651	-1.24%
Baseline NYHA class I/ II	£17,941	£17,709	-1.29%
Baseline NYHA III/ IV	£19,152	£18,836	-1.65%

Component		Company STA submission	Company STA addendum	Incre-mental
Baseline LVEF ≤ median		£17,471	£17,235	-1.35%
Baseline LVEF > median		£19,000	£18,738	-1.38%
Baseline SBP ≤ median		£17,801	£17,563	-1.34%
Baseline SBP > median		£18,665	£18,404	-1.40%
Baseline eGFR < 60		£17,420	£17,175	-1.41%
Baseline eGFR ≥ 60		£18,585	£18,336	-1.34%
Baseline NT-proBNP ≤ median		£19,458	£19,203	-1.31%
Baseline NT-proBNP > median		£16,539	£16,304	-1.42%
Diabetes at baseline		£17,593	£17,344	-1.42%
No diabetes at baseline		£18,474	£18,227	-1.34%
Hypertension at baseline		£18,371	£18,114	-1.40%
No hypertension at baseline		£17,775	£17,546	-1.29%
Prior use of ACEi		£18,280	£18,030	-1.37%
Prior use of ARB		£17,862	£17,620	-1.35%
Use of BB at baseline		£18,301	£18,051	-1.37%
No use of BB at baseline		£16,549	£16,321	-1.38%
Use of AA at baseline		£18,100	£17,852	-1.37%
No use of AA at baseline		£18,295	£18,047	-1.36%
≤ 1 year since diagnosis of HF		£18,848	£18,606	-1.28%
1-5 years since diagnosis of HF		£18,015	£17,764	-1.39%
> 5 years since diagnosis of HF		£17,677	£17,427	-1.41%
Ischaemic aetiology		£18,139	£17,885	-1.40%
Non-ischaemic aetiology		£18,255	£18,014	-1.32%
Prior AF at baseline		£18,170	£17,911	-1.43%
No prior AF at baseline		£18,197	£17,954	-1.34%
Prior HF hospitalisation		£17,855	£17,609	-1.38%
No prior HF hospitalisation		£18,717	£18,466	-1.34%
Probabilistic sensitivity analysis				
PSA ACEis		£18.955 (£8,599, £37,222)	£18.818 (£8,432, £38,091)	-0.72% (-1.94%, 2.33%)
PSA ARB		£18,180 (undefined)	£17,599 (undefined)	-3.20%
Deterministic sensitivity analysis ACEi				
All-cause mortality - Gompertz (coef.): sacubitril valsartan	ICER with low value	£13,506	£13,292	-1.58%
	ICER with high value	£32,900	£32,606	-0.89%
All-cause mortality - Gompertz (coef.): Constant	ICER with low value	£23,613	£23,327	-1.21%
	ICER with high value	£14,551	£14,333	-1.50%
All-cause mortality - Gompertz (coef.): Age^2*	ICER with low value	£23,138	£22,856	-1.22%
	ICER with high value	£15,048	£14,826	-1.48%
Utility (coef.): Sacubitril valsartan	ICER with low value	£20,180	£19,873	-1.52%
	ICER with high value	£16,553	£16,349	-1.23%
Hospitalisation (coef.): Constant	ICER with low value	£19,138	£18,867	-1.42%
	ICER with high value	£16,143	£15,938	-1.27%
Hospitalisation (coef.): Age^2*	ICER with low value	£19,091	£18,821	-1.41%
	ICER with high value	£16,240	£16,030	-1.29%
Hospitalisation (coef.): Sacubitril valsartan	ICER with low value	£16,926	£16,715	-1.25%
	ICER with high value	£19,556	£19,267	-1.48%
All-cause mortality - Gompertz (coef.): BB use	ICER with low value	£18,854	£18,601	-1.34%
	ICER with high value	£17,561	£17,318	-1.38%
All-cause mortality - Gompertz (coef.): Gamma	ICER with low value	£17,914	£17,668	-1.37%
	ICER with high value	£18,570	£18,322	-1.34%
Deterministic sensitivity analysis ARB				

Component		Company STA submission	Company STA addendum	Incre-mental
ARB Comparison - All-cause mortality hazard ratio for ARB vs. ACEi	ICER with low value	Dominated	Dominated	--
	ICER with high value	£9,420	£9,235	-1.96%
All-cause mortality - Gompertz (coef.): sacubitril valsartan	ICER with low value	£13,119	£12,886	-1.78%
	ICER with high value	£25,626	£25,277	-1.36%
All-cause mortality - Gompertz (coef.): Constant	ICER with low value	£22,128	£21,794	-1.51%
	ICER with high value	£13,278	£13,049	-1.72%
All-cause mortality - Gompertz (coef.): Age^2*	ICER with low value	£21,726	£21,394	-1.53%
	ICER with high value	£13,693	£13,460	-1.70%
ARB Comparison - hospitalisation rate ratio for ARB vs. ACEi	ICER with low value	£20,152	£19,777	-1.86%
	ICER with high value	£12,606	£12,457	-1.18%
Utility (coef.): sacubitril valsartan	ICER with low value	£18,212	£17,893	-1.75%
	ICER with high value	£15,510	£15,276	-1.51%
Hospitalisation (coef.): sacubitril valsartan	ICER with low value	£15,734	£15,493	-1.53%
	ICER with high value	£17,856	£17,551	-1.71%
All-cause mortality - Gompertz (coef.): BB use	ICER with low value	£17,398	£17,118	-1.61%
	ICER with high value	£16,151	£15,887	-1.63%
Hospitalisation (coef.): Constant	ICER with low value	£16,396	£16,140	-1.56%
	ICER with high value	£17,677	£17,366	-1.76%
Hospitalisation (coef.): Age^2*	ICER with low value	£16,404	£16,147	-1.57%
	ICER with high value	£17,762	£17,448	-1.77%
Subgroup analysis				
Baseline age < 65 years		£18,434	£18,189	-1.33%
Baseline age ≥ 65 years		£17,909	£17,657	-1.41%
Baseline age < 75 years		£18,384	£18,137	-1.34%
Baseline age ≥ 75 years		£17,195	£16,944	-1.46%
Region - North America		£18,374	£18,119	-1.39%
Region - Latin America		£16,839	£16,619	-1.31%
Region - Western Europe		£18,415	£18,173	-1.31%
Region - Central Europe		£19,502	£19,208	-1.51%
Region - Asia-Pacific		£16,860	£16,651	-1.24%
Baseline NYHA class I/ II		£17,941	£17,709	-1.29%
Baseline NYHA III/ IV		£19,152	£18,836	-1.65%
Baseline LVEF ≤ median		£17,471	£17,235	-1.35%
Baseline LVEF > median		£19,000	£18,738	-1.38%
Baseline SBP ≤ median		£17,801	£17,563	-1.34%
Baseline SBP > median		£18,665	£18,404	-1.40%
Baseline eGFR < 60		£17,420	£17,175	-1.41%
Baseline eGFR ≥ 60		£18,585	£18,336	-1.34%
Baseline NT-proBNP ≤ median		£19,458	£19,203	-1.31%
Baseline NT-proBNP > median		£16,539	£16,304	-1.42%
Diabetes at baseline		£17,593	£17,344	-1.42%
No diabetes at baseline		£18,474	£18,227	-1.34%
Hypertension at baseline		£18,371	£18,114	-1.40%
No hypertension at baseline		£17,775	£17,546	-1.29%
Prior use of ACEi		£18,280	£18,030	-1.37%
Prior use of ARB		£17,862	£17,620	-1.35%
Use of BB at baseline		£18,301	£18,051	-1.37%
No use of BB at baseline		£16,549	£16,321	-1.38%
Use of AA at baseline		£18,100	£17,852	-1.37%
No use of AA at baseline		£18,295	£18,047	-1.36%
≤ 1 year since diagnosis of HF		£18,848	£18,606	-1.28%
1-5 years since diagnosis of HF		£18,015	£17,764	-1.39%

Component	Company STA submission	Company STA addendum	Incre-mental
> 5 years since diagnosis of HF	£17,677	£17,427	-1.41%
Ischaemic aetiology	£18,139	£17,885	-1.40%
Non-ischaemic aetiology	£18,255	£18,014	-1.32%
Prior AF at baseline	£18,170	£17,911	-1.43%
No prior AF at baseline	£18,197	£17,954	-1.34%
Prior HF hospitalisation	£17,855	£17,609	-1.38%
No prior HF hospitalisation	£18,717	£18,466	-1.34%

Appendix G - professional organisation submission template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Sacubitril valsartan for treating chronic heart failure

Thank you for agreeing to make a submission on your organisation's view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your submission, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name: [redacted]

Name of your organisation: The British Society for Heart Failure
Are you (tick all that apply):

- a specialist in the treatment of people with the condition for which NICE is considering this technology? **X**

- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)?

- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc)? [redacted]**, BRITISH SOCIETY FOR HEART FAILURE**

- other? (please specify)

Appendix G - professional organisation submission template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Sacubitril valsartan for treating chronic heart failure

What is the expected place of the technology in current practice?

How is the condition currently treated in the NHS? Is there significant geographical variation in current practice? Are there differences of opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?

Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

HEART FAILURE IS A COMMON CLINICAL CONDITION WITH HIGH MORTALITY AND SIGNIFICANT IMPACT UPON QUALITY OF LIFE. IT IS ESTIMATED THAT APPROXIMATELY 750,000-800,000 PEOPLE IN THE UK HAVE CHRONIC HEART FAILURE. While clinically meaningful improvements in prognosis have been achieved over the past 20 years, the outlook for patients with heart failure remains poor. The National Heart Failure Audit indicates that in-patient mortality for patients hospitalised with heart failure is around 10%; following discharge from hospital, a further 6% die within the first month. Rates of readmission are also high. Outcomes for patients hospitalised with heart failure are better when patient management is under a cardiologist.

THE MANAGEMENT OF HEART FAILURE IS BASED UPON A MULTITUDE OF EVIDENCE FROM RANDOMISED CLINCAL TRIALS. THIS EVIDENCE IS SUMMARISED IN NATIONAL (NICE) AND INTERNATIONAL (EUROPEAN SOCIETY OF CARDIOLOGY, AHA/ACC GUIDELINES). THESE ARE CONSISTENT IN RECOMMENDATIONS REGARDING THE PHARMACOLOGICAL AND NON-PHARMACOLOGICAL MANAGEMENT OF HEART FAILURE: CONTEMPORARY GUIDELINE DRIVEN MANAGEMENT CONSISTS OF TREATMENT WITH TRIPLE PHARMACOLOGICAL THERAPY (ACE INHIBITOR (OR ARB IF ACEI NOT TOLERATED), BETA BLOCKER, AND MINERALOCORTICOID RECEPTOR ANTAGONIST (MRA)) AND DEVICE THERAPY (CRT-P OR CRT-D) FOR SPECIFIC SUBGROUPS OF PATIENTS.
WHILE SOME REGIONAL VARIATION EXISTS IN CURRENT PRACTICE, THIS APPLIES MORE TO DEVICE THERAPY THAN TO PHARMACOLOGICAL MANAGEMENT. THERE IS VERY LITTLE DISAGREEMENT AMONG HEALTH

CARE PROFESSIONALS AS TO “BEST PRACTICE” IN HEART FAILURE MANAGEMENT, AS THIS IS BASED UPON EXTENSIVE EVIDENCE FROM MULTIPLE RCTs.
PHARMACOLOGICAL MANAGEMENT IS DESIGNED TO PROVIDE NEUROHORMONAL BLOCKADE (RAAS INHIBITION WITH ACEI (OR ARB) PLUS MRA, AS WELL AS SYMPATHETIC NERVOUS SYSTEM BLOCKADE WITH BETA BLOCKER. THE TARGET DOSES OF THESE INDIVIDUAL THERAPIES ARE WELL DEFINED, ALTHOUGH IN CLINICAL PRACTICE TARGET DOSES MAY BE DIFFICULT TO ACHIEVE FOR A PROPROTION OF PATIENTS, IN THE CONTEXT OF TOLERABILITY ISSUES. TOLERABILITY OF ALL RECOMMENDED PHARMACOLOGICAL THERAPIES MAY BE LIMITED BY EXCESSIVE PHARMACOLOGICAL EFECT, IN PARTICULAR BLOOD PRESSURE LOWERING. BETA BLOCKER USE MAY BE LIMITED BY UNWANTED EFFECTS OF FATIGUE, AS WELL AS LOW BLOOD PRESSURE.

ACE INHIBITION HAS CONSTITUTED ONE MAINSTAY OF HEART FAILURE THERAPY FOR APPROXIMATELY 20 YEARS. OVERALL THESE AGENTS ARE WELL TOLERATED; IN ADDITION TO BLOOD PRESSURE LOWERING, ACE INHIBITON IS OFTEN LIMITED BY RENAL IMPAIRMENT; RENAL IMPAIRMENT IS A FREQUENT COMORBIDITY IN PATIENTS WITH HEART FAILURE, RATHER THAN BEING “CAUSED” BY TREATMENT OF THE CONDITION. HOWEVER ON OCCASION, TREATMENT WITH ACE INHIBITOR MAY WORSEN RENAL FUNCTION. IN REALITY, WHETHER OR NOT DIRECTLY CAUSED OR WORSENED BY ACE INHIBITION, RENAL IMPAIRMENT FREQUENTLY LEADS TO TREATMENT DOSE LIMITATION OR WITHDRAWAL. THIS CLINICAL SCENARIO LIMITS THE USE OF ACE INHIBITION, AND TO A VERY SIMILAR EXTENT ARB THERAPY, IN CLINICAL PRACTICE. IN THIS CONTEXT, THE OBSERVATION IN PARADIGM HF OF BETTER RENAL TOLERABILITY OF SACUBITRIL VALSARTAM COMPARED TO ENALAPRIL IS WELCOME.

ANY NEW PHARMACOLOGICAL ENTITY FOR USE IN PATIENTS WITH HEART FAILURE WOULD REQUIRE TO SHOW BENEFITS IN ADDITION TO, OR AS A SUPERIOR REPLACEMENT FOR, CURRENT THERAPY. IN THE PARADIGM HF TRIAL, SACUBITRIL VALSARTAN WAS COMPARED TO THE ACE INHIBITOR ENALAPRIL. THIS WAS THE MOST APPROPRIATE COMPARATOR, AS THIS IS THE ACE INHIBITOR WITH THE MOST EXTENSIVE EVIDENCE BASE IN HEART FAILURE. FURTHER, THE COMPARATOR DOSE, ENALAPRIL 10mg BID IS THE DOSE WITH THE GREATEST EVIDENCE BASE. INDEED, THIS WAS THE MOST APPROPRIATE CHOICE OF COMPARATOR FOR THE NOVEL AGENT. INDEED THE CHOICE OF AGENT AND ITS DOSE WAS MANDATED BY THE FDA, AS BEING THE ACE INHIBITOR AND DOSE WITH THE BEST EVIDENCE IN THE PATIENT POPULATION UNDER STUDY.

THE STUDY DEMONSTRATED CLINICAL SUPERIORITY FOR SACUBITRIL VALSARTAN OVER ENALAPRIL, IN TERMS OF CARDIOVASCULAR MORTALITY, HEART FAILURE HOSPITAL ADMISSION, THE COMBINATION OF THESE TWO, AND IN ALL-CAUSE MORTALITY. IN THIS CONTEXT, THE CLINICAL SUPERIORITY OF SACUBITRIL VALSARTAN IS NOT DRIVEN BY ONE ELEMENT OF THE TRIAL END POINT, BUT IS CONSISTENT ACROSS ALL END POINTS.

SACUBITRIL VALSARTAN WAS ALSO BETTER TOLERATED IN TERMS OF ITS EFFECTS ON RENAL FUNCTION, THAN ENALAPRIL, ALTHOUGH SACUBITRIL DID LOWER BLOOD PRESSURE TO A SLIGHTLY GREATER EXTENT.

AS ALREADY NOTED, HEART FAILURE IS ASSOCIATED WITH HIGH MORTALITY AND MORBIDITY. FOLLOWING HOSPITAL ADMISSION WITH HEART FAILURE, READMISSION IS COMMON; IN PARADIGM HF, RISK OF REPEAT HOSPITALISATION WAS REDUCED BY SACUBITRIL VALSARTAN COMPARED TO ENALAPRIL.

THE RISK OF ADVERSE OUTCOME FOR PATIENTS WITH HEART FAILURE CAN BE ASSESSED BY A NUMBER OF FACTORS. WHILE LEFT VENTRICULAR EJECTION FRACTION IS ASSOCIATED WITH PROGNOSIS (LOWER EF HAVING WORSE OUTCOME), THIS MEASURE IS RELATIVELY CRUDE. PATIENTS WITH GREATER SYMPTOM BURDEN (ASSESSD BY NYHA CLASS OR 6 MINUTE WALK TEST) HAVE WORSE PROGNOSIS. A MORE REFINED MEASURE OF PROGNOSIS IS PROVIDED BY MEASUREMENT OF B-TYPE NATRIURETIC PEPTIDES (BNP OR NTproBNP). ACCESS TO THESE BIOMARKERS, WHILE RECOMMENDED IN NICE GUIDELINES, IS NOT UNIFORM IN THE UK, OR EVEN BETWEEN PRIMARY AND SECONDARY CARE SERVICES IN INDIVIDUAL HEALTH CARE AUTHORITY AREAS. IT IS RELEVANT TO NOTE THAT IT IS OFTEN THE PRIMARY CARE SERVICES WHICH HAVE ACCESS, WHILE SECONDARY CARE DOES NOT, ALTHOUGH THE REVERSE IS THE CASE IN SOME AREAS. IT IS LIKELY THAT ACCESS TO THESE BIOMARKERS WILL INCREASE OVER TIME.

PATIENTS WITH MORE ADVANCED HEART FAILURE HAVE THE HIGHEST RISK OF ADVERSE OUTCOME (DEATH OR HOSPITALISATION). THESE PATIENTS OFTEN HAVE HIGH BURDEN OF CO-MORBIDITY SUCH AS CHRONIC KIDNEY DISEASE, AND OFTEN PRESENT THE GREATEST CHALLENGE IN TERMS OF ACHIEVING TARGET DOSES OF GUIDELINE- BASED PHARMACOLOGICAL THERAPY. IN THIS CONTEXT IT IS OFTEN THE PATIENT WITH THE MOST TO GAIN FROM PHARMCOLOGICAL THERAPY THAT FAILS TO ACHIEVE TARGET TREATMENT DOSES. IT IS KNOWN FROM PARADIGM HF (MANUSCRIPT IN PRESS) THAT THE RELATIVE RISK REDUCTION FROM SACUBITRIL VALSARTAN IS OF SIMILAR MAGNITUDE IRRESPECTIVE OF BASELINE RISK; THUS, IT APPEARS THAT SACUBITRIL VALSARTAN IS CLINICALLY MORE EFFECTIVE THAN ENALAPRIL, IRRESPECTIVE OF BASELINE RISK, AND THAT IF AVAILABLE IN CLINICAL PRACTICE, SACUBITRIL VALSARTAN SHOULD BE CONSIDERED AS A REPLACEMENT FOR ACE INHIBITOR IN ALL PATIENTS WITH HEART FAILURE AND REDUCED EJECTION FRACTION.

REGARDING THE USE OF SACUBITRIL VALSARTAN, IT IS LIKELY THAT INITIAL USE WILL BE UNDER THE SUPERVISION OF SPECIALISTS IN HEART FAILURE MANAGEMENT, AND IS LIKELY TO BE IN SECONDARY CARE IN THE FIRST INSTANCE. HOWEVER, IT IS THE CASE THAT MANY OF THE PATIENTS RECEIVING THIS AGENT WILL HAVE CLINICAL MANAGEMENT INPUT FROM COMMUNITY HEART FAILURE NURSE SERVICES, AND THE SERVICES/INDIVIDUALS WILL NEED EDUCATION IN THE MODE OF ACTION OF

SACUBITRIL VALSARTAN. IN PARTICULAR, ALL HEALTH CARE PROFESSIONALS WILL NEED TO BE AWARE OF THE DANGER OF CO-PRESCRIPTION OF ACE INHIBITOR WITH SACUBITRIL VALSARTAN, A COMBINATION WHICH IN THEAORY MAY INCREASE THE RISK OF ANGIO-OEDEMA, A POTENTIALLY FATAL OCCURRENCE.

IT IS LIKELY THAT WITH TIME, PRESCRIPTION OF SACUBITRIL VASARTAN WILL SPREAD TO HEALTH CARE PROFESSIONALS OUTSIDE OF SECONDARY CARE CARDIOLOGY SERVICES. SIMILAR PRACTICES WERE OBSERVED WHEN ACE INHIBITORS FISRT BECAME AVAILABLE, AND INDEED WHEN BETA BLOCKERS WERE FIRST SHOWN TO BE EFFECTIVE IN IMPROVING OUTCOME FOR PATIENTS WITH HEART FAILURE.

SACUBITRIL VAALSARTAN IS CURRENTLY AVAILABLE IN THE UK IN THE FOLLOWING CIRCUMSTANCES: (i) TO PATIENTS WHO PARTICIPATED IN PARADIGM HF. AVAILABILITY IS IN THE CONTEXT OFAN OPEN-LABEL EXTENSION STUDY, WHICH COMMENCED IN THE UK IN AUGUST 2015 OR (ii) IN INDIVIDIAL CASES ON COMPASSIONATE GROUNDS, VIA DIRECT APLICATION TO THE MANUFACTURER. I AM NOT AWARE OF ANY CASE OF SUCH USE AT THE TIME OF WRITING

IT IS LIKELY THAT SACUBITRIL VALSARTAN WILL BE INCORPORATED IN TO NATIONAL AND INTERNATIONAL GUIDELINES FOR THE MANAGEMENT OF HEART FAILURE WITH REDUCED EJECTION FRACTION. THESE GUIDELINES PROVIDE RECOMMENDATIONS BASED UPON THE STRENGTH OF THE EVIDENCE AVAILABLE; EVIDENCE FROM RANDOMISED CLINICAL TRIALS IS CONSIDERED TO BE OF THE GREATEST VALUE IN THIS CONTEXT.

The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the

trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes? What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?	1. SACIBITRIL VALSARTAN APPEARS TO HAVE CLINICAL SUPERIORITY TO THE GOLD-STANDARD RAS INHIBITOR ENALAPRIL. INDICATIONS FOR THESE AGENTS ARE VERY SIMILAR. 2. THE SIDE-EFFECT PROFILE FOR SACUBITRIL VALSARTAN AND ACE INHIBITOR ARE VERY SIMILAR. USED ALONE, THE RISK OF ANGIO-OEDEMA IS LIKELY TO BE LOWER WITH SACUBITRIL VALSARTAN THAN WITH ACE INHIBITOR 3. SACUBITRIL VALSARTAN IS LIKELY TO BE AS EASY/DIFFICULT TO USE AS ACE INHIBITORS IN THIS POPULATION. AS WITH ACE INHIBITORS, RENAL FUNCTION SHOULD BE CHECKED AFTER THE C=DOSE OF SACUBITRIL VALSARTAN IS INCREASED, AND INTERMITTENTLY DURING STABLE CHRONIC THERAPY. 4. GUIDELINES FOR STARTING (CHRONIC HEART FAILURE WITH REDUCED LEFT VENTRICULAR EJECTION FRACTION) AND STOPPING SACUBITRIL VALSARTAN (NOT TOLERATED FOR WHATEVER RASON) WILL BE VERY SIMILAR TO THOSE SEEN CURRENTLY WITH ACE INHIBITORS AND OTHER EVIDENCE-BASED THERAPIES 5. SACUBITRIL VALSARTAN, DUE TO ITS MODE OF ACTION, INCREASED PLASMA LEVELS OF BNP. THIS INCREASE IS PARADOXICAL, IN THAT "HIGH" BNP LEVELS ARE CLASSICALLY ASSOCIETED WITH ADVERSE PROGNOSIS AND INCREASES ARE CONSIDERED UNDESIRABLE. HOWEVER THE INCREASE IN BNP SEEN WITH SACUBITRIL IS AMANIFESTATION OF THE MODE OF ACTION OF THIS AGENT; SACUBITRIL INHIBITS NEUTRAL ENDOPEPTIDASE, THE ENZYME WHICH CATALYSES BREAKDOWN OF BNP. AS BNP LEVELS ARE USED TO ASSESS THE SEVERITY OF THE PATIENTS CONDITION, AND RESPONSE TO THERAPY, IN PATIENTS TREATED WITH SACUBITRIL VALSARTAN, BNP IS NOT A USEFUL BIOMARKER. HOWEVER NTproBNP LEVELS ARE LOWERED BY SACUBITRIL VALSARTAN AND THIS BIOMARKER WILL REMAIN CLINICALLY USEFUL IN SUCH PATIENTS. CONSIDERATION MAY HAVE TO BE GIVEN TO PROVISION OF NTproBNP RATHER THAN BNP IN CLINICAL SERVICES. 6. THE END POINTS MEASURED IN THE PARADIGM HF TRIAL ARE THOSE WHICH MATTER TO PATIENTS AND TO HEALTH CARE DELIVERY SYSTEMS: THE PRIMARY END POINT WAS THE COMBINATION OF CARDIOVASCULAR MORTALITY AND HEART FAILURE HOSPITALISATION. SACUBITRIL VALSARTAN WAS SUPERIOR TO ENALAPRIL IN THIS RESPECT, WITH A CLINICALLY MEANINGFUL 16% RELATIVE RISK REDUCTION. THE INDIVIDUAL COMPONENTS OF THIS END POINT WERE EAXH REDUCED BY A SMILAR EXTENT AND,

IMPORTANTLY, ALL-CAUSE MORTLAITY WAS ALSO REDUCED TO A MEANINGFUL EXTENT

7. OVER 250 PATIENTS WERE RECRUITED TO PARADIGM HF IN UK CENTRES. OVERALL, THE PATIENT POPULATION IS REFLECTIVE OF THAT SEEN IN CLINICAL PRACTICE IN THE UK.

Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

I AM NOT AWARE OF ANY SUCH SOURCES

Implementation issues

The NHS is required by the Department of Health to provide funding and resources for medicines and treatments that have been recommended by NICE technology appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.

If the technology is unlikely to be available in sufficient quantity, or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within 3 months, NICE may advise the Department of Health to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

THIS TECHNOLOGY IS LIKELY TO BE PRESCRIBED BY, AND PATIENTS MANAGED UNDER THE SUPERVISION OF, PROFESSIONALS WITH EXPERIENCE AND EXPERTISE IN THE MANAGEMENT OF HEART FAILURE. IN THE FIRST INSTANCE THIS IS LIKELY TO BE IN THE SECONDARY CARE SETTING. I DO NOT FORESEE ANY MAJOR ISSUES IN THIS REGARD AND IT IS UNLIKELY THAT ADDITIONAL RESOURCES WILL BE REQUIRED.

IN THE EARLY PERIOD OF CLINICAL USE, THERE IS LIKELY TO BE SOME VARIATION IN THE SETTING IN WHICH THIS AGENT WILL BE UTILISED IN PLACE OF ACE INHIBITORS. FOR INSTANCE, SOME CLINICIANS MAY ELECT TO SWITCH PATIENTS AS THEY ARE SEEN FOR REGULAR REVIEW IN

CLINICS. OTHERS MAY UTILISE THE OPPORTUNITY OFFERED BY ELECTIVE OR EMERGENCY HOSPITALISATION TO MAKE THIS SWITCH, OR INDEED TO START SACUBITRIL VALSARTAN, RATHER THAN ACE INHIBITOR, IN PATIENTS WITH A DE-NOVO DIAGNOSIS OF HEART FAILURE.

EDUCATION WILL BE REQUIRED IN THE MODE OF ACTION OF THIS TECHNOLOGY AND THE NEED TO AVOID CO-PRESCRIPTION OF ACE INHIBIORS. IT WILL BE IMPORTANT THAT PRESCRIBERS, INCLUDING GPs, PRESCRIBING NURSES, HEART FAILURE NURSES, AND OTHERS INVOLVED IN THE MANAGEMENT OF PATIENTS WITH HEART FAILURE, ARE MADE AWARE OF THIS ISSUE.

Equality

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this appraisal:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;
- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- could lead to recommendations that have any adverse impact on people with a particular disability or disabilities.

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts.

N/A

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Sacubitril valsartan for treating heart failure with systolic dysfunction

Thank you for agreeing to give us a statement on your view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your statement, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name:
Dr Lisa Anderson

Name of your organisation
British Society for Heart Failure

Are you (tick all that apply):

- a specialist in the treatment of people with the condition for which NICE is considering this technology? Yes
- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)? Yes
- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc.)? Yes, councillor for British Society for Heart Failure and clinical lead for Heart Failure at St George's Hospital, London
- other? (please specify)

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

What is the expected place of the technology in current practice?

How is the condition currently treated in the NHS? Is there significant geographical variation in current practice? Are there differences of opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?

Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

- Current medical treatment for heart failure (HF) with left ventricular systolic dysfunction (LVSD) is ACE inhibitors (or ARBs if not tolerated) plus beta blockers (BBs) - plus mineralocorticoid antagonists (MRAs). Device therapy with CRT +/- D is used in selected patients.
- There is no significant geographical variation in practice due to well established National and International guidelines for HF. The evidence base exceptionally strong so standard therapy as outlined above is well recognised.
- The current alternative to this therapy is ACE inhibition. The advantage for patients taking sacubitril valsartan (as set out in PARADIGM-HF trial) was reduced primary end point of both cardiovascular mortality and hospitalisation for HF as well as reduced all cause mortality when compared to Enalapril 10mg bd (ACE-)
- The benefits of ACE- are that they are cheap and familiar drugs for specialists and GPs alike and the side effect profile is well established.
- As in all major heart failure trials less pronounced benefit is shown in the elderly, owing to comorbidities and in severe heart failure, nyha class 3+. It is important however that older patients are not denied access to new therapies, and the cut offs for nyha class are notoriously arbitrary and unreliable.
- The Afro-Caribbean population are more at risk of angio-oedema with ACE- and a previously trialled drug, omipatrilat and are likely to be more at risk of angio-oedema with sacubitril valsartan. In the PARADIGM-HF trial sacubitril valsartan caused more angio-oedema than enalapril, although in the trial these events were ‘non-serious’.
- Heart failure patients are managed by GPs, community nurses and hospitals. The benefit shown in PARADIGM-HF over standard therapy with enalapril was striking (cardiovascular mortality risk 0.80, 95% C! 0.71-0.89), however the trial design was

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Single Technology Appraisal (STA)

such that patients underwent pre-treatment with 10mg bd enalapril for a median of 29 days before being exposed to sacubitril valsartan. During the two sequential run in phases a total of 20% of patients withdrew largely due to adverse events and abnormal blood results. Clear guidance on safe introduction of sacubitril valsartan would therefore be needed to replicate the PARADIGM-HFs results of safety and efficacy.

- A wholescale switch of heart failure patients from ACE- to sacubitril valsartan would require a huge resource in HF nurse specialist, GP and HF consultant time. Even introduction in new HF patients would require extra work if the patient needs to be established on ACE- before switching to sacubitril valsartan.
- Sacubitril valsartan is not currently available in the UK and has yet to be included in international guidelines, although approved by FDA in July.

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Single Technology Appraisal (STA)

The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

- Given the design of the PARADIGM-HF study, we lack safety information regarding the introduction of sacubitril valsartan in ACE- naïve patients. 99% of the patients in PARADIGM-HF were taking ACE- or ARBs at entry to the study and were uptitrated to 10mg bd enalapril and stable on this for 2 weeks before to switching to sacubitril valsartan. Despite this pre-treatment with 10mg bd of enalapril, a further >600 patients (of around 9000 reaching this stage of the trial) had an adverse event or abnormal blood result during the 4 week run-in phase of sacubitril valsartan. The introduction phase of sacubitril valsartan will therefore require very clear guidance to practitioners.
- Nonetheless striking advantages of sacubitril valsartan over current standard best medical care in terms of survival, hospitalisations and quality of life were demonstrated in PARADIGM-HF.
- Sacubitril valsartan was effective across all pre-specified sub-groups and although less impressive in older patients or in those with NYHA class 3+ these patients should not be excluded from the potential benefits of sacubitril valsartan.
- Given the higher rates of angio-oedema experienced in those of African descent exposed to ACE-, and the low numbers of this cohort included in the trial (5%), extra vigilance will be required for this cohort.
- As with all HF trials, the patients enrolled were younger (mean age 64) and more likely to be male (78%) than the UK HF population. The trial patients were on higher levels of background medication (93% BB and 60% MRA) than the UK HF population (see National HF Audit). Despite 20% of patients having LBBB, only 7% had device therapy with CRT, but low device rates have also been found in previous large HF trials. A large proportion of the patients in this trial were in NYHA class 2 (70%).

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Single Technology Appraisal (STA)

- The PARADIGM-HF study examined all the relevant outcomes for a HF trial including the primary end point of cardiovascular mortality and HF admissions, all cause mortality and quality of life.
- Once randomised to sacubitril valsartan or enalapril, the side effect profiles were similar. However, due to the design of the PARADIGM-HF study and the sequential enalapril followed by sacubitril valsartan run-in phases, the true side effect profile with de-novo introduction in ACE- naïve patients is not known.

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Single Technology Appraisal (STA)

Equality and Diversity

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this appraisal:

- Could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;
- Could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- Could lead to recommendations that have any adverse impact on people with a particular disability or disabilities

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts

- No

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Single Technology Appraisal (STA)

Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

Implementation issues

The NHS is required by the Department of Health and the Welsh Assembly Government to provide funding and resources for medicines and treatments that have been recommended by NICE technology appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.

If the technology is unlikely to be available in sufficient quantity, or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within 3 months, NICE may advise the Department of Health and the Welsh Assembly Government to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

- It would not be feasible to switch the entire UK LVSD HF population from ACE- to sacubitril valsartan in a 3 month time interval.
- Provided guidance is explicit the additional training requirement is not great.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Sacubitril valsartan for treating heart failure with systolic dysfunction

Thank you for agreeing to give us a statement on your view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your statement, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name: Simon Williams

Name of your organisation Wythenshawe Hospital, Manchester

Are you (tick all that apply):

- a specialist in the treatment of people with the condition for which NICE is considering this technology? yes
- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)? yes
- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc.)? no
- other? (please specify) I have received honorarium from Novartis for advisory work

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Single Technology Appraisal (STA)

What is the expected place of the technology in current practice?

How is the condition currently treated in the NHS? Is there significant geographical variation in current practice? Are there differences of opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

Chronic heart failure is treated according to standard guidelines across the UK (NICE 2012, ESC 2012). The treatment is standard and there are no real variations or differing opinions from physicians and nurse who treat this condition

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

There is a wide variation in prognosis in patients with chronic heart failure, this is assessed on an individual patient basis but does not affect optimal treatment

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?

Across all areas of treatment (primary & secondary care, physician and nursing led clinics)

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?

No

Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

No current guidelines exist for this treatment. It has recently had FDA approval in the US

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Single Technology Appraisal (STA)

The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

Will replace standard treatment (ACE inhibitors) – no increased resource will be needed

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

No other resource needed apart from standard care

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

Multinational trial including patients from UK – applicable to UK practice

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

No increased side effects from standard of care (ACE inhibitors)

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Single Technology Appraisal (STA)

Equality and Diversity

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- Could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;
- Could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- Could lead to recommendations that have any adverse impact on people with a particular disability or disabilities

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts

N/A

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Single Technology Appraisal (STA)

Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

N/A

Implementation issues

The NHS is required by the Department of Health and the Welsh Assembly Government to provide funding and resources for medicines and treatments that have been recommended by NICE technology appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.

If the technology is unlikely to be available in sufficient quantity, or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within 3 months, NICE may advise the Department of Health and the Welsh Assembly Government to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

No additional resource would be needed

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Patient/carer expert statement (STA)

Sacubitril valsartan for treating heart failure with systolic dysfunction [ID822]

Thank you for agreeing to give us your views on this treatment that is being appraised by NICE and how it could be used in the NHS. Patients, carers and patient organisations can provide a unique perspective on conditions and their treatment that is not typically available from other sources. We are interested in hearing about:

- the experience of having the condition or caring for someone with the condition
- the experience of receiving NHS care for the condition
- the experience of having specific treatments for the condition
- the outcomes of treatment that are important to patients or carers (which might differ from those measured in clinical studies, including health-related quality of life)
- preferences for different treatments and how they are given
- expectations about the risks and benefits of the treatment.

We have already asked your nominating organisation to provide an organisation's view. We are asking you to give your views as an individual whether you are:

- a patient
- a carer (who may be voicing views for a patient who is unable to) or
- somebody who works or volunteers for a patient organisation.

To help you give your views, we have provided a questionnaire. You do not have to answer every question — the questions are there as prompts to guide you. The response area will expand as you type. The length of your response should not normally exceed 10 pages.

1. About you

Your name: EMMA TAYLOR
Name of your nominating organisation: PUMPING MARVELLOUS FOUNDATION
Do you know if your nominating organisation has submitted a statement?

X Yes ☐ No

Do you wish to agree with your nominating organisation's statement?

X Yes ☐ No

(We would encourage you to complete this form even if you agree with your nominating organisation's statement.)

Are you:

- a patient with the condition?

X Yes ☐ No

- a carer of a patient with the condition?

X Yes ☐ No

- a patient organisation employee or volunteer?
-

X Yes ☐ No

Do you have experience of the treatment being appraised?

☐ Yes X No

If you wrote the organisation submission and do not have anything to add, tick here ☐ (If you tick this box, the rest of this form will be deleted after submission.)

2. Living with the condition

What is your experience of living with the condition as a patient or carer?

I was diagnosed with acute Heart Failure in 2006, I am currently living with the condition and taking appropriate medication/therapies. I also care for my father who has HF and is currently in end stage HF.

3. Current practice in treating the condition

Which treatment outcomes are important to you? (That is, what would you like treatment to achieve?) Which of these are most important? If possible, please explain why.

To be able to live a relatively normal life, reducing symptoms and therefore increasing quality of life and ability to undertake day to day tasks which in turn helps carer/family members and encourages self management.

What is your experience of currently available NHS care and of specific treatments? How acceptable are these treatments – which did you prefer and why?

As a carer I am aware that my father is on a drug regime including Beta Blockers, ACE's, diuretics and has a device, this in my opinion is the treatment I prefer as it allowed him to have a better quality of life.

4. What do you consider to be the advantages of the treatment being appraised?

Benefits of a treatment might include its effect on:

- the course and/or outcome of the condition- obvious advantage as it can improve quality of life and help give hope.
- physical symptoms – a reduction in this is an advantage for any HF patient as they can be quite debilitating.
- Pain – not sure?
- level of disability – again in line with the above, HF can mean people have limited mobility, this may help that.
- mental health – depression is a key side effect of HF

- quality of life (such as lifestyle and work) – HF can mean even every day tasks are difficult as such this would help to improve that and perhaps even mean a patient could work.
- other people (for example, family, friends and employers) – when the patient is improved this has a positive effect on others around them.
- ease of use (for example, tablets rather than injection) – tablets are generally easier to administer than injections.
- where the treatment has to be used (for example, at home rather than in hospital) – don't think this makes a great difference at all.
- any other issues not listed above

Please list the benefits that you expect to gain from using the treatment being appraised.

Enhanced quality of life, less hospital admissions, longer life and also give the patient more push to self-manage.

Please explain any advantages that you think this treatment has over other NHS treatments in England.

To me it seems the new therapy may produce better outcomes and in turn reduce the burden on hospitals and the NHS, saving money and resource.

If you know of any differences in opinion between you and other patients or carers about the benefits of the treatment being appraised, please tell us about them.

I don't know of any difference in opinion.

5. What do you consider to be the disadvantages of the treatment being appraised?

Disadvantages of a treatment might include:

- aspects of the condition that the treatment cannot help with or might make worse
- difficulties in taking or using the treatment (for example, injection rather than tablets) – this is not an issue to myself as a patient or carer?
- side effects (for example, type or number of problems, how often, for how long, how severe. Please describe which side effects patients might be willing to accept or tolerate and which would be difficult to accept or tolerate) – weight gain can be a difficult side effect, particularly for women and also this can obviously exacerbate HF. Memory can be affected or "brain fog" which is often associated with treatments such as BB's. Patients do accept these however anything more severe such as nausea, stomach issues or headaches can leave the patient feeling unable to tolerate.

- where the treatment has to be used (for example, in hospital rather than at home) – home should be preferable as the patient feels more relaxed at home as travelling can be a huge deal with someone with HF.
- impact on others (for example, family, friends and employers) – don't believe this would impact anyone else.
- financial impact on the patient and/or their family (for example, the cost of travel to hospital or paying a carer) – this would be a disadvantage as many HF sufferers are unable to work so any additional cost could have an impact.
- any other issues not listed above

Please list any concerns you have about current NHS treatments in England.

Care is not the same across England, a lack of a HF team such as cardiac nurse or support is not always available and I feel that everyone should be entitled to the same care regardless of where they live.

Please list any concerns you have about the treatment being appraised.

I have no concerns other than the patient voice should be heard.

If you know of any differences in opinion between you and other patients or carers about the disadvantages of the treatment being appraised, please tell us about them.

I do not know of any differences in opinion.

6. Patient population

Do you think some patients might benefit more from the treatment than others? If so, please describe them and explain why.

I feel that patients such as my father who have been stable but are now quite fragile as "older" therapies do not appear to be working as well may benefit more than others however that is not to say it would not be as suitable/successful for someone in a better position health wise.

Do you think some patients might benefit less from the treatment than others? If so, please describe them and explain why.

I am unsure as this could apply to any patient at any level.

7. Research evidence on patient or carer views of the treatment

Are you familiar with the published research literature for the treatment?

☐ Yes ☒ No

If you answered 'no', please skip the rest of section 7 and move on to section 8.

Please comment on whether your experience of using the treatment as part of routine NHS care reflects the experience of patients in the clinical trials.

Do you think the clinical trials have captured outcomes that are important to patients? Are you aware of any limitations in how the treatment has been assessed in clinical trials?

If the treatment being appraised is already available in the NHS, are there any side effects that were not apparent in the clinical trials but have emerged during routine NHS care?

Are you aware of any relevant research on patient or carer views of the condition or existing treatments?

☐ Yes ☐ No

If yes, please provide references to the relevant studies.

8. Equality

NICE is committed to promoting equality of opportunity and eliminating discrimination. Please let us know if you think that recommendations from this appraisal could have an adverse impact on any particular groups of people, who they are and why.

I don't believe this would have an adverse impact on any group.

9. Other issues

Do you consider the treatment to be innovative?

☒ Yes ☐ No

If yes, please explain what makes it significantly different from other treatments for the condition.

I consider it to be innovative as this will potentially increase quality of life and in turn the patients health which means they can live a relatively normal life with less of the terrible symptoms that can be part of HF.

Is there anything else that you would like the Appraisal Committee to consider?

No

10. Key messages

In no more than 5 bullet points, please summarise the key messages of your submission.

- Reduction in symptoms
- Better quality of life whilst living with HF
- Less hospital admissions
- Everyone should receive the same care regardless of post code
- Positive effect of the treatment on a patient could be a huge improvement in self management helping to give HOPE to the patient and their family.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Patient/carer expert statement (STA)

Sacubitril valsartan for treating heart failure with systolic dysfunction [ID822]

Thank you for agreeing to give us your views on this treatment that is being appraised by NICE and how it could be used in the NHS. Patients, carers and patient organisations can provide a unique perspective on conditions and their treatment that is not typically available from other sources. We are interested in hearing about:

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- the experience of having specific treatments for the condition
- the outcomes of treatment that are important to patients or carers (which might differ from those measured in clinical studies, including health-related quality of life)
- preferences for different treatments and how they are given
- expectations about the risks and benefits of the treatment.

We have already asked your nominating organisation to provide an organisation's view. We are asking you to give your views as an individual whether you are:

- a patient
- a carer (who may be voicing views for a patient who is unable to) or
- somebody who works or volunteers for a patient organisation.

To help you give your views, we have provided a questionnaire. You do not have to answer every question — the questions are there as prompts to guide you. The response area will expand as you type. The length of your response should not normally exceed 10 pages.

1. About you

Your name: Nick Hartshorne-Evans
Name of your nominating organisation: Pumping Marvellous Foundation
Do you know if your nominating organisation has submitted a statement?

x Yes ☐ No

Do you wish to agree with your nominating organisation's statement?

x Yes ☐ No

(We would encourage you to complete this form even if you agree with your nominating organisation's statement.)

Are you:

- a patient with the condition?

x Yes ☐ No

- a carer of a patient with the condition?

☐ Yes x No

- a patient organisation employee or volunteer?
-

x Yes ☐ No

Do you have experience of the treatment being appraised?

☐ Yes x No

If you wrote the organisation submission and do not have anything to add, tick here ☐ (If you tick this box, the rest of this form will be deleted after submission.)

2. Living with the condition

What is your experience of living with the condition as a patient or carer?

I was diagnosed with acute Heart Failure in Jan 2010. I am currently living with the condition and on the appropriate therapies.

3. Current practice in treating the condition

Which treatment outcomes are important to you? (That is, what would you like treatment to achieve?) Which of these are most important? If possible, please explain why.

Reduction of symptoms enabling better quality of life

Reduction in hospital admissions / impact on Mortality figures

Give HOPE as the current gold standard therapies have not changed for years. A new treatment option is welcome as it will generate optimism and may also enable patients to validate that there is a reason to be positive and develop their self-management skills around HF which would lead to better outcomes and a more informed HCP treating them. There is an “Air” of failure around HF!

What is your experience of currently available NHS care and of specific treatments? How acceptable are these treatments – which did you prefer and why?

ACE and ARB’s with beta blocker and or Ivabradine. Once patients have achieved their optimum dosage then this seems to be all that can be done apart from devices, there seems to be no further drug options other than those that are administered in acute settings. I believe this is a very insensitive question as to a patients preference to which do they prefer. Surely the obvious answer is if it works and the symptoms don’t affect my QOL then this is the best option.

4. What do you consider to be the advantages of the treatment being appraised?

Benefits of a treatment might include its effect on:

- It may delay or reduce the progression of HF with a reduction in mortality

- It may reduce symptoms and therefore increase mobility
- Not sure about pain???
- It may enable patients to have a better quality of life as HF symptoms can be very disabling especially in acute exacerbation and NYHA III
- It may produce a better state of mind based around optimism and HOPE. These are essential elements for effective self-management.
- It may increase the quality of life of patients and enable them to be more active and productive
- If the HF patient has a better QOL then this will have a knock on effect on the family, friends, support services, potential employment, health economy
- Assuming it is in tablet format then with the other raft of therapies especially where co-morbidities are very common in HF patients then this shouldn't be a consideration.
- Assuming it is self-administered in tablet format then this is convenient and not administered by a HCP.
- Irrespective of the clinical data from the Paradigm HF trial which indicates blockbuster potential over the existing gold standard therapies what I feel is very often underestimated and very rarely seems to be covered, is the optimism and HOPE that a new therapy can create. Unlike cancer, HF patients have a raw deal with little investment in the condition (known by the stakeholder community as the Cinderella syndrome) but an extremely large patient population to serve. The tsunami effect of "there is a new hope" can often stimulate positive outcomes however intangible by such large patient populations. I stress that this significant factor needs to be considered along with the typical health economics and clinical data.

Please list the benefits that you expect to gain from using the treatment being appraised.

Better QOL

Reduced admissions / readmissions

Reduced mortality

Increased interest in other potential stakeholders seeing positive effects – increased investment

More motivated patient population

Increased adoption of “how the patient can help themselves” manage their condition. If they feel they are being invested in then it may give them the impetus they need?

Potential decreased economic burden

Potential decreased logistical resource burden

Please explain any advantages that you think this treatment has over other NHS treatments in England.

See above reference the Paradigm-HF clinical data where the gold standard therapy seems to have been thoroughly put into 2nd place.

To have a potential effect of reducing hospital readmissions, making “brittle” patients more stable therefore reducing the burden of HF on A&E, beds, logistical resources and fiscal resources.

If you know of any differences in opinion between you and other patients or carers about the benefits of the treatment being appraised, please tell us about them.

Occupying the patient leadership position around HF I can say without hesitation that any new therapy that works and has better outcomes than the existing gold standard therapy and with the patients correct perception that HF is underinvested, any new advancements are welcome. There has been a lot of discussion around the clinical trial data and outcomes and this has only been positive. The patient population is hungry for new therapies to dismiss the word “Failure”.

5. What do you consider to be the disadvantages of the treatment being appraised?

Disadvantages of a treatment might include:

- As HF patients are very susceptible to co-morbidities then I HOPE this is not seen as a silver bullet for all their symptoms but that their HF is being treated as best as it can be
- I don’t see any issues with how and where the patient administers the therapy
- The trial precluded patients with hypotension. HF patients can have hypotension

- When patients are on ACE inhibitors they can experience persistent symptoms which means that they are swapped to an alternative therapy with ARB's. Does this indicate that those same patients may not be able to tolerate the new therapy due to persistent symptoms like a cough?
- I don't see disadvantages about the effect on carers or ability to work
- I believe that where there will be an issue is the motivation for those patients in primary care who don't have a cardiologist but are managed by GP's for the GP to be
- The trial did not cover the full population of HF patients only those with HFREF. That's not the drugs fault though.

    - Aware of the drug
    - Patients have been treated on generics for a long time therefore the economic price question comes into play
    - If the patients are stable then why move them off the cheap generics

- Will the fact that the new therapy will be at a disadvantage from the start due to the cost question and therefore cause disparity of prescribing in a fragmented system?

Please list any concerns you have about current NHS treatments in England.

Our concern would be the access of the best available therapies to all patients. The parity of care question has never been so heightened due to perceived economic restraints. A general concern will be that where HF patients sit under the GP's care, do the GP's understand the NYHA scale and it's alignment with how the patient feels and not clinical indicators?

Please list any concerns you have about the treatment being appraised.

I have no concerns as long as the patient's voice is heard and acted on, not for it to be a "tick" box add on.

If you know of any differences in opinion between you and other patients or carers about the disadvantages of the treatment being appraised, please tell us about them.

No

6. Patient population

Do you think some patients might benefit more from the treatment than others? If so, please describe them and explain why.

Patients who are traditionally more brittle or less stable in the swing state of NYHA II / NYHA III. These are the patients that would benefit from this therapy initially to reduce the burden of having to live with the disease and where management is more acutely focussed. Their quality of life is unpredictable and stabilisation is a good thing for them. This isn't to suggest that all HF patients wouldn't benefit, just get to those where the current set of gold standard therapies is not always working for them. I believe these are also the group of HFREF patients that are more susceptible to hospital admission and "deeper dives" in symptoms leading to acute HF.

Do you think some patients might benefit less from the treatment than others? If so, please describe them and explain why.

Relating to the Paradigm-HF trial data then it would seem that all patients might benefit however at the extreme ends of the NYHA scale then it may have a lesser effect for different reasons. As HF patients can suffer from hypotension then this may automatically prevent them from receiving this therapy

The trial was not designed around HFPEF patients only those with HFREF. It will be very interesting to see how further trials in the HFPEF population react to this new therapy.

7. Research evidence on patient or carer views of the treatment

Are you familiar with the published research literature for the treatment?

x Yes ☐ No

If you answered 'no', please skip the rest of section 7 and move on to section 8.

Please comment on whether your experience of using the treatment as part of routine NHS care reflects the experience of patients in the clinical trials.

From a lay position it does.

Do you think the clinical trials have captured outcomes that are important to patients? Are you aware of any limitations in how the treatment has been assessed in clinical trials?

The trial outcomes have absolutely captured the majority of important priorities.

If the treatment being appraised is already available in the NHS, are there any side effects that were not apparent in the clinical trials but have emerged during routine NHS care?

N/A

Are you aware of any relevant research on patient or carer views of the condition or existing treatments?

☐ Yes x No

If yes, please provide references to the relevant studies.

8. Equality

NICE is committed to promoting equality of opportunity and eliminating discrimination. Please let us know if you think that recommendations from this appraisal could have an adverse impact on any particular groups of people, who they are and why.

Looking at the trial parameters then it seems there are only clinical rule outs e.g. NYHA status and hypotension

9. Other issues

Do you consider the treatment to be innovative?

x☐ Yes ☐ No

If yes, please explain what makes it significantly different from other treatments for the condition.

As explained above just the clinical data from the Paradigm-HF trial makes it innovative and is a new class of therapy that seems to work. It is also innovative that it may create a new wave of interest in all stakeholders to further develop investment opportunities to raise the awareness of HF and therefore have an effect on the QOL of those affected.

Is there anything else that you would like the Appraisal Committee to consider?

No

10. Key messages

In no more than 5 bullet points, please summarise the key messages of your submission.

- Sacubitril valsartan demonstrates innovative status
- A robust trial has produced blockbuster results in HFREF patients
- The therapies and challenges are around acceptance in a market dominated by generics and the ability of it to have a profound and measured effect in a historically under invested condition area
- HF patients may never have had such a positive opportunity for a “pill” to have such a paradigm effect, more than man may realise
- HF failure management is not just a clinical challenge. With the positive element of a first in class new therapy having such positive results then the intangible element of HOPE could result in blockbuster outcomes downstream

Sacubitril valsartan for treating chronic heart failure

STA REPORT

Confidential until published

This report was commissioned by the NIHR HTA Programme as project number 15/64/06

BMJ Technology Assessment Group

Sacubitril valsartan for treating heart failure with systolic dysfunction [ID822]

Produced by: BMJ Technology Assessment Group (BMJ-TAG)

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None

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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: Edwards SJ, Crawford F, Osei-Assibey G Bacelar M, Berardi A, Salih F. Sacubitril valsartan for treating chronic heart failure: A Single Technology Appraisal. BMJ-TAG, 2015.

Contributions of authors:

Steve Edwards	Critical appraisal of the company's submission; carried out the statistical analyses; provided feedback on all versions of the report
Fay Crawford	Critical appraisal of the company's submission; critical appraisal of the clinical evidence; cross checking of company's search strategies; and drafted the summary and clinical results sections
George Osei-Assibey	Critical appraisal of the company's submission; critical appraisal of the clinical evidence; cross checking of company's search strategies; and drafted the summary and clinical results sections
Mariana Bacelar	Critical appraisal of the company's submission; critical appraisal of the economic model; cross checking of company's search strategies; critical appraisal of the economic evidence; carried out the economic analyses; and drafted the economic sections
Andrea Berardi	Critical appraisal of the company's submission; critical appraisal of the economic model; cross checking of company's search strategies; critical appraisal of the economic evidence; carried out the economic analyses; and drafted the economic sections
Fatima Salih	Contributed to the review of the cost-effectiveness systematic review and to the draft of the summary and clinical results sections

All authors read and commented on draft versions of the ERG report.

Table of contents

Abbreviations

A	Asian
A&E	Accident and emergency
AA	Aldosterone antagonist
AC	Any cause
ACEi	Angiotensin converting enzyme inhibitor
ACS	Acute coronary syndrome
ADL	Activities of daily living
ADP	Adenosine diphosphate
AE	Adverse event
AF	Atrial fibrillation
AIC	Akaike information criterion
ANCOVA	Analysis of covariance
ARB	Angiotensin II receptor blocker
ARNI	Angiotensin receptor neprilysin inhibitor
AT1	Angiotensin II type-1
BB	Beta blocker
BIC	Bayesian information criterion
bid	Twice daily
BL	Baseline
BMI	Body mass index
BNF	British National Formulary
BNP	B-type natriuretic peptide
BP	Blood pressure
C	Caucasian
CAD	Coronary artery disease
CADTH	Canadian Agency for Drugs and Technologies in Health
CC	Complication and comorbidity
CCS	Clinical composite score
CEA	Cost-effectiveness analysis
CEAC	Cost-effectiveness acceptability curve
CEP	Cost-effectiveness plane
CHF	Chronic heart failure
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
Coef	Coefficient
COPD	Chronic obstructive pulmonary disease

CPRD	Clinical Practice Research Datalink
CrI	Credible intervals
CRT	Cardiac resynchronisation therapy
CRT-D	Cardiac resynchronisation therapy defibrillator
CRT-P	Cardiac resynchronisation therapy pacemaker
CSR	Clinical study report
CSS	Clinical summary score
CV	Cardiovascular
DBL	Database lock
df	Degrees of freedom
DIC	Deviance information criterion
DSU	Decision support unit
EAMS	Early access to medicine scheme
ECG	Electrocardiogram
ECHO	Echocardiography
ECHOES	Echocardiographic Heart of England Screening
EF	Ejection fraction
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
EPAR	European Public Assessment Report
ESC	European Society of Cardiology
ESRD	End-stage renal disease
FAS	Full analysis set
FDA	US Food and Drug Administration
GCP	Good clinical practice
GP	General practitioner
H	Hispanic
HD	High dose
HF	Heart failure
HFpEF	Heart failure with preserved ejection fraction
HFrEF	Heart failure with reduced ejection fraction
HFSA	Heart Failure Society of America
Hosp	Hospitalisation
HR	Hazard ratio
HRG	Healthcare Resource Group
HRQoL	Health-related quality of life
HSUV	Health state utility value
HTA	Health Technology Assessment

i.v.	Intravenous
IC	Ischaemic cardiomyopathy
ICD	Implantable cardioverter-defibrillator
ICER	Incremental cost-effectiveness ratio
ICU	Intensive care unit
IF	I*f* ("funny" current) channel inhibitor
IQR	Interquartile range
IRR	Incidence rate ratio
ITT	Intention-to-treat
IVRS	Interactive voice response system
KCCQ	Kansas City Cardiomyopathy Questionnaire
LD	Low dose
ll	Log-likelihood*
ll	Lower limit*
LSM	Least squares mean
LV	Left ventricular
LVAD	Left ventricular assist device
LVEF	Left ventricular ejection fraction
LVSD	Left ventricular systolic dysfunction
LYG	Life years gained
MA	Marketing authorisation
MD	Medium dose
MeSH	Medical subject headings
MHRA	Medicines and Healthcare products Regulatory Agency
MI	Myocardial infarction
MTP	Multiple testing procedure
NA	Not applicable
NB	Negative binomial
NHS	National Health Service
NHS-EED	NHS Economic Evaluation Database
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
NOAC	Novel oral anticoagulant
NR	Not reported
NT-proBNP	N-terminal pro-brain natriuretic peptide
NYHA	New York Heart Association
O	Other
Obs	Observations

OD	Once daily
OECD	Organisation for economic co-operation and development
OR	Odds ratio
P	Probability
PARADIGM-HF	Prospective comparison of ARNI with ACEi to Determine Impact on Global Mortality and morbidity in Heart Failure
PBAC	Pharmaceutical Benefits Advisory Committee
PbR	Payment by results
PCI	Percutaneous coronary intervention
PDE-5	Phosphodiesterase-5
PIM	Promising Innovative Medicine
PK	Pharmacokinetics
PLBO	Placebo
PP	Per protocol
PSA	Probabilistic sensitivity analysis
PSS	Personalised social services
PSSRU	Personal Social Services Research Unit
QALY(s)	Quality adjusted life year(s)
QoL	Quality of life
RAAS	Renin angiotensin aldosterone system
RCT	Randomised controlled trial
RePEc	Research Papers in Economics
RR	Relative risk
SAE	Serious adverse event
SAF	Safety population
SAP	Statistical analysis plan
SBP	Systolic blood pressure
SD	Standard deviation
SE	Standard error
SG	Standard gamble
SIGN	Scottish Intercollegiate Guidelines Network
SmPC	Summary of product characteristics
SMC	Scottish Medicine Consortium
SMQ	Standardised MedDRA query
SR	Systematic review
STA	Single technology appraisal
TA	Technology appraisal
TIA	Transient ischaemic attack
TTO	Time trade off

VAS	Visual analogue scale
W	White
WHO	World Health Organization

1 SUMMARY

1.1 Critique of the decision problem in the company's submission

The company holding the marketing authorisation for sacubitril valsartan (henceforth referred to as sacubitril) (Entresto®; Novartis) submitted to the National Institute for Health and Care Excellence (NICE) clinical and economic evidence in support of the effectiveness and cost-effectiveness of sacubitril in the treatment of chronic heart failure (CHF). The Committee for Medicinal Products for Human Use (CHMP) has granted accelerated assessment to sacubitril. A CHMP opinion is expected in October 2015. A European Medicines Agency (EMA) decision on marketing authorisation is expected in December 2015.

The pivotal clinical evidence presented in the company's submission (CS) is derived from the PARADIGM-HF phase III randomised controlled trial. The PARADIGM-HF trial enrolled patients with New York Heart Association (NYHA) classification II–IV and left ventricular ejection fraction (LVEF) of ≤35%. The final scope issued by NICE specified the population of interest was people with chronic heart failure (NYHA class II–IV) with systolic dysfunction.

The Evidence Review Group (ERG) considers the population in PARADIGM-HF to be relevant to the decision problem. However the ERG notes the population was younger than those managed in UK clinical practice. The National Heart Audit from the UK reports 66% of CHF patients are over 75 years old as opposed to an average age of 64 years old in the PARADIGM-HF trial.(1, 2)

The intervention is sacubitril valsartan, an angiotensin receptor neprilysin inhibitor (ARNI) at a dose of 200mg BID. The comparator in the PARADIGM-HF trial was enalapril 10mg bid, an angiotensin converting enzyme inhibitor (ACEi). In the final scope issued by NICE, the comparators of interest were identified as ACEi with standard care, angiotensin II receptor blocker (ARB) with standard care (for people in whom an ACEi is unsuitable). The scope notes standard care includes treatment with a beta blocker and an aldosterone antagonist.(3)

The ERG considers that the comparator in the PARADIGM-HF trial is reasonably analogous to the management of CHF as would typically occur in UK clinical practice and was as specified in the final scope issued by NICE. However, clinical expert advice to the ERG highlighted that enalapril is not the most commonly prescribed ACEi in the UK.

All clinically relevant outcomes in the final scope issued by NICE were reported in the CS including symptoms of heart failure, cardiovascular (CV) related hospitalisation, all-cause hospitalisation, mortality, CV mortality, adverse effects of treatment.

1.2 Summary of clinical effectiveness evidence submitted by the company

The primary objective of the PARADIGM-HF trial was to compare the outcomes of patients receiving sacubitril 200mg BID with enalapril 10mg BID in the management of CHF. To be eligible for enrolment patients had to have CHF defined by LVEF below 35% or reported as reduced with a NYHA class II–IV. The PARADIGM-HF trial also produced data to inform the analysis of treatment-related adverse events which affected about 22% of the trial population.

The number of patients randomised (1:1) to either sacubitril or enalapril were 8,442. There were 4,209 patients randomised to sacubitril and 4,233 patients to enalapril. The company reports data from three different analysis sets in the PARADIGM-HF trial; the Full Analysis Set (FAS) consisted of all patients except those who did not meet the eligibility criteria or did not receive a single dose of the study drug and these data were used for the efficacy outcomes (8,399 patients; 4,187 in the sacubitril group and 4,212 in the enalapril group). The safety (SAF) population comprised all patients who received at least one dose of study drug and these data were used for the safety analysis. A per protocol population (PP) was a subset of the FAS that consisted of the patients who do not have major deviations from the protocol procedures and was used to support the primary analysis results.

Regarding comparators, there were no head-to-head comparisons for sacubitril with ARBs – the drugs specified within the NICE scope for those people who could not tolerate ACEis. The company therefore presented:

- A Network Meta-Analysis (NMA) comparing outcomes from placebo, ACEis, ARBs and ARNIs (sacubitril) with sacubitril data connected to placebo and ARBs data via the enalapril arm of the PARADIGM-HF trial;
- An extended NMA to compare the outcomes from trials with placebo, ACEis, ARBs and ARNIs (sacubitril) plus beta blockers (BBs) and aldosterone antagonists (AAs).

The core NMA indicates sacubitril may be better than placebo, ACEis and ARBs for all outcomes (all-cause mortality, CV mortality) however, the NMA comparison of ARB and sacubitril data produced similar estimates for the relative effectiveness in reducing all cause hospitalisation. The ERG notes the company used a random effects model to account for heterogeneity in the NMA. The wide range in drug doses used to manage HF and the differences in NYHA classification of patients recruited to the trials in the NMA are potential sources of clinical heterogeneity.

The primary outcome of the PARADIGM-HF trial was a composite of CV mortality and CV hospitalisation. Overall, the results were consistently in favour of sacubitril. The ERG notes the trial ended "early" when the *a priori* statistically significant difference between enalapril and sacubitril was observed in fewer-than-anticipated events. The ERG notes there was a protocol amendment in

order for patients with more severe CHF (LVEF ≤35% as opposed to <40–45%) to be included in the trial in order to allow the anticipated number of events to be achieved.

The results provided by geographical region from PARADIGM-HF appear to indicate that there may be a reduced effect of sacubitril compared to enalapril in the Western Europe subgroup. The ERG is also concerned that the rate of hypotension observed in UK clinical practice is higher than that observed in the PARADIGM-HF trial. The Western Europe subgroup had [redacted] blood pressure recordings than the overall trial population. Hypotension is one of the most common adverse events of sacubitril and this finding may indicate that the drug has a limited number of people for which it would be suitable for in the UK.

Another subgroup analysis of concern to the ERG is that which considers the effect of sacubitril in patients who had never taken ACEis (n=1867, ~25% of the trial population). No statistically significant effect is observed between sacubitril and enalapril in this group of patients. This could be due to the limited number of people in this subgroup or could indicate that sacubitril has reduced effectiveness in newly diagnosed patients.

The company also included data from a trial evaluating the safety and tolerability of sacubitril at two different up-titration doses. The TITRATION trial eligibility criteria included newly diagnosed heart failure patients naive to ACE inhibitors. The ERG notes that the TITRATION trial recruited very few ACEi/ARB naive patients (n=33 (6.6%)) and therefore has limited information to inform the effect of sacubitril in newly diagnosed patients.

The ERG's view is that the small number of ACEi/ARB naive patients in PARADIGM-HF and TITRATION provide little evidence to support sacubitril in as a first line treatment for CHF as proposed in the company submission.

The ERG notes less than 1% of patients in the sacubitril arm of PARADIGM-HF had NYHA class IV. This limited evidence is reflected in the company's summary of product characteristics (SmPC). (4) The SmPC also advises that patients with a history of angioedema were not studied in the PARADIGM-HF trial. As these patients are considered at generally higher risk of angioedema the SmPC recommends caution in the use of sacubitril for this group. The frequency of adverse reactions shows the rate of angioedema was reported as affecting 0.5% of patients in the sacubitril arm of the PARADIGM-HF trial vs 0.2% in the enalapril arm. The SmPC reports that a higher incidence of angioedema was observed in black patients, with the rate being higher in the sacubitril arm compared to the enalapril arm (2.4% vs 0.5%, respectively). The ERG therefore disagrees with the statement that, "the rate of adverse reactions was similar in the two investigational drugs and the overall frequency was not related to gender, age or race" (SmPC, pg 8).

The ERG notes there were statistically significant differences in adverse events (AEs) between the two groups with fewer hypotension and cardiac disorder events in the enalapril arm. On the other hand patients in the sacubitril arm experienced less hyperkalaemia, renal impairment, cough, cardiac death, more than one treatment related serious adverse event, discontinuation due to adverse events and overall deaths.

Health-related quality of life (HRQoL) data were collected in the PARADIGM-HF trial using generic (EQ-5D) and condition-specific (Kansas City Cardiomyography Questionnaire (KCCM)) health-related outcome measures. Sacubitril has a favourable HRQoL and CHF symptoms profile compared to enalapril as shown by KCCQ overall and domain scores. The results of the EQ-5D visual analogue scale (VAS) analysis also suggest that sacubitril has a favourable HRQoL profile compared with enalapril.

[redacted]

1.3 Summary of cost effectiveness evidence submitted by the company

The company developed a *de novo* two-state Markov model in Microsoft Excel®. The base case model assumes that patients receive lifelong treatment, either with sacubitril, enalapril or candesartan. The company reports that the model captures the most patient-relevant effects of heart failure (HF) on patients, carers and society.

The company's Markov model includes two health states, alive and dead. Within the alive health state patients can experience hospitalisation events, changes in their quality of life (QoL) and treatment-related adverse events (AEs). Given that these events were not captured through explicit health states in the Markov model, patients remain in the alive state until dead. In the main base case analysis patients begin the model either in the sacubitril or in the enalapril arms of the model to reflect the company's anticipated first-line positioning of sacubitril in the HFrEF pathway. A secondary base case model was also developed by the company, where patients enter the model in either the sacubitril or candesartan arms. While in the alive health state, patients can be hospitalised, suffer a treatment-related AE (for example hypotension, cough or angioedema) and can also experience changes in their QoL due to different causes such as experiencing AEs or worsening of their chronic condition due to disease progression. At any point in the model patients can die. In both treatment and comparator arms of the model, a proportion of patients receive standard care (and other background therapies) in addition to sacubitril or enalapril (or candesartan). Standard care was defined as beta blockers (BB) and aldosterone antagonists (AA). Additional background therapies consisted of diuretics, digoxin, anticoagulants, aspirin, adenosine diphosphate antagonists and lipid lowering drugs (i.e. statins).

The company's base case analysis uses individual patient-level data from the PARADIGM-HF trial. This means that the model was run using individual patient characteristics each time, and that the model was run the same number of times as the number of patients included in the FAS (8,399). The company made the model flexible, allowing the user to run the model as a cohort Markov model using average patient characteristics of the PARADIGM-HF population as model inputs. The cycle length in the economic model is 1 month (considered as 30.4 days) and a half-cycle correction was applied. The time horizon considered in the economic model was lifetime (the model was run for 360 cycles, the equivalent to 30 years).

Treatment effectiveness within the model was implemented through transition probabilities between the alive and the dead states (i.e. mortality) and also through the probability of hospitalisation which patients experience while in the alive state. Treatment effectiveness was also included in the model through an improvement in HFrEF symptoms, which impacted on patients' QoL. The company used the hospitalisation, mortality and QoL models to predict the within-trial period in the analysis, as well as the extrapolated period.

The company's base case analysis modelled the likelihood of a patient experiencing a hospitalisation event using a negative binomial regression model. Predicted all-cause hospitalisation rates were determined by the treatment received by the patient (sacubitril or enalapril) and patients' baseline characteristics, taken from the PARADIGM-HF trial. These were used to model the number of hospitalisations occurring in the initial period of the economic analysis but also permitted extrapolation beyond the end of the PARADIGM-HF trial. The rate of hospitalisation was assumed constant over time which means that in the economic model, hospitalisation is not related with disease progression over time.

All-cause mortality was estimated with survival regression analysis, using a Gompertz distribution. Predicted all-cause mortality was determined by the treatment received by the patient (sacubitril or enalapril) and patients' baseline characteristics, taken from the PARADIGM-HF trial. The mortality model was run using the FAS population of the PARADIGM-HF trial and the model outputs provided daily hazard rates. These were used to model the probability of patients dying in the initial period of the economic analysis but also permitted extrapolation beyond the end of the PARADIGM-HF trial.

The company used a linear mixed regression model based on EQ-5D trial data to predict the utility scores for patients in the economic model. Since the economic model did not explicitly include mutually exclusive health states (other than the alive and the dead states), mean utility values over time were calculated for each patient profile (or average cohort). The predictive QoL model took into account:

- Patient baseline characteristics (including EQ-5D index values at baseline);
- The treatment received (i.e. sacubitril or ACEi);
- Time elapsed since beginning of the model;
- Hospitalisation and AEs which were accounted for by including utility decrements based on the average event rate by treatment arm.

The company's model included costs associated with HF from the perspective of the NHS and Personal Social Services (PSS), according to the NICE reference case.(5) Resource use and costs considered in the model consist mainly on:

- Intervention and comparator's costs (including background therapies);
- Treatment initiation costs;
- Hospitalisation costs;
- HF management costs;
- AE costs.

The company's primary base case results show that sacubitril combined with standard care presents a cost per QALY gained of £17,939 compared with enalapril plus standard care. The secondary base case results comparing enalapril with ARB (candesartan) show that sacubitril combined with standard care presents a cost per QALY gained of £16,481 compared with candesartan combined with standard care.

The results obtained using the CV mortality approach and the mean cohort model are £15,529 per QALY gained for the company's primary analysis and £15,343 for the secondary analysis.

1.4 ERG commentary on the robustness of evidence submitted by the company

1.4.1 Strengths of the clinical evidence

The PARADIGM-HF trial recruited a large number of patients with CHF (n=8,442) worldwide. The ERG believes the trial was well conducted with the randomisation of patients to the allocated study drug conducted remotely and blinding maintained using matched placebos. The trial compared an ACEi with sacubitril and the majority of trial participants were taking beta blockers (BBs) as concomitant therapies, which reflect UK clinical practice.

1.4.2 Strengths of the economic analysis

The company's analysis was based on the PARADIGM-HF trial, a high quality randomised controlled trial. The formulae within the economic model are generally sound and the economic model is a good predictor of the trial outcomes. The company conducted scenario and subgroup analyses which were not requested in the NICE final scope but added value to the submission.

1.4.3 Weaknesses and areas of uncertainty in the clinical analysis

The ERG notes several concerns regarding the generalisability of the evidence for sacubitril in the management of CHF submitted by the company. Firstly, the population of trial participants was younger and comprised of a higher proportion of males than would be seen in routine clinical practice in the UK. The ERG is advised by clinical experts that these patient characteristics are associated with improved outcomes. Secondly, the subgroup analysis of data from the Western Europe population did not reach statistical significance, despite the sample size being almost 25% of trial participants. Thirdly, the small amount of data provided for patients who had never taken an ACEi means there is little evidence to support the use of sacubitril as a first line treatment in newly diagnosed patients.

1.4.4 Weaknesses and areas of uncertainty in the economic analysis

The company's anticipated positioning of sacubitril in the HFrEF pathway is first-line treatment nonetheless the ERG considers that a first-line ICER for sacubitril compared with enalapril cannot be plausibly estimated based solely on the PARADIGM-HF trial data. The extrapolation of sacubitril's effectiveness in the PARADIGM-HF trial to a first-line treatment scenario is inappropriate given that:

- The PARADIGM-HF trial population does not reflect a newly diagnosed HFrEF population. About 78% and 23% of patients had received ACEi or ARB treatment, respectively, before randomisation. Additionally 70% of patients had been diagnosed for over 1 year at baseline and 31% had been diagnosed more than 5 years ago. Clinical opinion sought by the ERG indicates that based on the trial design, population and outcomes, the evidence supports the use of sacubitril in clinical practice is as a second-line treatment option, given to HFrEF patients who are still symptomatic despite being on an ACEi drug therapy. The trial (and therefore the model) population reflects a chronic, stable and symptomatic (95% of patients in the NYHA class II–IV) HFrEF population who has been on ACEi (or ARB) treatment for at least 1 month;

- The mortality in the trial (and in the model) portrays a scenario representative of the use of sacubitril for established patients. Less than 10% of patients in the trial had died by the end of year 1 and only 20% were dead in both treatment arms by the end of the second year. When compared to the NICE CG108 prognosis that 30% to 40% of patients diagnosed with HF die within a year, the observed mortality in the trial is substantially different (less than half)(6);

- Given that the PARADIGM-HF trial's patients are symptomatic, despite having been treated with ARBs and ACEi, the impact of continuing these patients on ACEi is likely to be a misrepresentation compared to what would happen in treatment-naïve patients. Given that, in principle, the ACEi treatment regimen has been demonstrated to not improve these patients' HFrEF symptoms, randomising them to the same treatment regime is unlikely to show any improvements. This has an impact on the observed relative effectiveness of sacubitril, which might be overestimated in the trial population when compared to treatment-naïve patients.

In light of this, the ERG believes that the ICER presented by the company should be considered in the context of second-line treatment for chronic, stable and symptomatic HFrEF patients who have been on ACEi (or ARB) treatment for at least 1 month. Nonetheless the ERG is concerned with the validity of using the ICER presented by the company as an estimate of the cost-effectiveness of sacubitril compared to enalapril as there is too much uncertainty around the relative effectiveness when analysed in the context of UK clinical practice. This uncertainty is related mainly to:

- The lack of representativeness of the trial treatment regimens compared to the UK clinical practice, more specifically with regards to the dose of valsartan (in combination with sacubitril) given to patients. The ERG has reasons to believe that the tolerability to the observed dose of valsartan (in combination with sacubitril) in the PARADIGM-HF trial is overestimated and that patients in real-life clinical practice are unlikely to be able to tolerate, on average, the dose of valsartan received in the trial. Caution should be taken when interpreting the effectiveness outcomes in the PARADIGM-HF trial as it is difficult to understand how the trial could inform the effectiveness of sacubitril if given at a lower mean dose of valsartan;

- The lack of generalisability of the PARADIGM-HF trial population for second-line HFrEF UK patients. Firstly not only the PARADIGM-HF trial portrays a younger HFrEF population compared to the UK HFrEF average, but might also include slightly "different" HFrEF patients, who present with heart problems from a very young age. This could explain the higher CV mortality in younger patients, when compared to slightly older patients, who present with more "typical" HFrEF. Secondly, opinion provided by the ERG's clinical experts advised that the device use at baseline in PARADIGM-HF was lower than what would be expected in UK clinical practice and that this is an important prognostic factor in HFrEF;

- The fact that the Western European subgroup analysis in the PARADIGM-HF trial reports a non-statistically significant HR CV mortality. While the PARADIGM-HF trial was not designed to estimate the effectiveness of sacubitril across different regions, and the sample size of the subgroup is smaller than that of the entire trial population, statistically significant

differences between treatments groups were shown for regions considerably smaller in size than Western Europe (2,051 patients). For example, North America (602 patients) and Latin America (1,433 patients) were associated with statistically significant results even though the number of patients were more than three times smaller in the case of North America or half in case of Latin America. The ERG believes this might indicative of a different relative effect of sacubitril compared to enalapril across geographical areas;

- It is uncertain if the effectiveness of sacubitril differs across different age groups. While sacubitril appears to maintain the same direction of effect across different age groups, the size of the effect is not as easily established. The authors in Jhund *et al.* conclude that the effect of sacubitril compared with enalapril was consistent across age groups even though HRs were non-statistically-significant in older groups.(7) This non-significant result in older people is consistent with expert opinion provided to the ERG which advised that for patients around 80 years-old presenting with HFrEF, clinicians expect treatment (with ACEi or other drugs) to improve patients' QoL but not mortality. This is particularly relevant to the UK given that the average age of HFrEF patients is between 75 and 80 years-old. This adds to the uncertainty of having a non-statistically significant CV and all-cause mortality HR in the Western European subgroup analysis;

- The inflexibility of the economic model to reflect an older population at baseline. The modelling approach taken by the company, while necessary to capture the PARADIGM-HF trial data, resulted in an inflexible economic model. The model cannot be changed to accurately portray an older population at baseline and generalise the model results. The trend observed in CV (and all-cause) mortality by age group at baseline shows that younger patients have higher mortality rates than 60-year old patients in the trial. This reinforces the ERG's point that the PARADIGM-HF trial population might not be representative of the average UK HFrEF population, especially when deviations are made from the mean age trial population (63 years);

- The company's decision to use a Gompertz distribution was based on this distribution presenting the most plausible (i.e shortest) survival time. The ERG believes that the company should have presented different modelling options, such as spline models. No other approach outside parametric curves was tried, and this might have produced suboptimal results. Even though the Gompertz distribution produces the most plausible survival curves amongst the group of alternative distributions considered, it could represent an overestimate of treatment effects compared to different (and potentially more appropriate) approaches.

- The ERG is concerned with the validity of the QoL analysis undertaken by the company. Firstly the ERG cannot be certain if there was a baseline statistically significant difference, or not, in patients' EQ-5D scores. The two-sample *t* test that was performed to compare the two distribution means at baseline which [redacted] (p-value = [redacted]) might not be appropriate to capture differences in these distributions given the [redacted] shape of the distribution of QoL data at baseline. The immediate implication of this is problematic; if there were clinically significant differences in patients' disease severity at baseline ([redacted]) and QoL across treatment and comparator arms, there would be a population imbalance at baseline which could potentially have biased the trial and consequently the model outcomes. Assuming patients in a healthier state would have better outcomes, the potential imbalance in disease severity ([redacted]) might have favoured the sacubitril arm in the PARADIGM-HF trial. Given the relationship between the QoL at baseline and the trial outcomes the ERG is concerned that the overestimation of patients' QoL at baseline might impact the benefits observed in the trial when compared with real clinical practice.

- The ERG is concerned that parameter uncertainty in the economic analysis was not appropriately accounted for. The ERG believes that patients' baseline characteristics should have been included in the PSA and varied stochastically. Baseline characteristics are key parameters in the economic model given that these have been included as prognostic factors of mortality, hospitalisation, QoL and costs in the regression analyses.

In summary, even though the PARADIGM-HF trial results indicate that sacubitril (compared to enalapril) is effective in preventing hospitalisations and reducing mortality in the trial population, there is too much uncertainty to make definitive predictions around the effectiveness of sacubitril for:

- A first-line treatment scenario;
- Western European patients;
- Patients older (or younger) than 63 years old;
- Different doses of sacubitril valsartan (in both first and second-line treatment scenarios).

1.5 Summary of exploratory and sensitivity analyses undertaken by the ERG

The scenario analyses undertaken by the ERG are the following:

1. The ERG changed the CV mortality HR in the model to reflect the Jhund *et al.* HR estimates for the 55–64 year category.(7) The HR used was 0.79 (95% CI: 0.64 to 0.98);

    - As the 95% confidence interval for the HR of CV mortality in the 55–64 years population is wide, the ERG also used both limits of the confidence interval;

2. The ERG used the baseline utility score of 0.712 reported by Berg *et al.*(8);

3. The ERG used the baseline utility score of 0.660 reported by Austin *et al.*(9);

4. Given the issues found in the modelling approach of QoL in the model, the ERG adopted a simplified approach, where the impact of sacubitril on patients' QoL was linked to the incidence of AE, hospitalisation events, and disease progression (i.e. time) in both treatment arms. Therefore, the QoL regression model was not used, even though some of its estimates were used as these were validated by clinical experts. The impact of sacubitril on QoL (other than through hospitalisations and AEs) was also removed to reflect the lack of robust evidence to support a measurable improvement in patients' QoL caused by sacubitril other than through hospitalisation, mortality and AEs. The impact of treatment regimens on QoL was assessed by the ERG through :

    - AEs and hospitalisation events: the ERG applied the same utility decrements used by the company to estimate the loss in QoL due to the incidence of AEs and hospitalisation;

    - Disease progression: the ERG applied the same utility decrement used by the company to reflect the loss of QoL as time progresses for HF patients.

5. The ERG changed the drug doses used in the model to reflect a consistent approach to the estimation of drug costs. The re-estimated drug costs are presented in Table 59, Section 5.5.9.1;

6. The ERG included the cost of ramipril (using the ERG drug dose assumption) to reflect clinical practice in the UK;

7. The ERG used the company's option in the economic model to run the ERG corrected model considering treatment discontinuation;

8. The ERG used the company's subgroup analysis results to run the ERG corrected model considering the Western European population. To note is that the mean baseline age for the Western European population is [redacted] years.

Additional scenario analyses were run for a 75-year-old population. The scenarios ran were the following:

1. The ERG changed the CV mortality HR in the model to reflect the Jhund *et al.* HR estimates for the ≥75 year category.(7) The HR used was 0.84 (95% CI: 0.67 to 1.06);

    - As the confidence interval for the HR of CV mortality in the 55–64 years population is wide, the ERG also used both limits of the confidence interval;

    - As the HR of CV mortality in the ≥75years is non-statistically significant the ERG ran the model with an HR of 1.

The ERG ran other scenario analyses for the 75-year-old population, which are the same as the ones reported for the 64-year-old group.

The model results have shown to be most sensitive to changes in the HR for CV mortality. Using the Western Europe subgroup characteristics, effectiveness measures and costs also had a considerable impact on the final ICER.

The ERG's assumptions to estimate the second-line ICER with a CV mortality approach and a mean cohort model are:

- A different baseline utility value for both treatment arms in the model;

- The effectiveness measures, costs and QALYs of the Western European subgroup;

- An alternative, simplified approach for the estimation of QoL in the model.

The second-line ICER estimated by the ERG amounts to £29,478 per QALY gained for sacubitril compared with enalapril. The results for sacubitril compared with candesartan (ARB) were consistently similar, with the final second-line ICER resulting in £30,140 per QALY gained. However the ERG advises that the second-line ICERs must be interpreted with caution. The ERG considers there to be too much uncertainty around the effectiveness of sacubitril compared with enalapril when analysed in the context of UK clinical practice, as explained in Section 1.4.

An example of the quantification of this uncertainty is that if the HR for CV mortality in the Western European subgroup is assumed to be 1 (to reflect the non-statistical significance of the HR), the

ERG's second-line ICER increases to **£491,879** per QALY gained. Furthermore, using the 95% CIs of the HR for CV mortality in this population [redacted], leads to a variation in the final ICER which ranges from **£15,584** to a **dominated** ICER, with sacubitril being more expensive and producing less QALYs than enalapril. Another example of this is the second-line ICER for all-cause mortality, which amounts to **£49,009** per QALY gained, when the ERG's assumptions are used. While the ERG considers that, form a methodological point of view, the CV mortality approach is more robust than the all-cause mortality approach the results using all-cause mortality are provided for comparison with the company's base case analysis.

2 BACKGROUND

2.1 Critique of company's description of underlying health problems

The company holding the marketing authorisation for sacubitril valsartan (Entresto®; hereafter known as sacubitril) submitted clinical and economic evidence to the National Institute for Health and Care Excellence (NICE) in support of the effectiveness of sacubitril in the treatment of chronic heart failure (hereafter referred to as CHF). The marketing authorisation for sacubitril states that the drug is indicated to reduce the risk of cardiovascular mortality and morbidity in adult patients with symptomatic CHF and reduced ejection fraction in conjunction with standard therapy, including aldosterone antagonists (AA) and beta-blocker (BB) therapy.

All information presented in the following sections that appears in boxes is taken directly from the company submission (CS) unless otherwise stated and the references have been renumbered. The CS contains a description of the underlying health problem of CHF (Box 1). The ERG has considered all relevant aspects of CHF including epidemiology, aetiology, prognosis, pathophysiology and natural history of heart failure as part of the assessment of the company's submitted description of the underlying health problem.

Box 1. Summary statement of the underlying health problem (CS, pg 28)

> Heart failure is a complex clinical syndrome in which the heart fails to pump enough blood to meet the body's demands. The global prevalence of HF is over 23 million and represents a major public health issue (17), with an estimated one in five individuals developing HF in their lifetime (17). There are approximately 550,000 patients in the UK who suffer from HF (1). The most commonly recognised and studied type of HF is caused by compromised systolic heart function and is characterised by reduced LVEF termed HFrEF. HFrEF is due to the left ventricle losing its ability to contract normally. Heart failure is associated with poor survival rates, repeated hospitalisations (10) and a significant reduction in quality of life compared with the general population (10, 11). Approximately 50% of patients with HF will die within five years of diagnosis (10). One-year mortality estimates for patients from England diagnosed with HF vary, ranging from 9% to 38%. Heart failure imposes a significant burden on individuals, families, and healthcare systems, and

patients with HF experience higher rates of disability, geriatric conditions, and nursing home admissions (12)
Abbreviations used in box: Heart Failure; HF, heart failure; HFrEF, heart failure reduced ejection fraction.

The ERG is aware that epidemiological studies show men have higher prevalence of moderate to severe reduced ejection fraction (accepted to be ejection fraction ≤40%) than women and the prevalence in both sexes increases with age (13). The ERG notes that the age of onset of CHF differs between men and women: on average, men are admitted to hospital for CHF at an age 5 years younger than women (72.9 years for men vs 77.7 years for women (14). The incidence of CHF has been estimated to be 0.6% in UK men in the 45–54 years age group and the estimated prevalence of women in the same age group is zero. Prevalence increases with age, rising to 4.9% in men over the age of 75 years and 2.6% in women of the same age (15). The ERG identified published statistics on the epidemiology of CHF that suggest the overall prevalence of CHF is 3% in UK men and 1.7% in women in the UK (15). Above the age of 75 years, the proportions of men and women with HF are comparable but over the age of 80, women are more likely to have CHF (1).

The ERG considers the company's description of the underlying health problem could be more fully explained. CHF is considered to be a clinical presentation of particular symptoms and outcomes, not characterised by a single aetiology or pathology but usually caused by coronary artery disease (CAD), which is estimated to account for approximately 2/3 of cases (16). Diabetes and hypertension are also considered to have an important etiological role in heart failure with reduced ejection fraction (HFrEF) (16, 17). However, more transient pathological conditions can also cause HFrEF (such as viral myopericarditis) from which patients may experience a complete recovery of their systolic ventricular function (16).

The ERG considers the company's description of the symptoms (Box 2) of CHF is broadly accurate but would add that often the diagnosis of CHF is complicated because symptoms in the early stages of the disease can be non-specific. Typical HF symptoms of fatigue, tiredness, increased time to recover after exercise and ankle swelling can be due to other underlying pathologies and CHF is diagnosed using aspects from the patient's history, laboratory investigations and diagnostic tests (6, 16, 17).

Box 2. The symptoms of heart failure (CS, pg 28)

Typical symptoms of chronic HF includes breathlessness, orthopnoea, paroxysmal nocturnal dyspnoea, reduced exercise tolerance, fatigue, tiredness, increased time to recover after exercise and ankle swelling (18). The course of HF includes deterioration in symptoms, which leads to repeated hospitalisations for acute decompensations, and eventually death from progressive pump failure (19).
Abbreviations used in box: HF, heart failure.

The severity of HF is classified according to the New York Heart Scale (NYHA) Functional Classification which places patients in one of four categories according to the extent to which they are limited during physical activity (Table 1).

Table 1. New York Heart Association classification of heart failure(20)

Class	Description
I	No limitation of physical activity: ordinary physical activity does not cause undue fatigue, palpitations, or dyspnoea
II	Slight limitation of physical activity: comfortable at rest but ordinary physical activity results in fatigue, palpitations, or dyspnoea
III	Marked limitation of physical activity: comfortable at rest, but less than ordinary activity causes fatigue, palpitations, or dyspnoea
IV	Unable to carry out any physical activity without discomfort: symptoms of cardiac insufficiency are present at rest and discomfort increases with any physical activity is undertaken

With reference to the association between CHF and left-ventricular systolic dysfunction (LVSD), the ERG considers it relevant to the decision problem to note that LVSD is typically defined in clinical practice as a left-ventricular ejection fraction (LVEF) of <40% of normal ejection fraction. The ERG has adopted the working definitions of CHF terms contained in the guidance from the European Society for Cardiology, tabulated in Table 2 below.

Table 2. Heart failure terms (20)

Term	Definition
Left ventricular ejection fraction (LVEF)	A measurement of how much blood the left ventricle pumps out with each contraction (normal range 55–70%)
Heart failure reduced ejection fraction (HFrEF)	NYHA classification II-IV (symptomatic) with reduced ventricular ejection fraction of ≤35%
Systolic dysfunction	Defined as an LVEF less than 40%.

2.2 Critique of company's overview of current service provision

The algorithm contained in the NICE guideline on the management of CHF recommends that those with symptoms of CHF plus a history of myocardial infarction (MI) should be urgently referred to specialist assessment and transthoracic 2D Doppler echocardiography within two weeks (6). For those people with symptoms of CHF but no history of MI, a blood test to measure levels of serum brain natriuretic peptide (BNP) is the quality standard. A BNP level of >400 pg/mL (116 pmol/litre) or an N-terminal amino acids (NTpro) BNP level above 2000 pg/ml (236 pmol/litre) are indicative of CHF and require an urgent referral to a specialist for assessment and diagnosis (6).

The ERG notes that HF most commonly presents acutely as emergency admissions in hospital and has a poor prognosis, with 30% to 40% of HF patients dying within the first year (Box 3).

Box 3. Mortality associated with heart failure (CS, pg 18)

One-year mortality estimates for English patients diagnosed with HF vary, ranging from 9% (21) to 38% (22). In the NICE quality standard on chronic HF, it is stated that 30% to 40% of patients diagnosed with HF die within one year (23). In the ECHOES (Echocardiographic Heart of England Screening) study including 6,162 subjects, recruited from GP practices/hospitals in England, five year mortality was 47.5% (104/219) in the cohort of patients with a diagnosis of HFrEF (mean age of 70.5 years) compared with 9.7% (546/5604) in those patients without a diagnosis of HFrEF (mean age of 63.3 years, (21)). People with HF have an increased risk of death compared to age and sex matched people without HF (HR 1.19 (95% CI 1.06–1.33)), and the risks of death increased with HF symptoms and limitations of physical activity, patients with NYHA II, III or IV class respectively (compared with NYHA I class) were found to be 1.22 (95% CI 1.09–1.35), 1.57 (95% CI 1.35–1.82) and 1.64 (95% CI 1.36–1.97, (21)).
Abbreviations used in box: HF, heart failure; HFrEF, heart failure reduced ejection fraction; NICE, National Institute for Health and Care Excellence.

After the first year, survival improves and mortality is less than 10% per year (6). The CS contains descriptions of the incidence and mortality associated with CHF (Box 5) and the ERG considers these to be reasonable. However, the ERG would add that improvements in the rate of mortality in the first 6 months after diagnosis have been observed to reduce from 26% in 1995 to 14% in 2005 (6). . The ERG is also aware that the rate of mortality of those with access to care from a cardiologist or specialist cardiac services is significantly lower (24).

The ERG is aware that CHF is also associated with reduced quality of life and high health care costs (15). The CS mentions the poor health related quality of life (HRQoL) and increased rates of hospitalisation for the HF compared with the general population. (CS, pg 14) The CS cites the ageing population as the cause of an anticipated increase in hospitalisation (Box 4).

Box 4. Hospital admissions (CS, pg 28)

Heart failure related hospital admissions are projected to rise by 50% over the next 25 years – largely as a result of the ageing population (25). Patients with HF are also at high risk of sudden (usually arrhythmic) death at any time during the course of their illness. Despite a decline of the age-adjusted hospitalisation rate at 1–1.5% per annum since 1992/93 (26) improving implementation of NICE clinical guidelines and recommended HF treatment options over the past five years, mortality and hospitalisation rates are still high among patients, indicating an unmet need in the management of HF in England (27).
Abbreviations used in box: NICE, National Institute for Health and Care Excellence.

The ERG notes that an analysis of data from Hospital Episode Statistics (24) showed there were 73,752 hospital spells (coded as a first position) and the mean length of stay was 11.76 days (median

8 days) with 10% of people being re-admitted within 28 days. In NHS improvement, a guide for review and improvement of hospital-based HF services, the UK government outlined the proposal to stop payment for hospital re-admissions of this type and the ERG is advised by the clinical expert that early readmissions are not given further tariff in the NHS in England (24).

The CS suggests the annual cost of HF-related hospitalisations to the NHS is approximately £16 billion and includes an estimate of the cost to patients and their carers of £8,453 (Box 5).

Box 5. The cost of heart failure to society (CS, pg 29)

The direct cost burden of HF to society consists of GP and cardiology outpatient visits and hospital admissions based on Scottish data (28), no English data was identified in published literature. An estimate from NICE indicates that the NHS spends approximately 2% of its total budget on HF (approximately £2.3 billion); 70% of this is due to hospitalisation (29). Globally, indirect costs of HF to society are caused by informal (i.e. unpaid) care costs, premature mortality and lost productivity (30) and have been estimated to account for approximately 40% of the total costs of HF (30). [redacted].

Abbreviations used in box: GP, general practitioner; HF, heart failure; NHS, National Health Service; NICE, National Institute for Health and Care Excellence.

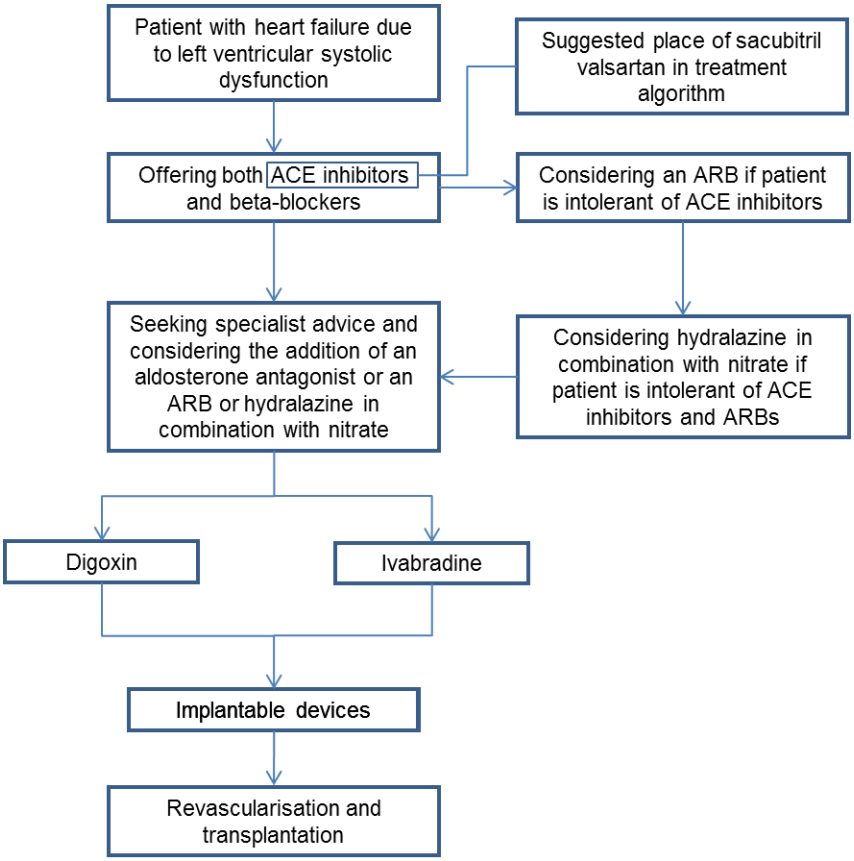
The ERG accepts that there are limited data in existence upon which to estimate these costs and those cited by the company appear to be reasonable.

The company presents the treatment algorithm for symptomatic CHF as recommended by NICE (Figure 1) and indicates the proposed position of sacubitril in the treatment pathway, and estimates the number of patients in the England who would be eligible for treatment with sacubitril. The company lists NICE guidelines and technology appraisals relevant to the decision problem (summarised in Box 6).

The current treatment pathway for people with symptomatic CHF recommends patients are offered an angiotensin-converting enzyme inhibitor (ACEi) and beta blocker as first-line management with the order of commencement of these two drugs left to the discretion of the clinician providing care (6). An angiotensin receptor blocker (ARB) can also be used as an alternative to ACEi in patients who cannot tolerate an ACEi (Box 8). In cases where the patient then remains symptomatic, or has moderate to severe heart failure (NYHA class III–IV) or has experienced an MI in the last month, an AA for HF is indicated.

The ERG notes sacubitril is intended to be used as a first-line treatment in the UK, replacing ACEi, for patients with HFrEF (CS, pg 27) (Box 6). The company justifies this proposed change in the first-line management of people with CHF because CHF has a high mortality rate and patients require frequent hospitalisations, the implication being that sacubitril demonstrates significant improvements in mortality and hospitalisation.

Figure 1. Treatment algorithm for symptomatic HF as recommended by NICE (CS, pg 30)



Box 6. Current management of heart failure (CS, pg 14)

The current first-line treatment for the management of HFrEF in England is an angiotensin converting enzyme inhibitor (ACEi) in combination with a beta blocker (BB). In case of insufficient efficacy, an aldosterone antagonist (AA) may be added. An angiotensin II receptor blocker (ARB) may be substituted in case of ACEi intolerance (25). Despite the widespread use of these existing treatment options (in greater than 90% of patients) HF remains a progressive syndrome with a high mortality rate, frequent hospitalisations (27) and with an unmet need for new therapies to improve health outcomes.
Abbreviations used in box: HF, heart failure; HFrEF, heart failure reduced ejection fraction.

The resource implications stated in the CS for the use of sacubitril in the NHS described in the CS can be found below in Box 7.

Box 7. Resource implications (CS, pg 14)

When initiating sacubitril valsartan in patients previously treated with ACEi or ARB, one titration visit with either a General Practitioner (GP) (£35 per visit (32)), cardiologist (£130.86 per visit (33)) or HF specialist nurse (£33 per visit (32)) will be required (to the target dose of 200 mg) as patients would be initiated on 100 mg. In newly diagnosed patients, titration may require two visits, to titrate patients from 50 mg to100 mg and then from 100 mg to the 200 mg target dose (34). As part of current standard practice initiation of ACEi or ARB treatment requires titration and this cost should therefore not be considered incremental for sacubitril valsartan over and above standard care provided with ACEi or ARB treatment. No additional tests or monitoring are required with sacubitril valsartan above those that are already part of current clinical practice. Therefore, it is anticipated that no further additional NHS resources will be required. Sacubitril valsartan is used in the home setting and will be commissioned by clinical commissioning groups.
Abbreviations used in box: ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; mg, milligram.

The company suggests that, other than acquisition cost, no additional resources will be required to initiate treatment. Eligible patients will previously have had a diagnosis for HF associated with LVSD and should be receiving optimised standard therapy, as outlined in the NICE guideline CG108 (6). With reference to service provision, the company anticipates that minimal additional resource will be required to implement treatment with sacubitril and no additional monitoring is required. The company anticipates that sacubitril treatment would be initiated by a GP, cardiologist or nurse for patients who have previously been treated with either an ACEi or ARB in a single visit but that two visits would be required for those patients who had never received any form of medication previously. The ERG has received clinical expert opinion to support the company's view that no additional resources will be required but the numbers of visits to the cardiologists are considered an under estimate of the actual number required in clinical practice.

The CS acknowledges the anticipated increase in the prevalence of CHF over time as a result of the ageing population and, based on the British Society for Heart Failure (BSHF) (1), the company predicts the number of CHF patients eligible for sacubitril will be 227,849 by 2020 (Box 8 and Table 3).

Box 8. Estimated eligibility and uptake of sacubitril (CS, pg 21)

The estimated eligible patient population for sacubitril valsartan in England in 2016 is 222,727 patients with HFrEF. The expected uptake of sacubitril valsartan is [redacted] in 2016 rising to [redacted] by 2020.

The key drivers of the budget impact analysis are the cost of sacubitril valsartan and savings incurred by reduction of hospitalisations leading to an estimated net budget impact of [redacted] million in 2016 increasing to [redacted] million in 2020. It is estimated that in 2020 alone, based on an uptake of [redacted] in the eligible HF population, sacubitril valsartan would prevent [redacted] CV-related deaths and [redacted] hospitalisations.
HFrEF = heart failure reduced ejection fraction; CV = Cardio Vascular

Table 3. Estimates of the eligible patient population in England over the next 5 years (reproduced from CS, pg 200).

	2016	2017	2018	2019	2020
Population of England (35)	54,872,953	55,202,373	55,527,390	55,835,285	56,134,779
Prevalence of HF England† (36)	0.74%	0.74%	0.74%	0.74%	0.74%
Number of prevalent pts with HF in England	406,809	409,251	411,661	413,943	416,164
Incidence of heart failure (HF) England (37)	0.05%	0.05%	0.05%	0.05%	0.05%
Number of incident pts with HF in England	29,138	29,312	29,485	29,649	29,808
Total number of prevalent and incident pts in England	435,947	438,564	441,146	443,592	445,971
Percentage of pts with HFrEF (27)	72%	72%	72%	72%	72%
Percentage of HF pts with NYHA II-IV (38)	89%	89%	89%	89%	89%
Percentage of HF pts with eGFR > 30 mL/min/1.73m^2 (39)	89%	89%	89%	89%	89%
Total estimated number of pts in England with HFrEF, NHYA II-IV and eGFR > 30 mL/min/1.73m	248,626	250,118	251,3591	252,986	254,343
Mortality risk per year (40)	10.42%	10.42%	10.42%	10.42%	10.42%
Net estimated number of pts with HF in England	222,772	224,064	225,384	226,633	227,849

† Number of patients with HF in England in 2014 (401,729) divided by number of people in England in 2014 (54,187,718) (36)

Abbreviations: eGFR, estimated glomerular filtration rate; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; NHYA, New York Heart Association class II to IV; pts, patients.

The ERG considers the estimates used by the company to be reasonable given the epidemiological data currently available but notes a 2015 update of the BSHF National Heart Failure Audit is due to be released in [redacted].

3 CRITIQUE OF COMPANY'S DEFINITION OF DECISION PROBLEM

The company provided a summary of the decision problem and tabulated a comparison with the final scope from the National Institute for Health and Care Excellence (Table 1; CS, pg 15).

Table 4. Summary of the decision problem and tabulated a comparison with the final scope from the National Institute for Health and Care Excellence (Reproduced from Table 1, CS, pg 15)

	Final scope issued by NICE	**Decision problem addressed in the company submission**	**Rationale if different from the final NICE scope**
Population	People with chronic HF (New York Heart Association [NYHA] class II-IV) with systolic dysfunction	People with symptomatic HF (NYHA II-IV) with reduced LVEF, referred to as patients with HFrEF	Aligned with population from PARADIGM-HF pivotal trial – primary evidence source in submission and anticipated license.
Intervention	Sacubitril valsartan in combination with standard care (including treatment with a BB and an AA)	Sacubitril valsartan in combination with standard care (including treatment with a BB and an AA)	Same as final NICE scope
Comparator(s)	ACEi in combination with standard care ARB in combination with standard care (for people in whom an ACEi is unsuitable) Standard care includes treatment with a BB and an AA	ACEi in combination with standard care ARB in combination with standard care (for people in whom an ACEi is unsuitable) Standard care includes treatment with a BB and an AA	Same as final NICE scope
Outcomes	Symptoms of HF Hospitalisation for HF All-cause hospitalisation Mortality Cardiovascular (CV) mortality Adverse effects of treatment Health-related quality of life (HRQoL)	Symptoms of HF Hospitalisation for HF All-cause hospitalisation Mortality CV mortality Adverse effects of treatment HRQoL	Same as final NICE scope
Economic analysis	The cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year	The cost effectiveness of treatments is expressed in incremental cost per quality-adjusted life year	Same as final NICE scope
	The time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being Compared	The time horizon for estimating clinical and cost effectiveness is lifetime	
	Costs will be considered from an NHS and Personal Social Services perspective Standard care includes treatment with a beta blocker	Costs are considered from an NHS and Personal Social Services perspective Standard care includes treatment with a beta blocker and an aldosterone	

	and an aldosterone antagonist The cost of background therapies, such as diuretics, should also be included in cost effectiveness analyses	antagonist The costs of background therapies, such as diuretics, are included in cost effectiveness analyses	
Subgroups to be considered	Not specified	The PARADIGM-HF study demonstrates consistently superior clinical endpoints (primary and secondary) for sacubitril valsartan compared with ACEi across all pre-specified trial subgroups (Section 4.8). Cost-effectiveness is determined by absolute benefit, and as such the incremental cost-effectiveness ratio (ICER) may be expected to vary across subgroups – this has been explored and the impact on the ICER is minimal (Section 5.9).	Not specified in final NICE scope
Not specified	No equality issues identified	Not specified in final NICE scope	

Abbreviations: AA: Aldosterone Antagonist; ACEi: Angiotensin Converting Enzyme Inhibitor; ARB: Angiotensin Receptor Blockers; HF: Heart Failure; BB: Beta Blocker; CV:Cardiovascular; HRQoL: Health-related quality of life; ICER: Incremental Cost Effective Ratio.

3.1 Population

In general the ERG considers the data presented in the CS as evidence for sacubitril valsartan, henceforth known as sacubitril, to be representative of the heart failure (HF) population in England and Wales. The target population of the NICE final scope is people with chronic heart failure (NYHA class II–IV) with systolic dysfunction (Box 9).

Box 9. Statement of the decision problem (CS, pg 14)

The decision problem addressed in this submission is largely in line with the scope issued by NICE (National Institute for Health and Care Excellence). The key difference is that the scope states systolic dysfunction while in this submission we consider patients with HFrEF. This is aligned with the population in the pivotal Phase III trial (PARADIGM-HF, see table 1) as well as the anticipated marketing authorisation and population for which clinicians would prescribe sacubitril valsartan. Table 1 provides an overview of the decision problem addressed in this submission in relation to the scope.

Abbreviations used in table: HFrEF, heart failure reduced ejection fraction.

The ERG notes that the patients participating in the PARADIGM-HF trial were initially recruited if they had a NYHA classification of II to IV, which is in accordance with the target population in the final scope from NICE. However, the CS reports a protocol amendment from the population specified in the final scope issued by NICE; "LVEF": An amendment to the study was made to change the LVEF entry criterion from ≤40% to ≤35% (41) with patients with HFrEF (≤35%) recruited into the trial instead. The CS contains a justification of this protocol amendment (Box 2, see paragraph therein for a justification of the change to LVEF).

Box 10. PARADIGM-HF trial patient eligibility criteria (CS, pg 42)

A summary of the key inclusion and exclusion criteria in PARADIGM HF is provided in table 9. The inclusion criteria for NHYA, LVEF and BNP are summarised below.

NYHA: All patients screened at study admittance were NYHA functional class II-IV, however, a small number of patients had an improvement in their NYHA class between screening and randomisation, and so nearly 5% of randomised patients were NYHA class I (2).

LVEF: An amendment to the study was made to amend the LVEF entry criterion from ≤40% to ≤35%. This modification was essential to ensure an adequate event rate in the study population where use of evidence-based, disease-modifying agents was increasing. 961 patients who were randomised had LVEF ≤35% (2).

BNP: Mildly elevated BNP or NT-proBNP was required as an inclusion criterion to ensure that patients enrolled were at risk for CV events in order to ensure a reasonable event incidence rate over the duration of the trial (2). The patient characteristics were similar to those of study populations in other relevant trials and patients in the community (42-44)

Abbreviations: BNP: Brain Natriuretic Peptide; LVEF; Left Ventricular Ejection Fraction; NHYA: New York Heart Association; NT-proBNP; N-terminal pro hormone of Brain Natriuretic Peptide.

The ERG notes that 89% of participants (n=7,438) in PARADIGM-HF had a CHF classification of ≤35%. The results from the trial are therefore likely to be representative of this more severe CHF patient population.

The ERG's overall opinion of the PARADIGM-HF trial is presented in Section 4 of this report. It should be noted that the ERG's clinical experts have advised that the small amount of data provided for patients who had never taken an ACEi means there is little evidence to support the use of sacubitril as a first line treatment in newly diagnosed patients.

The ERG's clinical experts believe the PARADIGM-HF trial supports the use of sacubitril only in patients that have a profile matching the one in the trial; i.e. chronic patients, who have been maximally titrated on an ACEi (or ARB) but remain symptomatic.

The ERG also notes the CS contains an explanation of differences which exist between patients who are treated for CHF in the NHS in England and Wales and those patients who were recruited into the PARADIGM-HF trial (Box 11).

Box 11. Description of patient characteristics for the PARADIGM-HF trial (CS, pg 18)

The proportion of patients on various HF standard care and background therapies was reflective of English clinical practice. Patient characteristics in PARADIGM-HF were mostly reflective of the English HF population. However, patients were, on average, younger than the average patients in England (approximately 65 versus 75 years) and more patients were male. However, in PARADIGM-HF, 49% of patients were ≥65 years of age (n=4120) and 18.6% of patients were ≥75

years of age (n=1563) with the oldest patient aged 96 at randomisation (45), and 21.8% (n=1,832) were female (2).
Abbreviations used in table: HF, heart failure.

Based on advice from clinical experts the ERG is aware that the data from the PARADIGM-HF trial have been collected from patients who are a chronic, but stable, HF population. Concerns that the population might not be representative of the UK and the ERG requested subgroup analysis for people recruited from Western Europe and then these are discussed in greater detail in Section 4.

As described in Section 2 the ERG has adopted the CHF terms issued by the European Society for Cardiology.

3.2 Intervention

The named intervention in the NICE final scope is sacubitril valsartan (henceforth referred to as sacubitril). The CS contains an explanation of the pharmacological specification of sacubitril (Box 12).

Box 12. Description of the intervention (CS, pg 22)

Sacubitril valsartan (previously known as LCZ696) is an angiotensin receptor neprilysin inhibitor (ARNI), a salt complex comprising two active moieties, sacubitril and valsartan, which have been co-crystallised in a 1:1 molar ratio. Sacubitril valsartan is a novel first-in-class therapy proposed for the treatment of HFrEF. Following oral administration, sacubitril valsartan dissociates into the pro-drug sacubitril (also known as AHU377), which is further metabolised to the neprilysin inhibitor (LBQ657), and valsartan, an ARB. Sacubitril valsartan has the mechanism of action of an neprilysin inhibitor and an ARB (angiotensin receptor neprilysin inhibitor; ARNI), by simultaneously inhibiting neprilysin via LBQ657 and blocking the angiotensin II type-1 (AT1) receptor via valsartan, resulting in complementary effects on the CV system that are beneficial in HF patients.
Abbreviations used in table: ARB, angiotensin receptor blocker; CV, cardiovascular; HF, heart failure; HFrEF, heart failure reduced ejection fraction.

The ERG notes the innovative nature of sacubitril in the management of HF, the inhibition of neprilysin being a novel development in the pharmacological management of HF. The ERG notes the marketing authorisation application for sacubitril was submitted to the EMA on 16 December 2014. The CHMP has granted accelerated assessment to sacubitril valsartan. An EMA decision on marketing authorisation is expected in December 2015 (CS, pg 22).

Clinical effectiveness data in the CS are derived from one pivotal trial PARADIGM-HF (n = 8,399). The PARADIGM-HF trial is an international multi-centre randomised controlled trial designed to evaluate the efficacy of sacubitril 200mg compared with the ACEi, enalapril 10mg, (both in combination with standard care) in patients with HFrEF (New York Heart Association [NYHA]

classifications II to IV) (CS, pg 17). A second trial TITRATION (n = 498) compares different doses of sacubitril. As the TITRATION trial does not address the decision problem it is not discussed further in Section 3. Instead, the ERG's assessment of the TITRATION trial can be found in Appendix 1.

3.3 Comparators

The ERG notes the comparators of interest in the final scope issued by NICE are an ACEi in combination with standard care or an ARB in combination with standard care (for people in whom an ACEi is unsuitable). The ERG acknowledges the definition of standard care in the NICE final scope as including treatment with a BB and an AA. The CS contains data for patients who received the ACEi, enalapril, in conjunction with standard care: a BB and AA. Thus, the comparator in the evidence submitted by the company is relevant to the final scope issued by NICE. However the ERG has been advised by clinical experts that enalapril is not the most commonly prescribed ACEi in the UK; the ERG's clinical experts' opinion is that the most commonly used ACEi is ramipril, which is believed to be better tolerated and appears to be more convenient for patients as it is taken once per day. This issue is considered in further detail in Sections 4 and 5 of the ERG report.

3.4 Outcomes

The company presents direct evidence for sacubitril versus enalapril for all of the outcomes listed in the final scope issued by NICE:

- Symptoms of HF;
- Hospitalisation for HF;
- All-cause mortality;
- Cardiovascular mortality;
- Adverse effects of treatment;
- Health-Related Quality of Life.

The ERG notes that the primary efficacy variable was time to first occurrence of either CV death or HF hospitalisation from CV causes and these were combined and presented as a composite variable. The ERG is advised by clinical experts that this is a standard approach to the analysis of outcome data in trials of drugs for CHF.

The ERG notes that the Kansas City Cardiomyopathy Questionnaire (KCCQ) was used to measure the symptoms of HF. The company states it is clinically meaningful in CV research, patient management and quality assessment (CS, Table 10, pg 43). The CS contains an overview of the domains measured by the KCCQ and an explanation of how the scores are interpreted, "The KCCQ covers physical function, clinical symptoms social function, self- efficacy and knowledge and QoL. Higher scores (on

the scale of 0 to 100) indicate better HRQoL/reduced HF symptoms. KCCQ scores were assessed at baseline 4, 8, 12, 24 and 36 months as well as the end of each study visit." (CS, summary, pg 34). The ERG notes the PARADIGM-HF investigators also used EQ5D, a generic HRQoL outcome measurement tool and the preferred method for eliciting health-related outcomes (46), in combination with the KCCQ and the NYHA Classification to measure NYHA class shift. The ERG believes these are valid and reliable approaches to the measurement of HF symptoms and signs and are likely to capture HRQoL and changes in CHF status.

The ERG notes the company provides data about the safety of sacubitril compared to enalapril in the PARADIGM-HF trial; the CS presents data for 44 different adverse events where ≥2% of patients in any group were affected (Table 42, CS, pg 99 and 100). The ERG provides a narrative of the most important adverse events and reactions in Section 4 (pg 54).

In summary, the ERG considers the CS to be consistent with the final scope by NICE but deviates from the scope with regard to the NYHA classification of CHF.

3.5 Timeframe

The PARADIGM-HF trial had an actual duration of follow-up of 51 months (CSR pg 23). The ERG notes that the intended duration of the trial was 43 months (recruitment of 22 months and a follow-up period of 32 months) (trial protocol pg 31). The PARADIGM-HF trial exceeded its target sample size (randomised n=8,442 as opposed to the target n=7,980) and the trial ended after 51 months when [redacted] events were observed. The reason for the termination of the trial was the Data Monitoring Committee (DMC) recommendation based on compelling efficacy of sacubitril in achieving the primary composite end point of CV mortality and CHF-related hospitalisation in 2,031 patients.

4 CLINICAL EFFECTIVENESS

4.1 Critique of the methods of review

4.1.1 Searches

The CS includes a systematic review to identify the evidence for the effectiveness of sacubitril and relevant comparators in the management of chronic HF (New York Heart Association [NYHA] class II–IV) and left ventricular ejection fraction (LVEF) from the published literature. The ERG notes the CS appendix contains the search terms and strategies (Company Submission [CS], Appendix 2).

The ERG notes several of the electronic searches were not conducted from inception of the database to 2011, but from 1987 only. The ERG believes this is justified because the interventional therapies were developed in the late 1980s. The electronic searches were run initially until 2011 and then updated from July 2013 to September 2014. In April 2015 the searches were updated again from September 2014 to April 2015 and the eligibility criteria modified, which according to the company is less restrictive. The ERG notes the changed inclusion/exclusion criteria were then retrospectively applied to all the previous searches. The company provided the revised inclusion/exclusion criteria in Table 7 of the CS (pg 37). The initial and updated searches were carried out via OVID (EMBASE, MEDLINE(R) In-Process and Other Non-Indexed Citations and Ovid MEDLINE(R)) and in the Cochrane Library.

The proceedings of the following conferences were searched from 2012 to 2015 for additional relevant studies: American College of Cardiology (ACC); American Heart Association (AHA); European Society of Cardiology (ESC); European Society of Cardiology – Heart Failure (HF).

From the CS, it is not clear to the ERG whether the company supplemented the electronic databases searches with searches in clinical trial registry (clinicaltrials.gov). The ERG also notes in the flow diagram in Figure 2 of the CS (pg 38) that hand searching of the included studies and review articles was conducted (CS, Appendices, pg 83).

The ERG considers the search strategy used by the company to contain appropriate search terms and a randomised controlled trial (RCTs) search filter. The company used multiple search terms for HF and sacubitril. However the ERG notes that the yield from each separate electronic database during the initial search and details of the individual updated searches were not reported in the CS (both Appendix 2 and Figure 2), but were merged as one search in Figure 2 in the CS. Due to time constraints, the ERG was unable to validate or replicate the company's search and appraisal of identified abstracts. The ERG considers the exclusion of trials published in languages other than English language a potential source of bias.

The company reports in the CS that identified trials were initially assessed based on abstract and title, and studies not meeting inclusion criteria were excluded with a reason documented with the rationale for exclusion. Trials included after this stage were then assessed based on full text. The ERG is uncertain whether identified studies were independently assessed for inclusion/exclusion and how uncertainties were resolved.

In summary, the company conducted searches of the key electronic databases including MEDLINE, Embase and the Cochrane Library, for RCT evidence relevant to the decision problem and the context of the decision problem. The ERG is of the view that the company may not have included all the RCT evidence relevant to the decision problem because uncertainties among reviewers assessing studies for inclusion do not appear to have been resolved by a third or independent reviewer. Due to time constraints, and the company failing to assign a reason for each of the 341 studies excluded at second pass, the ERG is unable to corroborate the trial selection process.

4.1.2 Inclusion criteria

The eligibility criteria of the systematic review of evidence for sacubitril and its comparators are summarised in Table 5 below. The ERG notes that the company did not conduct a separate search for evidence of adverse events.

The company provided a flow diagram, outlining the processes for the merged initial and updated searches (CS, Figure 2, pg 38). The flow diagram indicates that 138 publications covering 108 studies were identified in the company's systematic review. Of these, two are based on sacubitril, and 106 studies reported on comparator interventions of which 63 were included in the network meta-analysis (NMA). Of the two studies evaluating on sacubitril, one is the pivotal RCT assessing the effects of sacubitril in the treatment of heart failure (PARADIGM-HF) (2). The other RCT, TITRATION (47), was obtained from hand searching and evaluates the safety and tolerability of two different dosing regimens of sacubitril in the management of chronic HF.

The ERG wishes to highlight that this study does not meet the PICO criteria used by the company does not match the final scope from NICE as it's looking at two dosing regimens (and would be excluded from the systematic review based on the listed comparators). However, the company has included TITRATION to support the use of sacubitril in newly diagnosed patients. This issue is discussed further in Section 4 and the ERG presents a critique of the TITRATION trial in the appendices (Appendix 1).

Reasons given by the company for the exclusion of 341 studies (Figure 2) at second pass (based on full text) included patient population out of scope (n=126), trial design was out of scope (n=114),

intervention was out of scope (n=6), non-English language publication (n=3), comparison out of scope (n=4), duplicate (n=3), full text unavailable (n=5), and reported outcomes out of scope (n=80).

The ERG considers that the clinical-effectiveness literature review process, as described in the CS, follows systematic review practices outlined by the Centre for Reviews and Dissemination (48) and as such is methodologically reasonable**.**

Table 5. Eligibility criteria used in search strategy for the RCT systematic review

Clinical effectiveness	**Inclusion criteria**	**Exclusion criteria**
Population	Adult patients with chronic HFrEF (defined by LVEF below 40-45% or simply reported as "reduced") and NYHA class II-IV	Studies including 100% patient populations with the following characteristics will be excluded: Acute HF Non-North American, non-European NYHA class I Preserved EF
Interventions	In addition to ARNI [sacubitril valsartan], all guideline recommended treatment classes will be included: ACEi, ARB, BB, AA, and IF channel inhibitors administered alone or in combination.	
Comparators	Comparators of interest are placebo or any active interventions, except interventions limited to different doses or routes of administration of the active agent.	
Outcomes	Outcomes of interest include: Deaths due to any cause, CV events (or cardiac events), and HF Hospitalisations due to all causes, CV events (or cardiac events), and HF NYHA class change from baseline LVEF change from baseline Withdrawals Withdrawals due to adverse events	
Study design	RCTs (Phase II and III).	Substudies of RCTs providing only prognostic or subgroup data
Language restrictions	English-language publications	Non-English language publications

Abbreviations: AA, aldosterone antagonist; ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; ARNI, angiotensin receptor neprilysin inhibitor; BB, beta blockers; CV, cardiovascular; EF, ejection fraction; HF, heart failure; HFrEF, HF with reduced ejection fraction; IF, If ("funny" current) channel inhibitor; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; RCT, randomised controlled trial

4.1.3 Critique of data extraction

The ERG notes data from included RCTs were extracted into a Microsoft Excel document by one researcher, and verified by another researcher against the original reports. Disagreements were resolved through discussion and consensus (CS, Appendix 5, Tables 112–117) The ERG considers duplicate data extraction by two independent reviewers as the gold standard method of data extraction and the company's approach is reasonable.

4.1.4 Quality assessment

The company conducted an assessment of trial quality for those studies included in the systematic review of RCTs using a quality assessment tool that appears to be based on the Cochrane risk of bias

tool. A summary of the company's quality assessment for the PARADIGM-HF is presented in Table 6 below. The majority of the ERGs critique of the TITRATION trial can be found in appendix 1.

The ERG notes that the company's approach to quality assessment for PARADIGM-HF trial meets the standard practice for the assessment of bias in RCTs and agrees with company's approach to the assessment of quality.

Table 6. Summary of company's quality assessment for PARADIGM-HF (adapted from Table 108 of the CS, pg 25 of the Appendices)

	PARADIGM-HF
Was randomisation carried out appropriately?	Yes
Was the concealment of treatment allocation adequate?	Yes
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes
Were there any unexpected imbalances in drop-outs between groups?	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No
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

Based on the methods outlined in the CS, the ERG considers that the company followed standard systematic review processes and considers the approach to the selection of studies and data extraction for the systematic reviews to be reasonable.

4.2 Critique of trials of the technology of interest, their analysis and interpretation

The company's systematic review identified one trial PARADIGM-HF (2) comparing the sacubitril with enalapril in patients who had heart failure with reduced ejection fraction (HFrEF). The company also included data from the TITRATION trial which evaluated the safety and tolerability of sacubitril at 2 different up-titration doses.

4.2.1 PARADIGM-HF

The main eligibility criteria of PARADIGM-HF are presented in Table 7 below.

Table 7. Eligibility criteria of PARADIGM-HF trial (Adapted from Table 9; pg 43 of CS)

- **Key inclusion criteria**	- **Key exclusion criteria**

Patients aged ≥18 years with CHF (NYHA functional class II-IV) with LVEF ≤40% (changed to ≤35% by an amendment to the protocol) Plasma BNP ≥150 pg/mL (or NT-proBNP ≥600 pg/mL at screening visit or a BNP ≥100 pg/mL (or NT-proBNP ≥400 pg/mL) and a hospitalisation for heart failure within the last 12 months Receiving stable dose of an ACEI or an ARB for at least 4 weeks before entering the study Receiving stable dose of BB for ≥4 weeks before screening visit (unless contraindicated or not tolerated) Receiving stable dose of AA for ≥4 weeks before screening visit (if prescribed) Patients not tolerating enalapril 10 mg bid during the run-in phase were considered run-in failures, did not enter the sacubitril valsartan run-in phase and were withdrawn from study Patients not tolerating sacubitril valsartan 200 mg bid during the run-in phase were considered run-in failures and were withdrawn from the study	Any contraindications to study drugs or other drugs required in the inclusion criteria History of angioedema Treatment requirement for both ACEi and ARB Current acute decompensated HF Symptomatic hypotension or systolic BP <100 mmHg at Visit 1 or <95 mmHg at Visit 3 or 5 eGFR <30 mL/min per 1.73 m2 at Visit 1, 3 or 5 or ≤35% decline in eGFR between Visit 1 and 3 or 5 ACS, stroke, TIA, major CV surgery, PCI or carotid angioplasty within 3 months prior to Visit 1 CAD likely to require surgical or percutaneous intervention within 6 months after Visit 1 CRT device implanted within 3 months of screening visit or plan to implant History of/planned heart transplant History of severe pulmonary disease Peripartum or chemotherapy induced cardiomyopathy (within 12 months) Untreated ventricular arrhythmia with syncopal episodes (within 3 months) Haemodynamically significant obstructive lesions of the LV outflow tract Any surgical or medical condition which might significantly alter the absorption, distribution, metabolism or excretion of study drugs
Abbreviations used in the table: AA, Aldosterone antagonist; ACEi, Angiotensin converting enzyme inhibitor; ACS, Acute coronary syndrome, ARB, Angiotensin II receptor blocker; BB, Beta blocker; bid, twice daily; BNP, B-type natriuretic peptide; BP, Blood pressure; CAD, Coronary artery disease; CRT, Cardiac resynchronisation therapy; CV, cardiovascular; eGFR, Estimated glomerular filtrate; HF, Heart failure; LVEF, Left ventricular ejection fraction; NYHA, New York Heart Association; TIA, Transient ischaemic attack	

The PARADIGM-HF trial was conducted in 985 sites in 47 different countries. A total of 10,513 patients were recruited. The ERG notes that a large number of exclusion criteria were applied. However, the ERG's clinical experts consider the exclusion criteria to be appropriate for the population and therapies under investigation.

In the PARADIGM-HF trial, randomisation took place following after the run-in phase. Eligible patients were screened based on criteria in Table 7. After screening, patients entered the run-in phase where patients were switched from the ACE inhibitor or ARB that they had been receiving to single-blind treatment with enalapril (at a dose of 10 mg twice daily) for two weeks followed by single-blind treatment with sacubitril for an additional 4-6 weeks (initially at a dose of 100 mg twice daily, which was increased to 200 mg twice daily) in the absence of unacceptable side effects. Trial participants not able to tolerate the sacubitril or enalapril were excluded from the trial.

Following run-in, patients were randomised to receive either sacubitril (200 mg bid) or enalapril (10 mg bid) in addition to optimal CHF therapy, in a double-blind fashion with the use of a computerised randomisation system involving concealed study-group assignments. As stated in the CSR (pg 31), "at visit 5, the investigator called the interactive voice response system (IVRS), entered the patient's number, and the IVRS assigned a randomisation number to the patient, that was used to link the

patient to a treatment arm and specified unique medication numbers for the packages of the first supply of the study drugs dispensed to the patient. The IVRS provided unique medication numbers for both the sacubitril or its matching placebo and enalapril or its matching placebo". Thus to maintain a double-blind, double dummy design, patients were required to take their assigned active treatment tablet along with matching placebo twice daily (morning and evening dose) in addition to their conventional concomitant therapy. The ERG acknowledges these arrangements as sufficient to maintain blinding amongst participants. The baseline characteristics of the participants of the PARADIGM-HF trial appear similar at baseline and are presented in Table 8.

Table 8. Baseline characteristics for patients in the PARADIGM-HF trial (CS, Table 13, pg 54)

PARADIGM HF Baseline characteristics		**Sacubitril valsartan (n=4,187)**	**Enalapril (n=4,212)**
Age	Mean ±SD Range, years	63.8±11.5 18-96	63.8±11.3 21-96
	<65 years, n (%) ≥65 years, n (%)	2011 (50.4) 2076 (49.6)	2168 (51.5) 2044 (48.5)
	<75 years, n (%) ≥75 years, n (%)	3403 (81.3) 784 (18.7)	3433 (81.5) 779 (18.5)
Females, n (%)		879 (21.0)	953 (22.6)
Race/ ethnicity, n (%)	White	2,763 (66.0)	2,781 (66.0)
	Black	213 (5.1)	215 (5.1)
	Asian	759 (18.1)	750 (17.8)
	Other	452 (10.8)	466 (11.1)
Region, n (%)	North America	310 (7.4)	292 (6.9)
	Latin America	713 (17.0)	720 (17.1)
	Western Europe, South Africa, Israel	1,026 (24.5)	1,025 (24.3)
	Central Europe	1,393 (33.3)	1,433 (34.0)
	Asia-Pacific	745 (17.8)	742 (17.6)
SBP, mmHg, mean ±SD		122±15	121±15
Heart rate, beats/min, mean ±SD		72±12	73±12
BMI, mean ±SD		28.1±5.5	28.2±5.5
Serum creatinine, mg/dL, mean ±SD		1.13±0.3	1.12±0.3
Clinical features of HF	IC, n (%)	2,506 (59.9)	2,530 (60.1)
	LVEF, %, mean ±SD	29.6±6.1	29.4±6.3
	Median BNP (IQR), pg/mL	255 (155–474)	251 (153–465)
	Median NT-proBNP (IQR), pg/mL	1,631 (885–3154)	1,594 (886–3305)
NYHA class, n (%)	I	180 (4.3)	209 (5.0)
	II	2,998 (71.6)	2,921 (69.3)
	III	969 (23.1)	1,049 (24.9)
	IV	33 (0.8)	27 (0.6)
	Missing data	7 (0.2)	6 (0.1)
Treatments at randomisation (standard care/ background	Diuretic	3,363 (80.3)	3,375 (80.1)
	Digitalis	1,223 (29.2)	1,316 (31.2)
	BB	3,899 (93.1)	3,912 (92.9)

therapies), n (%)	AA	2,271 (54.2)	2,400 (57.0)
Medical history, n (%)	Hypertension	2,969 (70.9)	2,971 (70.5)
	Diabetes	1,451 (34.7)	1,456 (34.6)
	AF	1,517 (36.2)	1,574 (37.4)
	Hospitalisation for HF	2,607 (62.3)	2,667 (63.3)
	MI	1,818 (43.4)	1,816 (43.1)
	Stroke	355 (8.5)	370 (8.8)
	Pre-trial use of ACEi	3,266 (78.0)	3,266 (77.5)
	Pre-trial use of ARB	929 (22.2)	963 (22.9)

Abbreviations: AA, aldosterone antagonists; ACEi, angiotensin converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin II receptor blocker; BB, beta blocker; BNP, B-type natriuretic peptide; BMI, body mass index; HF, heart failure; IC, ischaemic cardiomyopathy; IQR, interquartile range; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NT-proBNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association; SBP, systolic blood pressure; SD, standard deviation.

The ERG notes that the PARADIGM-HF trial recruited relatively few patients from England (n=242/10513 [2.3%]) (CS, Table 11, pg 45). The company states (CS, pg 54) that, "compared with the English HFrEF population, patients in PARADIGM-HF were younger, more likely to be male, and that a lower average age is seen in HF trials as a result of clinical trials requiring clear pre-determined eligibility criteria and rigorous follow-up making recruitment of significant numbers of older patients difficult". The ERG's clinical experts advised that typically patients presenting with HF in the UK are older (≥75 years in men and ≥85 years in women) than those in the PARADIGM-HF trial (mean age was 63.8 years) (CS, Table 13 pg 54) but the younger age population in PARADIGM-HF is typical of all HF trials.

PARADIGM-HF initially recruited patients with LVEF ≤40% before the study protocol was amended to ≤35%. According to the company (CS, pg 42), this was to ensure an adequate event rate in the study population. However, the ERG's clinical experts advised that patients in the PARADIGM-HF trial were patients with severe HF (based on LVEF≤35%), and that the observed benefits of treatment with sacubitril would be greater than in patients with mild/moderate CHF.

The ERG's clinical experts highlighted that a proportion of patients with severe HF in the UK would have been fitted with cardiac devices. Although no information is presented on clinical effectiveness in the subgroup of people fitted with a cardiac device in the CS, the ERG notes data are presented in the CSR to show around [redacted] of the trial population used devices (CSR, Table 11-14, pg 100).

The ERG notes that approximately 25% of the trial population were recruited from sites in Western Europe. The ERG report contains a critique of the generalisability of the Western Europe population in the subgroup analysis in Section 4.

4.2.2 Interventions and comparisons

The primary objective of PARADIGM-HF trial was to compare the ARNI, sacubitril, with the ACEi, enalapril, in patients who had symptomatic HF with a reduced ejection fraction.

As stated in Section 4.2, patients first entered a run-in phase where they were switched from the ACEi or ARB that they had been receiving to single-blind treatment with enalapril (at a dose of 10 mg twice daily although could be initiated at 5 mg bid for one or two weeks before up-titration in patients who were on ARBs or lower doses of ACEis) for two weeks followed by single-blind treatment with sacubitril for an additional 4-6 weeks (initially at a dose of 100 mg twice daily, which was increased to 200 mg twice daily) in the absence of unacceptable side effects.

Patients who had no unacceptable side effects of the target doses of the study medications during the run-in period were randomised in a double-blind, double-dummy fashion to receive sacubitril (200 mg bid) and enalapril placebo or enalapril (10 mg bid) and sacubitril placebo, in addition to their conventional concomitant therapy.

According to the CSR (pg 34–35) [redacted].

Sacubitril 200mg is a composite of valsartan and sacubitril and the company report the equivalent dose of valsartan contained is 160mg. The ERG's clinical expert advised that the dose of valsartan in combination with sacubitril is higher than that typically prescribed in UK clinical practice. [redacted]

According to the company (CS, pg 41), enalapril was chosen because it is the ACEi that has been studied in the largest number of trials of patients with HFrEF and it has a well-documented mortality benefit in HF. However the ERG's clinical experts advised that, in the UK, the standard ACEi is ramipril. Therefore, comparing sacubitril with enalapril does not reflect UK clinical practice. In addition, the assumption in the CS (pg 72) that all ACEi are the same in terms of effectiveness may not be valid; the ERG is unaware of any study demonstrating the equivalence of ACEis generally, and more specifically enalapril and ramipril. However the ERG notes that this same assumption is made by the authors of a Cochrane review of treatments for CHF and this is discussed later in Section 4.(49)

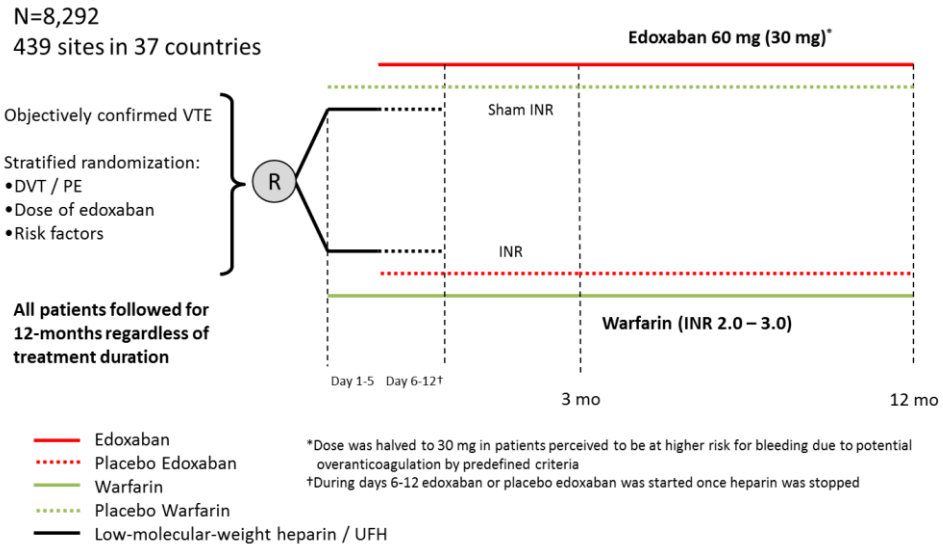
There was monitoring of patients for tolerability of study medications including laboratory assessments and measurement of potassium and estimated glomerular filtration rate (eGFR) during the active run-in period up to the randomisation visit to determine eligibility of the patient into the

trial. This was continued during the active double-blind phase to monitor the tolerability to the study medication dose administered and adjusted medication dose if needed.

The ERG notes the large number of withdrawals/discontinuations during different phases of the PARADIGM-HF trial. [redacted] patients who failed the enalapril run-in period and [redacted] (CSR, pg 87–88 and Tables 10-1 and 10-2). After randomisation, 18 patients (8 in sacubitril group and 10 in enalapril group) discontinued, 4 patients (2 from each group) died, 12 patients were lost to follow-up (5 in sacubitril group and 7 in enalapril group), and one patient from each group requested withdrawal. The ERG's clinical expert believes the number of discontinuations/withdrawals reflects those observed in CHF trials generally.

Figure 2 summarises the treatment pathways in PARADIGM-HF.

Figure 2. PARADIGM-HF study schematic (from CS Figure 3 pg 41)



4.2.3 Outcomes

The primary outcome in the PARADIGM-HF trial was a composite of death from cardiovascular (CV) causes or a first hospitalisation for HF assessed at every study visit (0 weeks, 2, 4, and 8 weeks, 4 months, and then every 4 months). The target number of primary composite endpoint events was planned to be [redacted] at the end of the study; the target number of CV deaths was planned to be [redacted] (CSR, Section 9.5.2.1, pg 45). In addition to the primary composite endpoint, the CV mortality component was also analysed at each interim efficacy analysis.

The company's rationale for choosing the primary endpoint (CSR, Section 9.2.1, pgs 21–22) is that, "there is a general agreement that the major goal of treating HFrEF is to reduce the major fatal and non-fatal consequences of this illness, i.e. CV death and hospitalization for worsening HF. CV death

and HF hospitalization have also been shown to be modifiable by treatments improving this condition. This understanding of HF and its treatment has led to this disease-specific composite endpoint being the most commonly used primary endpoint in recent HF outcomes trials". The ERG's clinical experts agree that PARADIGM-HF used a composite primary outcome which is commonly used in HF trials.

The secondary outcomes in PARADIGM-HF included time to death from any cause (assessed at all study visits); change from baseline to eight months in the clinical summary score on the Kansas City Cardiomyopathy Questionnaire (KCCQ) (on a scale from 0 to 100, with higher scores indicating fewer symptoms and physical limitations associated with HF). KCCQ scores were assessed at baseline/randomisation visit (Visit 5), at four, eight and 12 months (visits 8, 9 and 10), at 24 and 36 months (visits 14 and17), as well as at the end of study visit; time to a new onset of atrial fibrillation (AF) (assessed at all study visits); and time to the first occurrence of a decline in renal function (which was defined as end stage renal disease [ESRD] or as a decrease in the eGFR of at least 50% or a decrease of more than 30 mL/min per 1.73 m^2 from randomisation to <60 mL/min per 1.73 m^2).

According to the CS (Table 9, pg 44), adjudication of these outcomes was carried out in a blinded fashion by an endpoint adjudication committee which was responsible for classifying all deaths and for determining whether pre-specified endpoint criteria are met for the fatal events. The ERG notes all clinical effectiveness outcomes and HRQoL outcomes specified in NICE's final scope on sacubitril for treating CHF were reported in PARADIGM-HF trial.

The SAF, which was used for the analyses of safety variables, consisted of all randomised patients who received at least one dose of study medication, and patient data was analysed according to the treatment actually received. The per protocol (PP) population was a subset of the full analysis set (FAS) that consisted of all the patients who did not have major deviations from the protocol procedures during the double-blind stage.

The ERG considers the PARADIGM-HF trial to have been well conducted but has some concerns about whether the recruited population represents those with CHF in the UK and that the use of enalapril 10mg twice daily as the comparator does not reflect UK clinical practice. These elements are further discussed below.

4.2.4 Results

In PARADIGM-HF a total of 10,513 patients were recruited to be screened for eligibility in 985 sites in 47 countries (49 centres and 242 patients in England) between 8 December 2008 through 23 November 2012; out of which 9,413 entered the single-blind run-in phase (CS, Figure 4, pg 53). Patients (n=9,413) who had no unacceptable side effects of the target doses were randomised in a double-blind, double-dummy fashion to receive either sacubitril 200mg bid or enalapril 10 mg bid with the use of a computerised randomisation system involving concealed study group assignments.

The primary outcome in the PARADIGM-HF trial was a composite of death from cardiovascular (CV) causes or a first hospitalisation for heart failure assessed at every study visit (0 weeks, 2, 4, and 8 weeks, 4 months, and then every 4 months). The secondary outcomes included time to death from any cause (assessed at all study visits); change from baseline to eight months in the clinical summary score on the Kansas City Cardiomyopathy Questionnaire (KCCQ), whose scores were assessed at baseline/randomisation visit (visit 5), at four, eight and 12 months (visits 8, 9 and 10), at 24 and 36 months (visits 14 and17), as well as at the end of study visit; time to a new onset of atrial fibrillation (AF) (assessed at all study visits); and time to the first occurrence of a decline in renal function. The ERG's clinical experts note outcomes used in PARADIGM-HF are those typically used in HF trials.

The PARADIGM-HF study protocol was amended four times (CSR, Section 9.8.1, pg 83–83). The key features of the amendments are: change in the LVEF entry criterion from ≤ 40% to ≤ 35% to ensure an adequate event rate in the study population, [redacted] Reasons for the amendments are reported in the CSR (Section 9.8.1, pg 83–84). The ERG considers the change from 45% to ≤35% LVEF means that the population recruited from then would have more severe CHF.

PARADIGM-HF was described as a double-blind, double-dummy study. As stated in Section 4.2, randomisation was performed by computerised Interactive Voice Responsive System (IVRS) in which the IVRS assigned a randomisation number to the patient, that was used to link the patient to a treatment arm and specified unique medication numbers for the packages of the first supply of the study drugs dispensed to the patient. The IVRS provided unique medication numbers for both the sacubitril or its matching placebo and enalapril or its matching placebo. To maintain the double-blind, double dummy design, patients were required to take their assigned active treatment tablet along with matching placebo twice daily (morning and evening dose) in addition to their conventional

concomitant therapy. The ERG considers the trial arrangements for the random allocation of the trial drugs and the maintenance of blinding were in accordance with good practice and are adequate.

The company states in the CS (pg 53) that, "there were no significant differences between groups regarding any of the baseline characteristics apart from some differences between English population with heart failure and the study population". The ERG was unable to verify this as no measures of statistical significance were reported in the CS (Table 13 pg 54), CSR (Table 11-2, pg 95) or the published PARADIGM-HF trial (2) (Table 1, pgs 996-997).

4.2.5 Description and critique of statistical approach used

The CS contains comprehensive details on the statistical analyses approaches used in the PARADIGM-HF trial. In the PARADIGM-HF trial, it was estimated that the annual rate of the primary outcome in the enalapril group would be 14.5% and the rate of CV death would be 7.0%. Calculation of the sample size was based on CV death in estimating a follow-up of 8,000 patients for 34 months, with 1,229 CV deaths to give the study 80% power to detect a relative reduction of 15% in the risk of CV death in the sacubitril group. On the basis of these power calculations, it was estimated the primary outcome would occur in 2,410 patients and provide 97% power to detect 15% risk reduction (CS, pg 50) (2).

The primary objective of PARADIGM-HF trial was to examine whether the long-term effects of sacubitril on morbidity and mortality were superior to enalapril in patients with CHF and a reduced ejection fraction. To achieve this, the primary efficacy variable (composite outcome of CV death or a first HF hospitalisation) was analysed using Cox's proportional hazards model with treatment and region as fixed factors. The FAS was used for the primary outcome analysis and type I error was set at 2.5%, with a one-sided significance level of alpha (α) used for the final analysis (adjusted for interim analysis).

For secondary efficacy outcomes time to event data (time to all-cause mortality, time to new onset of AF, time to composite renal endpoint) were evaluated using Kaplan-Meier estimates and Cox proportional hazards models with treatment group and region as fixed factors. The estimated hazard ratios and the corresponding 95% Confidence Interval and two-sided p-values were provided for the FAS. Changes in KCCQ scores from baselines were assessed by total score and individual sub-domain scores and analysed as exploratory outcomes. The clinical summary score (CSS) of KCCQ was calculated as the mean of the physical limitation and total HF symptom scores, and changes from baseline were analysed as repeated measures of covariance (ANCOVA) model in which treatment, region, visit, and treatment-by-visit interaction were included as fixed effect factors. Fisher's exact test was used to compare rates of adverse events using the SAF.

A number of pre-specified subgroups including age, gender, race, region NYHA class, diabetes, systolic blood pressure (SBP), LVEF, AF, etc., were analysed to assess the consistency of the treatment effect. This was pre-planned with the exception of a post-hoc analysis to assess the treatment effect of subgroup of patients in Western Europe.

In addition, (CSR, Section 8.7.13; pg 83) the end of the PARADIGM-HF trial was planned to occur when the pre-specified number of patients [redacted] experienced the primary composite endpoint of cardiovascular deaths or HF hospitalizations, unless the study was terminated early due to critical safety concerns. Accordingly the trial was terminated after a median follow-up of 27 months (actual trial duration post randomisation was 51 months), when the pre-specified events for the primary outcome, death from CV causes or first hospitalisation for worsening HF was observed (CS, pg 50).

The ERG notes that in the PARADIGM-HF trial, the protocol reports the stopping rule indicated that both the primary composite endpoint (CV death or HF hospitalisation) and CV death alone required a one-sided p-value <0.001 favouring sacubitril over enalapril at the interim analysis for established efficacy. Based on these criteria, on the 31March, 2014, the decision was made to stop the trial.

The ERG notes the intended duration of the PARADIGM-HF double-blind randomised treatment period is variously described as 34 months (CS, pg 50), and 43 months (protocol pg 18), whereas the actual trial duration was [redacted] months (CSR pg 20). The ERG is aware of the potential bias arising from stopping a trial early when the data observed in the interim might be a "random high" effect (50).

Populations used for statistical analyses in PARADIGM-HF included the full analysis set (FAS), the safety population (SAF), and the per-protocol (PP) population (CS, pg 49). The FAS which was used for efficacy variables was based on the intention-to-treat (ITT) principle. The company defined this as all validly randomised patients who have received at least one dose of study drug with patients assigned to their randomised treatment group regardless of actual drug taken.

4.2.6 Description and critique of the meta-analysis

The ERG notes no pair-wise meta-analyses were presented in the CS but the company conducted network meta-analyses (NMAs) to provide relative treatment effect estimates between ACEis, ARBs, ARNIs and placebo regarding efficacy and safety for the treatment of CHF. The company used a Bayesian approach to the NMA, using R2OpenBUGS linked with OpenBUGs version 3.3.2 software to carry out the NMA. The OpenBUGS code used was supplied to the ERG in the company's response to clarification questions.

The CS highlighted the absence of data from trials directly comparing sacubitril with ARBs and therefore the objective of the NMA was to allow an indirect comparison of sacubitril with ARBs (Box 1). ARBs are typically used for people for whom ACEis are not suitable.

The ERG notes that the company used methods that are in-line with the NICE Decision Support Unit (46) .

Box 13. The main objective of the network meta-analysis (NMA) (CS, pg 71)

Therefore, the main objective of this NMA was to estimate the effectiveness of sacubitril valsartan compared with ARBs, as well as the effectiveness of ARBs compared with ACEi to inform the economic model inputs.
Abbreviations: NMA, network meta-analysis; angiotensin converting enzyme (ACE) Inhibitor.

The company justifies conducting an NMA as the NICE final scope requests ARBs are included in the comparisons in the NICE scope for people for whom ACEis are unsuitable . The same searches used to identify trials for the systematic review were used to identify trials for inclusion in the NMA.

The ERG's critique of the company's search strategy can be found on page 30 of this report. The flow diagram of RCTs included in the CS depicts the flow of studies for inclusion in the NMA. After de-duplication 5672 records were available for consideration, abstract and full text articles were assessed and a total of 63 RCTs were available for potential inclusion in the indirect comparison (CS, pg 38). The CS then reports refinements made to the systematic review's exclusion criteria (CS, pg 37) and as a result of the new eligibility criteria the total number of trials in the NMA was reduced to 28 (CS, pg 72) (Box 14).

Box 14. The primary exclusion criteria of the network meta-analysis (NMA) (CS, pg 73).

The primary exclusion criteria for the core NMA were as follows: • Intra-class studies (e.g. enalapril versus ramipril) that did not report relative treatment effects between different classes of drug and therefore could not inform the NMA • Studies reporting zero events in all arms for a given outcome as this data could not inform the NMA and would only lead to greater uncertainty. This was of particular importance when a study reported safety data simply as "no deaths", or when studies report no deaths as a reason for withdrawal • Studies that did not report data on the outcomes of interest (See Section 4.10.6) for further detail on selection of outcomes).
Abbreviations: NMA, network meta-analysis.

The ERG notes RCTs were included if they met the criteria for the population, comparators and design as well as including at least one of the interventions and outcomes of interest. In addition, only full-text publications were included and only those published in English were eligible for inclusion.

The ERG notes the inclusion criteria of interest in the NMA differ from those in the systematic review and the final scope by NICE in the following ways; the NYHA classification, LVEF; withdrawals due to adverse events which were part of the PICO for the systematic review were not a prerequisite for

the NMA. Furthermore some outcomes included in the final scope by NICE were omitted in the NMA, these were symptoms of HF, adverse effects of treatment and health-related quality of life. (Box 15).

Box 15. Outcomes included in the NMA: (CS, pg 73)

- Deaths due to any cause
- Deaths due to CV events (or cardiac events)
- Hospitalisations due to all causes
- Studies reporting outcomes from drug classes that were not included in the NICE scope as the SR had a broader scope (i.e., ivabradine)

Abbreviations: NMA, network meta-analysis; NICE, National Institute for Health and Care Excellence; SR = systematic review.

The ERG notes the core NMA is based on data from 28 trials of placebo controls, ACEis and ARBs with one ARNI (sacubitril) linked to an ACEi in the PARADIGM-HF trial. The ERG notes that the company NMA focuses on single interventions at the drug class level, i.e. ACEis, ARBs, and sacubitril (ARNI) (CS, pg 72). The inclusion of trials was irrespective of the concomitant therapies being taken by trial patients. The CS cites work (51) reporting an NMA showing no differences in ACEis in 10 trials with outcomes of risk of death, sudden cardiac death, death due to pump failure, re-hospitalisations or drug discontinuation. The CS cites a Cochrane systematic review (49) that assumes a class effect of ACEis and ARBs. The ERG notes the inclusion of data from patients with concomitant therapies is in accordance with the final scope from NICE and therefore considers the company submission is reasonable.

The ERG notes the company has been influenced in its approach to meta-analysis by the Cochrane systematic review which also includes patients with and without concomitant therapies and assumes a drug class effect (49) (CS pg 72).

The CS refers to the evidence from the Cochrane systematic review as to the relative effects of ARBs and ACEis in HF. The ERG understands the Cochrane systematic review includes HF patients in whom the ejection fraction is preserved (HFrEF) (unlike the company's NMA – only data from trial populations with HFrEF were analysed, CS pg 71).

The ERG referred a trial (52), reporting the only direct comparison of an ARB with an ACEi included in a Cochrane systematic review (49). This 3-arm trial compares valsartan with lisinopril versus placebo in patients who had never previously received an ACEi. The main outcomes for this trial were mean pulmonary capillary wedge pressure, systematic vascular resistance and increased cardiac output and no data for hospitalisation were reported. The ERG notes this trial was not included in the NMA and agrees that only some of the studies from the Cochrane systematic review by (49) are applicable to the NICE scope.

The ERG notes the baseline intervention of interest in the NMA is sacubitril (ARNI) which is linked to the other treatments in the network though the ACEi data from the PARADIGM-HF trial. The CS contains NMA for the outcomes of all-cause mortality (CS, Figure 10, pg 76), CV mortality (CS, Figure 11, pg 77) and all-cause hospitalisation (CS, Figure 12, pg 77). The core NMA (all-cause mortality) includes 28 trials, 8 of which are included in the main comparison of interest. The primary outcomes of the trials included in the ACEi versus ARB comparisons are symptoms of HF during exercise, the 6 minute walk test, a bicycle test, clinical status (dyspnoea-fatigue index), treadmill test, ejection fraction and quality of life and not deaths or hospitalisation but the CS has used data for deaths from all-causes collected as an adverse event as the surrogate outcome measure.

The CS tabulates the results of the core NMA and a pair-wise meta-analysis from a Cochrane systematic review (49) (Table 9).

Table 9. Comparison of results from NMA and Cochrane systematic review (49)

Scenario	All-cause mortality HR P(better)	CV mortality HR P(better)	All-cause hospitalisation HR P(better)
Core NMA			
ARB vs ACEi	[redacted]	[redacted]	[redacted]
Cochrane meta-analysis			
ARB vs ACEi	1.05 (95% CI: 0.91, 1.22)	1.08 (95% CI: 0.91, 1.28)	1.00 (95% CI: 0.92, 1.08)

Abbreviations: 95% CI, 95% confidence interval; 95% CrI, 95% credible interval; ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CrI, credible intervals; CV, cardiovascular; HR, hazard ratio; NMA, network meta-analysis; P, probability

The ERG agrees that this convergence of the results from the two different approaches to meta-analyses of data gives some reassurance that the results are valid but, because of the inclusion of populations that are not within the scope issued by NICE in both meta-analyses, these results need to be interpreted with caution. (Note, the Cochrane systematic review reports confidence intervals rather than credible intervals).

There is a wide range of doses of ACEis and ARBs in the trials included in the NMA. The ERG notes these range from 6.25mg to 50mg x 3 daily for captopril, whereas patients are allocated to enalapril at doses of 20mg daily for ACEis. For ARBs the doses range from 10mg to 80mg daily for telmisartan and from 4mg to 16mg daily for candesartan. The ERG has also noticed that patients in one of the trials (REPLACE 2001) (53) included patients with HF NYHA class II to III and not as stated in the CS "NYHA class II-IV, which is aligned to the population in the PARADIGM–HF trial" (CS, pg 79). The ERG believes the wide range in drug doses used to manage HF and the differences in NYHA classification of patients recruited to the trials in the NMA are potential sources of clinical

heterogeneity. This could manifest in the analysis as wide 95% credible intervals. The ERG notes the rationale in the CS for using a random effects model was based on the Deviance Information Criterion (DIC) (CS, pg 92).

In summary the ERG is concerned that some patients in the core NMA comparison of ACEi and ARBs do not match the population of interest as stated by the company and the wide variability in the drug doses. The ERG notes the CS also reports a high risk of bias in many of the studies in the NMA arising mainly from a lack of information about the conduct of the randomisation and the manner of concealments for the allocation. The threats to validity of the findings arising from the unclear conduct of the majority of trial, the differences in drug doses and the NYHA classes in some of the included populations could produce results from the NMA which are potentially misleading.

The ERG notes the hazard ratios for the outcomes of interest for ARBs versus ACEis (Table 10) show ACEis have the highest probability of being more effective in reducing all-cause mortality and CV mortality, but ARBs have the highest probability of reducing all-cause hospitalisations.

Table 10. Summary of random effects results from NMA (reproduced from CS, Table 29, pg 88)

Scenario	All-cause mortality HR (95% CrI) P(better)	CV mortality HR (95% CrI) P(better)	All-cause hospitalisation HR (95% CrI) P(better)
ARB vs ACEi	[redacted]	[redacted]	[redacted]
ARNI vs ARB	[redacted]	[redacted]	[redacted]

Abbreviations: ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; ARNI, angiotensin receptor neprilysin inhibitor; BB, beta blockers; CrI, credible intervals; CV, cardiovascular; HR, hazard ratio; NMA, network meta-analysis; P, probability

The ERG interprets the hazard ratios from the NMA comparing ARNI versus ARBs to indicate that ARNIs have the highest probability of reducing all-cause mortality and CV mortality but the probability that ARNIs reduce hospitalisation is only marginally in the favour of ARNIs. The ERG also observes that none of the credible intervals (Crl) in Table 10 would be considered statistically significant at the 5% significance level. The ERG also notes a slight discrepancy exists between the indirect and direct probabilities and the effectiveness for ACEis (p (better) = [redacted]) is higher than that of the ARNIs (p (better) = [redacted]) in the placebo controlled part of the network (CS, pg 89).

The effect of treatment effect modifiers LVEF, NYHA class and digoxin use were explored in sensitivity analyses using meta-regressions and are reported in the CS (pg 91) for both comparisons

(ARBs vs ACEis and ARNIs vs ARBs) show no statistically significant interactions as noted by the company (pg 90).

The ERG notes that while the evidence included in the NMA shows that it is likely that sacubitril reduces the risk of both all-cause and CV mortality more than ARBs, the NMA analyses shows all-cause hospitalisation to be similar (p (better) [redacted] for sacubitril vs [redacted] for ARBs)) (CS, Table 32, pg 90). The ERG notes the credible intervals around the HRs from the NMA indicate the differences between ARNI vs ACEi would not be considered statistically significantly (table 7).

The company presents an NMA of the investigational therapies (PLAC; ACEi; ARB; ARNI) plus the concomitant therapies (AA and BBs) comparing the following combinations; ACEi +BB; ARB+BB; ACEi + ARB; ACEi +AA; ACEi + ARB +BB; ACEi+BB+AA and ARNI+AA+BB. The ERG notes that the CS presents network diagrams for NMA scenarios of concomitant standard care therapies for the outcomes all-cause mortality, CV mortality and all cause hospitalisation. The CS presents tabulated data for the ACEis in the NMA and states these results are consistent with the results from the PARADIGM-HF trial (CS, Table 39, pg 96) (Table 11).

Table 11. Results of ACEi comparison from NMA versus PARADIGM-HF (reproduced from CS, Table 39, pg 96)

Outcome measure	**ARNI vs ACEi**	
	Core NMA HR (95% CrI)	PARADIGM-HF trial HR (95% CI)
All-cause mortality	[redacted]	0.84 (0.76,0.93)
CV mortality	[redacted]	0.80 (0.71, 0.89)
All-cause hospitalisation	[redacted]	0.88 (0.82, 0.94)
Abbreviations: ACEi, angiotensin converting enzyme inhibitor; ARNI, angiotensin receptor neprilysin inhibitor; CV, cardiovascular; CI, confidence interval; CrI, credible intervals; HR, hazard ratio; NMA, network meta-analysis		

Overall the ERG regards the results of the NMA conducted by the company to be uncertain and potentially unreliable based on the clinical heterogeneity in the RCTs underpinning the network. The ERG considers the clinical effectiveness of sacubitril compared to ARB in newly diagnosed patients with CHF remains an important and yet unanswered question that may require evaluation in an RCT.

4.3 Clinical effectiveness results

The findings from the PARADIGM-HF trial show that sacubitril was more effective than enalapril in the management of HF in the PARADIGM-HF trial population. The hazard ratios and 95% CIs show a statistically significant effect in all three trial outcomes (Table 12).

Table 12. Primary composite outcome and component outcomes of PARADIGM-HF (FAS) (Table 14 reproduced from CS, pg 57)

	Sacubitril valsartan n=4,187 n, %	Enalapril n=4,212 n, %	HR (95% CI)	p-value†
Death from CV causes or first hospitalisation for worsening HF	914 (21.8)	1117 (26.5)	0.80 (0.73–0.87)	<0.001
Death from CV causes	558 (13.3)	693 (16.5)	0.80 (0.71–0.89)	<0.001
First hospitalisation for worsening HF	537 (12.8)	658 (15.6)	0.79 (0.71–0.89)	<0.001

† p values are two-sided and were calculated by means of a stratified log-rank test without adjustment for multiple comparisons.
Events which occurred in the double-blind period up to 31 Mar 2014 are included in the analysis.
Abbreviations: CI, confidence interval; CV, cardiovascular; FAS, full analysis set; HF, heart failure; HR, hazard ratio.

The ERG has concerns about the generalisability of the findings of the PARADIGM-HF trial into UK clinical practice: The trial recruited relatively few patients from England (n=242/10,513 [2.3%]) (CS, Table 11, pg 45) and the company acknowledges that, "compared with the English HFrEF population, patients in PARADIGM-HF were younger, and were more likely to be male". The company's justification of the lower age is, "clinical trials require clear pre-determined eligibility criteria and rigorous follow-up making recruitment of significant numbers of older patients difficult" (CS, pg 54). The ERG's clinical experts advised that patients in the UK presenting with HF are typically older (≥75 years in men and ≥85 years in women) than those in the PARADIGM-HF trial (mean age was 63.8 years) (Table 13 of CS, pg 54).

The higher proportion of men recruited to the trial may be important. The ERG has been advised by clinical experts that men generally have better outcomes when treated for HF, possibly because they present with HF at a younger age than women (an average of 76 years for men and 80 years for women National heart failure audit 2013/14) (54)). However, the ERG notes this effect would be observed across both arms of the trial and would not confer a relative advantage on either of the trial interventional drugs. Rather, the trial population may have exhibited better outcomes than would be observed in clinical practice. However, the ERG's clinical experts have advised that the younger age population in PARADIGM-HF is typical of HF trials.

The ERG notes that the scope from NICE includes standard care as part of the comparisons and the ERG is advised by the clinical experts that most patients in the UK would be taking concomitant therapies; beta blockers (BBs) and an aldosterone antagonist (AAs). The ERG notes that almost all trial patients were taking a BB (>93%) but just over half (~54%) were taking an AA (table 8 ERG report). The ERG's clinical experts highlighted that a proportion of patients with severe HF in the UK would have been fitted with cardiac devices.

The ERG considers that the effect of lowering the trial inclusion criteria from an LVEF of <40% to ≤35% would have led to an increase in the numbers of severe HF patients enrolled in the trial. The protocol amendment was made to increase the event rate and, given the early stopping of the PARADIGM-HF trial, the ERG concludes that this appears to have occurred.

The lack of evidence about the effect of sacubitril in people newly diagnosed with CHF in both the PARADIGM-HF trial and TITRATION trials is problematic and the ERG is unable to comment on what the effectiveness of sacubitril would be in people not previously treated with an ACEi.

4.3.1 Subgroup analyses

The company present tables of results from subgroup analyses of the data collected from patients on the PARADIGM-HF trial (CS, pg 68–70). The ERG discusses the patient characteristics which did not demonstrate statistically significant effects. The ERG acknowledges that it is possible that some of these comparisons were underpowered to detect a statistically significant difference.

As highlighted in the preceding paragraphs there is a lack of evidence about the effectiveness of sacubitril in newly diagnosed patients. The subgroup analysis from PARADIGM-HF in the 1,867 patients who were considered ACEi naive had no significant benefit in the primary outcome (HR 0.92, 95% CI: 0.76 to 1.10). These data reinforce the ERG's view that the comparative effectiveness of sacubitril vs enalapril in newly diagnosed HF patients is unclear.

The ERG considers the Western Europe population to be the most representative of the UK. The primary outcome in this subpopulation was also non-significant (HR 0.89, 95% CI: 0.74 to 1.07) (CS, pg 68) The ERG therefore requested the characteristics of participants (n= 2,057) for the Western European population from the company and this was supplied during clarification (Table 13).

The ERG notes from this subgroup analysis that the mean age is [redacted] years, similar to the whole trial population, is predominantly of white race ([redacted] compared to 66% of the total trial population), with a NYHA classification of II ([redacted] vs ~70% of the trial population) with the same mean LVEF of [redacted]. The ERG also notes ~[redacted] had received ACEis at baseline ([redacted] than the ~78% reported in the total population). [redacted].

However, the ERG notes the differences in the numbers of the Western Europe population who are hypertensive ([redacted] vs 70% of the overall trial population) which may suggest that the Western Europe HF population are in receipt of more intensive "standard care" compared to other regions in the trial.

Table 13. Western Europe subgroup data provided at clarification by the company.

Variable	Value	
	Sacubitril valsartan N=1,029	Enalapril N=1,028

Mean age, years (±SD)	[redacted]	[redacted]
Female, n (%)	[redacted]	[redacted]
Race – White, n (%)	[redacted]	[redacted]
Race – Black, n (%)	[redacted]	[redacted]
Race – Asian, n (%)	[redacted]	[redacted]
Race – Other, n (%)	[redacted]	[redacted]
NYHA class I, n (%)	[redacted]	[redacted]
NYHA class II, n (%)	[redacted]	[redacted]
NYHA class III, n (%)	[redacted]	[redacted]
NYHA class IV, n (%)	[redacted]	[redacted]
NYHA class III/IV, n (%)	[redacted]	[redacted]
LVEF %, mean (±SD)	[redacted]	[redacted]
SBP mm HG, mean (±SD)	[redacted]	[redacted]
Heart rate beats/min, mean (±SD)	[redacted]	[redacted]
eGFR (mL/min/1.73m2), mean (±SD)	[redacted]	[redacted]
Median NT-proBNP (IQR), pg/mL	[redacted]	[redacted]
Sodium (mmol/L) mean (±SD)	[redacted]	[redacted]
Potassium (mmol/L) mean (±SD)	[redacted]	[redacted]
QRS duration (ms)	[redacted]	[redacted]
BMI (kg/m2), mean (±SD)	[redacted]	[redacted]
Diabetes (%), n (%)	[redacted]	[redacted]
Hypertension, n (%)	[redacted]	[redacted]
Prior ACEi use, n (%)	[redacted]	[redacted]
Prior ARB use, n (%)	[redacted]	[redacted]
Beta blocker use, n (%)	[redacted]	[redacted]
Mineralocorticoid receptor antagonist use, n (%)	[redacted]	[redacted]
Digoxin use, n (%)	[redacted]	[redacted]
Lipid lowering medication use, n (%)	[redacted]	[redacted]
Allopurinol use, n (%)	[redacted]	[redacted]
≤ 1 year since HF diagnosis, n (%)	[redacted]	[redacted]
1-5 years since HF diagnosis, n (%)	[redacted]	[redacted]
>5 years since HF diagnosis, n (%)	[redacted]	[redacted]
Ischaemic aetiology, n (%)	[redacted]	[redacted]
Prior stroke, n (%)	[redacted]	[redacted]
Prior atrial fibrillation/flutter, n (%) Paroxysmal Permanent	[redacted]	[redacted]
Prior angina, n (%) † Stable angina pectoris Prior unstable angina	[redacted]	[redacted]
Prior cancer, n (%)	[redacted]	[redacted]
Current smoker, n (%)	[redacted]	[redacted]
Prior HF hospitalisation, n (%)	[redacted]	[redacted]
EQ-5D, mean (±SD)	[redacted]	[redacted]
Abbreviations: EQ-5D EuroQol (EQ5D™); HF = heart failure; SD = standard deviation		

The ERG considers that the non-statistically significant effect of sacubitril in the Western Europe population may relate to their having lower blood pressure, less severe HF and more intensive "standard care" (as indicated by a [redacted]). As the size of the Western Europe population is 25% of the overall trial population a type II error in this analysis is less likely than in other subgroup analyses based on smaller numbers of patients. The ERG notes that regions with smaller numbers of patients did demonstrate a significant difference in the primary outcome measure in favour of sacubitril vs enalapril for example patients in North and Latin America (CS pg 68, figure 9).

4.3.2 Adverse events

The discontinuation rate due to adverse events in the PARADIGM-HF trial were similar being 10.7% in the patients taking sacubitril (n=450) and 12.2% in the patients taking enalapril (n=516).

The ERG notes the company's summary of product characteristics (SmPC) recommends caution in prescribing sacubitril for patients with NYHA class IV due to the limited clinical experience this population and that the company warn that BNP is not a good marker of HF in patients taking sacubitril because of its neprilysin substrate nature.

The SmPC also advises that patients with a history of angioedema were not studied in the PARADIGM-HF trial. As these patients are considered at generally higher risk of angioedema the SmPC recommends caution in the use of sacubitril for this group. The frequency of adverse reactions shows the rate of angioedema was reported on 0.5% of patients in the sacubitril arm of the PARADIGM-HF trial vs 0.2% in the enalapril arm. The SmPC reports a higher incidence of angioedema was observed in black patients and the rate was highest in the sacubitril arm (2.4% vs 0.5%). The ERG therefore disagrees with the statement that, "the rate of adverse reactions was similar in the two investigational drugs and the overall frequency was not related to gender, age or race" (SmPC, pg 8 (55)).

The SmPC ranks adverse drug reactions by frequency and "very common" equates to ≥1/10. There were three adverse reactions ranked very common; hyperkalaemia (11.6% in the sacubitril arm vs 14% in the enalapril arm), renal impairment (10.1% in the sacubitril arm versus 11.5% in the enalapril arm), hypotension (17.6% in the sacubitril arm vs 11.9% in the enalapril arm). The sacubitril SmPC recommends caution in its use for people with HF who have impaired, worsening renal function or renal artery stenosis.

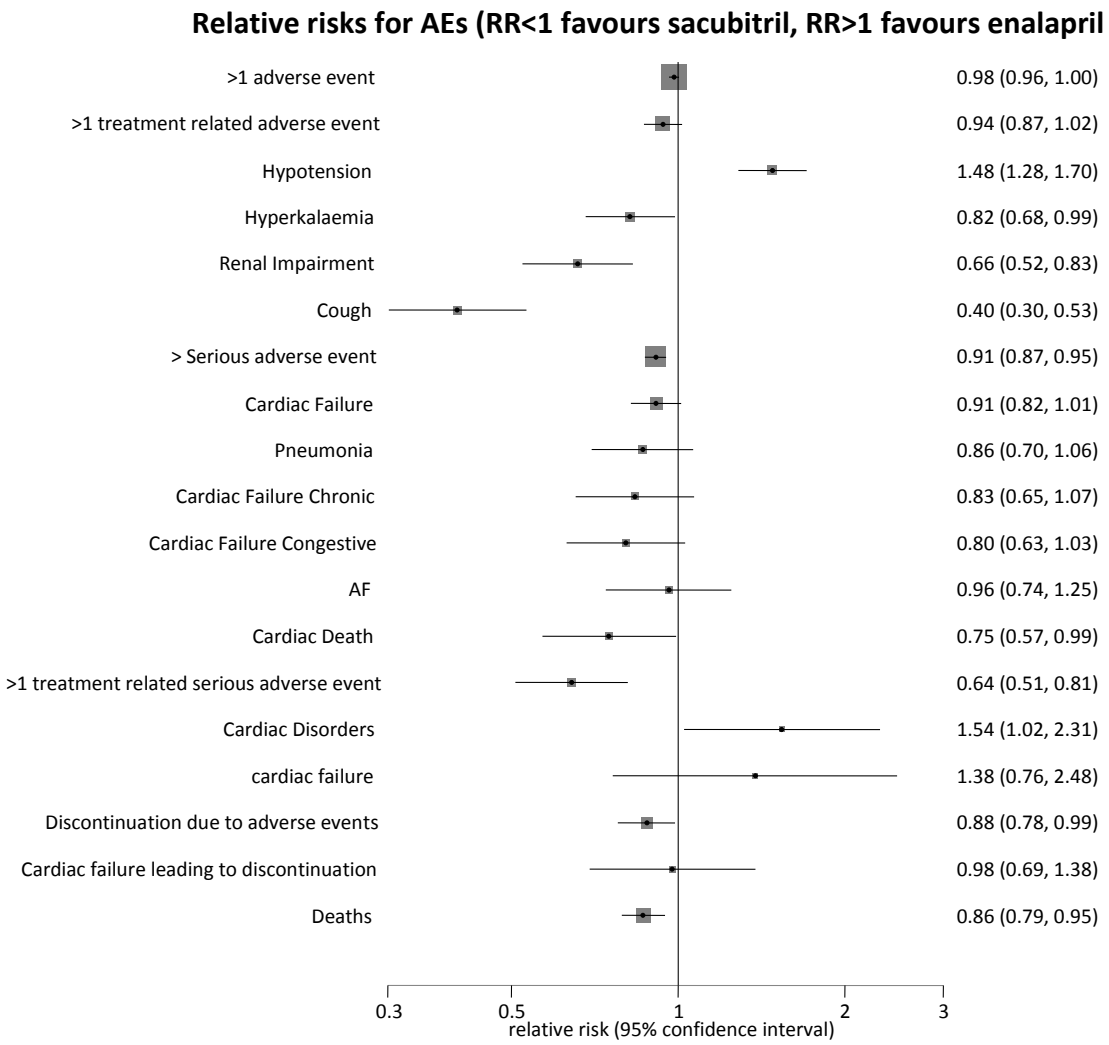
The ERG notes that sacubitril can influence the ability to drive and use machines and the company advises that occasional dizziness or fatigue may occur during these activities. The company concedes the lack of data to inform the safety of sacubitril for those who drive or use machines.

In the CS (Table 41, pg 98) the company reports that the adverse event profile was comparable between sacubitril and enalapril during the double-blind phase of PARADIGM-HF and ~22% of patients experienced a treatment related AE. The CS does not contain tests of statistical significance so the ERG produced a forest plot (Figure 3) with relative risks and 95% CIs for all the adverse events listed in Table 41 of the CS.

The ERG notes there were statistically significant differences in AEs between the two groups with regards to AEs including hypotension and cardiac disorders (from sacubitril) hyperkalaemia, renal impairment, cough, cardiac death, > 1 treatment related serious adverse event, discontinuation due to adverse events and overall deaths (from enalapril).

The ERG considers it plausible that there could be an increase in the proportion of patients who experience hypotension in a population of patients with a lower baseline BP than the trial population (e.g. the Western Europe population in PARADIGM-HF, (CS pg 68, figure 8).

Figure 3. Forest plot of AEs in the double-blind phase of PARADIGM-HF



4.3.3 Summary of clinical effectiveness

This CS provides evidence for the effectiveness of sacubitril valsartan (200mg BID) compared to enalapril (10mg BID) in patients with chronic stable HF with a HFrEF of ≤35% from a single trial. The primary composite outcome measure of CV death and HF hospitalisation demonstrated statistical significance after a trial duration of 51 months (median = 27 months) (HR 0.80, 95% CI: 0.73 to 0.87, p-value <0.001). However the ERG notes the PARADIGM-HF includes patients approximately 10 years younger than those seen in UK clinical practice and the majority of whom had previously been treated for HF and does not evaluate the effect of sacubitril in patients who are newly diagnosed with HF. The additional trial provided by the company, TITRATION, does not provide evidence of the effects of sacubitril in newly diagnosed patients as only 6.6% were treatment naïve.

The PARADIGM-HF trial includes patients who were still symptomatic despite the majority receiving ACEi/ARB, BB and AA prior to randomisation. As such, the ERG considers the trial to be assessing the effectiveness of sacubitril in patients who have failed on first-line therapy. The subgroup analysis of data from people in Western Europe suggests that the benefits of sacubitril over enalapril observed in the trial population may not be observed in clinical practice in the UK. The ERG is concerned about the small number of UK patients in the PARADIGM-HF trial (n=242) and believes the generalisability of the effect of sacubitril from the trial population to the UK population is unclear.

4.4 Conclusions of the clinical effectiveness section

- The primary objective of the PARADIGM-HF trial was to compare the effectiveness of sacubitril 200mg BID with enalapril 10mgn BID in the management of CHF. To be eligible for enrolment, patients had to have CHF (defined by LVEF below 35% or reported as reduced and NYHA class II–IV;
- The PARADIGM-HF trial also produced data to inform the analysis of treatment-related adverse events which affected ~22% of the population;
- The primary outcome of the PARADIGM-HF trial was a composite outcome of CV mortality or CV hospitalisation. Overall, the results were consistently in favour of sacubitril;
- The ERG considers the trial to be assessing the effectiveness of sacubitril in patients who have failed on first-line therapy.
- The company's inclusion of TITRATION provides limited evidence for the effectiveness of sacubitril in newly diagnosed patients as only a fraction (6.6%) of patients included in the trial were treatment naïve;
- The results of the subgroup analyses suggest that the effect of sacubitril observed in the trial population might not be observed when used in clinical practice in the UK due to differences in the baseline characteristics of the Western Europe population;
- A decision on marketing authorisation for sacubitril from the European Medicines Agency is expected in December 2015. The Committee for Medicinal Products for Human Use (CHMP) granted accelerated assessment to sacubitril and a CHMP opinion is due in October 2015.

5 COST EFFECTIVENESS

5.1 Introduction

This section provides a structured description and critique of the systematic literature review and de novo economic evaluation submitted by the company. The company provided a written submission of the economic evidence along with an electronic version of the Microsoft Excel® based economic

model. Table 14 summarises the location of the key economic information within the company's submission (CS).

Table 14. Summary of key information within the company's submission

Information	Section (CS)
Details of the systematic review of the economic literature	Section 5.1
Model structure	Section 5.2
Clinical parameters and variables	Section 5.3
Measurement and valuation of health effects and adverse events	Section 5.4
Resource identification, valuation and measurement	Section 5.5
Results	Section 5.7
Sensitivity analysis	Section 5.8
Subgroup analysis	Section 5.9
Validation	Section 5.10
Strengths and weaknesses of economic evaluation	Section 5.11
Abbreviations used in table: CS, company's submission.	

5.2 Summary of the company's key results

In their base-case analysis, the company presented deterministic and probabilistic results for the comparisons of sacubitril valsartan (hereafter referred to as sacubitril) versus ACEi (more specifically enalapril) and ARB (more specifically candesartan) for patients with heart failure with reduced ejection fraction (HFrEF), for a lifetime treatment duration. A summary of the base case incremental cost-effectiveness ratios (ICERs) presented by the company is provided in Table 15 for ease of reference. The ERG notes that the results presented are the ones reported after the clarification stage, where the ICER comparing sacubitril with enalapril decreased from £18,187 to £17,939.

Table 15. A summary of the ICERs presented by the company

Sacubitril versus >>	ACEi (enalapril)	ARB (candesartan)
Deterministic		
ICER	£17,939	£16,481
Probabilistic		
ICER	£18,818	£17,599
Probability of sacubitril being considered cost-effective at a threshold of £20,000 per QALY gained versus selected comparator	64%	60%
Abbreviations used in table: ACEi, angiotensin-converting-enzyme inhibitor; ARB, angiotensin receptor blocker; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.		

5.3 ERG comment on company's review of cost-effectiveness evidence

The company carried out a systematic review of the economic literature to identify cost-effectiveness publications relevant to the use of sacubitril for HFrEF. Details of the literature review were not reported in the main submission but in Appendix 8 of the CS, Section 8.8; page 74–83.

The following electronic databases were searched: Medline; Embase; EconLit; and NHS Economic Evaluation Database (EED) and Health Technology Assessment (HTA) within the Cochrane Library. The search was carried out in March 2014 and updated in October 2014 and May 2015. Search terms captured the conditions of interest (chronic HF / HFrEF), a range of interventions within the separate classes of drugs (ACEis, BBs, AAs, ARBs) in addition to ivabradine, aliskerin, implantable cardioverter defibrillator and cardiac resynchronization therapy and economic evaluation studies; no limits on the date of publication were applied.

In addition to database searches, bibliographies of systematic reviews articles were examined to obtain additional references. Bibliographies of accepted references were also reviewed to identify other potentially relevant references. The Cost-Effectiveness Analysis (CEA) registry, NICE HTA submissions, Pharmaceutical Benefits Advisory Committee (PBAC) submissions and Canadian Agency for Drugs and Technologies in Health (CADTH) submissions were hand searched to identify additional relevant studies. The proceedings of the following conferences were also searched; International Society for Pharmacoeconomics and Outcomes Research (ISPOR), European Society of Cardiology (ESC) Heart Failure Congress and the Heart Failure Society of America (HFSA) annual meeting. The population, intervention, comparators, outcomes and study design (PICOS) criteria of the search are reported in the CS appendix 8.11.6, page 136.

A total of 69 cost-effectiveness analyses were identified from the original search (27 studies) and from the first and second search updates (39 and 3, respectively). None of the studies analysed sacubitril, 15 studies analysed ivabradine plus standard care, nine studies evaluated eplerenone, while five studies evaluated valsartan and another five studies assessed enalapril. The remaining 32 studies assessed other treatments or combinations.

A total of 13 UK studies were identified in the review. Three of them evaluated ivabradine (including the NICE ivabradine submission).(56-58) Eplerenone was analysed in three studies(59-61), bisoprolol in two(62, 63); candesartan(64), valsartan(65), nebivolol(66) and ramipril(67) were evaluated in one study each.

The ERG considers that the search terms used by the company to identify economic evaluations are comprehensive and appropriate; moreover, the economic filters are comparable to those recommended by SIGN.(68) The inclusion and exclusion criteria applied are considered to be reasonable. Due to time constraints, the ERG was unable to replicate the company's search and

appraisal of identified abstracts for all databases. Quality assessments, based on Drummond and Jefferson (1999), were provided in the CS in the Appendices, Section 8.9.(69)

The company conducted a search of the key electronic databases, including MEDLINE, EMBASE and the Cochrane Library, for cost-effectiveness studies relevant to the decision problem and within the context of the decision problem. The ERG considers that the company is likely to have identified all cost-effectiveness evidence relevant to the decision problem that is the focus of this STA.

5.4 Overview of company's economic evaluation

5.4.1 Model structure

In this section the ERG presents the economic model developed by the company. We begin by briefly describing the model and then discuss the modelling approach and the model structure in Section 5.5.2.

The company developed a *de novo* two-state Markov model in Microsoft Excel®. The base case model assumes that patients receive lifelong treatment, either with sacubitril, enalapril or candesartan. The company reports that the model captures the most patient-relevant effects of heart failure (HF) on patients, carers and society.

The company's Markov model (presented in Figure 4) includes two health states, alive and dead. Within the alive health state patients can experience hospitalisation events, changes in their quality of life (QoL) and treatment-related adverse events (AEs). Given that these events were not captured through explicit health states in the Markov model, patients remain in the alive state until dead. In the main base case analysis patients begin the model either in the sacubitril or in the enalapril arms of the model to reflect the company's anticipated first-line positioning of sacubitril in the HFrEF pathway. A secondary base case model was also developed by the company, where patients enter the model in either the sacubitril or candesartan arms. Patients are assumed to remain in their original treatment arm for the rest of the economic analysis (this assumption was varied in scenario analysis) thus assuming a lifelong treatment effect. While in the alive health state, patients can be hospitalised, suffer a treatment-related AE (for example hypotension, cough or angioedema) and can also experience changes in their QoL due to different causes such as experiencing AEs but also improvement in overall symptoms or worsening of their chronic condition due to disease progression. At any point in the model patients can die.

In both treatment and comparator arms of the model, patients receive the standard of care therapy (and other background therapies) in addition to sacubitril or enalapril (or candesartan). Standard care was defined as beta blockers (BB) and aldosterone antagonists (AA). Additional background therapies

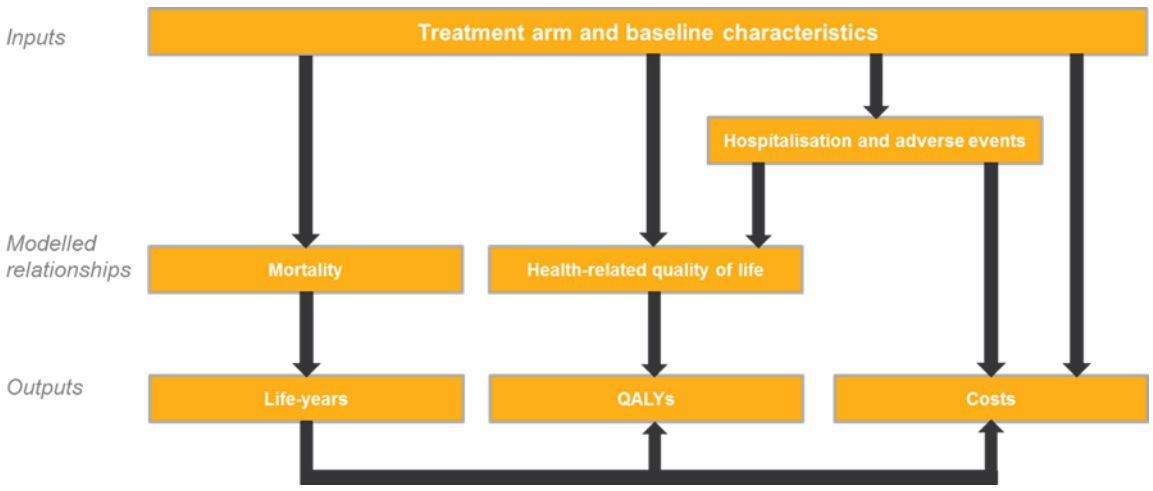
consisted of diuretics, digoxin, anticoagulants, aspirin, adenosine diphosphate antagonists and lipid lowering drugs (i.e. statins).

The company's base case analysis uses individual patient-level data from the PARADIGM-HF trial. This means that the model was run using individual patient characteristics each time, and that the model was run the same number of times as the number of patients included in the analysis (8,399). Model outcomes were obtained at the mean level by averaging across the different 8,399 patients' outcomes. The company points to the fact that this approach differs from a patient-level simulation as the model was evaluated deterministically and not stochastically. The company made the model flexible, allowing the user to run the model as a cohort Markov model using average patient characteristics of the PARADIGM-HF population as model inputs. The company states that the single cohort approach does not account for non-linearities within the model and it is therefore considered less accurate. It was also reported that model results were consistent across both approaches and therefore the cohort approach was only used for analyses in which the use of the patient-level approach was deemed impractical.

The cycle length in the economic model is 1 month (considered as 30.4 days) and a half-cycle correction was applied.

The time horizon considered in the economic model was lifetime (the model was run for 360 cycles, the equivalent to 30 years).

Figure 4. Company model schematic (CS; Figure 25, pg 123)



5.4.2 Treatment effectiveness

The CS reports that the PARADIGM-HF study was terminated early due to sacubitril's compelling efficacy (compared with enalapril) in terms of:

- Reducing mortality;
- Reducing hospitalisations;
- Reducing HFrEF symptom progression.

Treatment effectiveness within the model was implemented through transition probabilities between the alive and the dead states (i.e. mortality) and also through the probability of hospitalisation which patients experience while in the alive state. Treatment effectiveness was also included in the model through an improvement in HFrEF symptoms, which impacted on patients' QoL. The company used the hospitalisation, mortality and QoL models to predict the within-trial period in the analysis, as well as the extrapolated period.

In this section the ERG focuses on the probability of hospitalisation estimated within the different arms of the economic model. The mortality section of this report (Section 5.4.4) focuses on the company's estimation of the transition probabilities between the alive and the dead states and finally Section 5.4.5 covers the improvement in patients' symptoms, which is estimated within the QoL model.

5.4.2.1 All-cause hospitalisation model

All-cause hospitalisation observed in the PARADIGM-HF trial captured HF, other CV and non-CV related hospitalisations. The total number of hospitalisations by type of hospitalisation was reported in Packer *et al.*(70), and is presented in Table 16 below. All-cause hospitalisation in the trial incorporated serious AEs therefore these were not modelled separately. However less serious AEs were considered separately (Section 5.4.3).

Table 16. Total hospitalisation in PARADIGM-HF, by hospitalisation type

Type of hospitalisation	Sacubitril, N (%)	Enalapril, N (%)
HF diagnosis	851 (23.88%)	1079 (26.62%)
Other CV diagnosis	1365 (38.30%)	1458 (35.97%)
Non-CV diagnosis	1348 (37.82%)	1516 (37.40%)
All cause (total)	3564	4053
Abbreviations in table: CV, cardiovascular; HF, heart failure.		

The company's base case analysis modelled the likelihood of a patient experiencing a hospitalisation event using a negative binomial regression model. Predicted all-cause hospitalisation rates were determined by the treatment received by the patient (sacubitril or enalapril) and patients' baseline characteristics, taken from the PARADIGM-HF trial. The company explained that the negative binomial model was the pre-specified model used in the primary analysis of the PARADIGM-HF trial for hospitalisation counts, and was therefore preferred over alternative approaches such as a Poisson regression. The hospitalisation model was run using the FAS population of the PARADIGM-HF trial and the model outputs consist on annual hospitalisation rates. These were used to model the number of hospitalisations occurring in the initial period of the economic analysis but also permitted extrapolation beyond the end of the PARADIGM-HF trial.

Baseline characteristics from the PARADIGM-HF trial population were included as covariates in the hospitalisation regression model. The company justifies this approach in the all-cause mortality section of the submission (CS, Section 5.3). The company explains that the inclusion of covariates in the models was used to enable patient-level heterogeneity to be captured and also to include variables which inform subgroup analysis. There was no justification provided specifically to the hospitalisation (or QoL) model, however the ERG assumes that the reasons behind this approach are the same across the three models.

The company reports that candidate covariates to be included in the models were selected from the subgroups listed *a priori* in the statistical analysis plan for the PARADIGM-HF trial. Additionally, other prognostic factors included in the ivabradine submission to NICE and variables suggested by the company's clinical experts were also included as candidate covariates.(57) These are reported in Table 17.

The company reports that continuous variables were centred on their mean values and that the functional form and potential presence of non-linearities of continuous variables was explored by visual inspection of Martingale residuals. It is stated that NT-proBNP, eGFR and age exhibited non-linear trends thus the natural logarithm of NT-proBNP and eGFR were taken, and a quadratic transformation of age (age^2) was included in addition to the non-transformed variable. The company claims that these transformations were selected based on a ladder of powers approach which seeks transformations that convert a variable into a normally distributed variable.

Table 17. Candidate covariates (reproduced from CS, pg 131, Table 53)

Candidate covariates based on pre-specified subgroups in PARADIGM-HF	**Candidate covariates based on the ivabradine submission to NICE** (57) **& suggestions by clinical experts**
• Age • Gender: male, female • Race: Caucasian, Black, Asian, Other • Region: North America, Latin America, Western Europe, Central Europe, Asia/Pacific and other • NYHA Class: I/II, III/IV† • eGFR • Diabetic: yes, no • SBP • LVEF • AF based on ECG at Visit 5: yes, no • NT-proBNP • Hypertension: yes, no • Prior use of ACEi: yes, no • Prior use of ARB: yes, no • Use of AA: yes, no • Time since diagnosis of HF: ≤1 year, 1–5 years, >5 years • Prior HF hospitalisation: yes, no	• Digitalis use: yes, no • Lipid medications: yes, no • Heart rate, bpm • BB use: yes, no • Prior stroke: yes, no • Sodium • Potassium • Allopurinol: yes, no • Current smoker: yes, no • Ischaemic aetiology: yes, no • Baseline EQ-5D • QRS on ECG duration • Bundle branch block: yes, no • Prior cancer: yes, no • Prior angina: yes, no • BMI
Abbreviations: AA, aldosterone antagonist; ACEi, angiotensin converting enzyme inhibitor; AF, atrial fibrillation; ARB, Angiotensin II receptor blocker; BB, beta blocker; BMI, body mass index; bpm, beats per minute; ECG; electrocardiogram; eGFR, estimated glomerular filtration rate; HF, heart failure; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association; SBP, systolic blood pressure † Please note that the full four category version of this variable was retained for the EQ-5D analysis.	

The company explained that the covariate selection process used in the hospitalisation model was the same as the one used in the mortality model. However it is not mentioned if interaction between subgroups was tested. The covariate selection process used was a stepwise procedure which the company explained as the following:

- An initial set of covariates was identified using backwards stepwise elimination (using a p-value of <0.1);
- This was validated using forwards stepwise selection (using a p-value of <0.1);
- The interim statistical model was reviewed by the company's' clinical experts. In addition to suggesting alternative parameters for inclusion, the company's clinical experts recommended that potassium was removed from the predictive model due to unexpected directional effects.

The final predictive model for all-cause hospitalisations is presented in Table 18. The company reported that based on common explanatory variables, the hospitalisation model was consistent with the results presented in TA267.(57) No concordance measures were reported. The predicted rate ratio

for sacubitril was 0.84 (95% CI: 0.78 to 0.91; p<0.0001). The rate of hospitalisation was assumed constant over time which means that in the economic model, hospitalisation is not related with disease progression over time.

Table 18. Negative binomial regression for all-cause hospitalisation (reproduced from CS, pg 135, Table 55)

Mortality	IRR	Coef.	SE	z	P>z	95% CI	
Sacubitril valsartan	0.84	-0.173	0.038	-4.550	0.000	-0.247	-0.098
Age†	0.95	-0.054	0.013	-4.080	0.000	-0.081	-0.028
Age^2*	1.00	0.000	0.000	4.290	0.000	0.000	0.001
Female	0.74	-0.297	0.049	-6.020	0.000	-0.393	-0.200
Region							
Latin America	0.70	-0.362	0.084	-4.300	0.000	-0.528	-0.197
Western Europe	1.02	0.017	0.074	0.230	0.820	-0.128	0.162
Central Europe	0.73	-0.322	0.075	-4.260	0.000	-0.470	-0.174
Asia-Pacific	0.71	-0.350	0.085	-4.120	0.000	-0.516	-0.183
Heart rate†	1.01	0.007	0.002	4.290	0.000	0.004	0.010
Log (eGFR)†	0.62	-0.477	0.072	-6.600	0.000	-0.618	-0.335
Log (NT-proBNP)†	1.26	0.228	0.020	11.250	0.000	0.188	0.268
Sodium†	0.98	-0.021	0.007	-3.210	0.001	-0.034	-0.008
QRS duration†	1.00	0.003	0.001	5.330	0.000	0.002	0.004
Diabetes	1.40	0.333	0.040	8.250	0.000	0.254	0.412
Prior ACEi use	0.90	-0.104	0.047	-2.230	0.026	-0.196	-0.013
BB use	0.72	-0.328	0.073	-4.520	0.000	-0.470	-0.185
Lipid lowering medication use	1.08	0.073	0.043	1.690	0.091	-0.012	0.157
Time since HF diagnosis							
1-5 years	1.30	0.265	0.049	5.390	0.000	0.168	0.361
>5 years	1.49	0.402	0.052	7.720	0.000	0.300	0.503
Ischaemic disease	1.09	0.085	0.044	1.920	0.054	-0.002	0.172
Prior stroke	1.16	0.147	0.065	2.270	0.023	0.020	0.275
AF	1.10	0.095	0.042	2.280	0.023	0.013	0.176
Prior cancer	1.18	0.164	0.088	1.870	0.061	-0.008	0.336
Current smoker	1.23	0.209	0.054	3.880	0.000	0.103	0.314
Prior HF hosp.	1.40	0.334	0.041	8.230	0.000	0.254	0.413
Baseline EQ-5D†	0.62	-0.487	0.089	-5.440	0.000	-0.662	-0.311
Constant	-	-2.844	0.473	-6.010	0.000	-3.772	-1.917

†Variable centred on mean
* Age exhibited a non-linear effect, and therefore a quadratic transformation was included.
Abbreviations: ACEi, angiotensin converting enzyme inhibitor; AF, atrial fibrillation; BB, beta blocker; Coef, coefficient; CI, confidence interval; eGFR, estimated glomerular filtration rate; HF, heart failure; hosp., hospitalisation; IRR, incidence rate ratio; NT-proBNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association; SE, standard error.

5.4.2.2 Secondary base case analysis

A secondary base case analysis was undertaken by the company with the aim to evaluate the effectiveness of sacubitril compared with ARBs (both in combination with standard care). This

analysis was meant to reflect patients who are intolerant to ACEi and therefore receive ARB therapy. As there is a lack of evidence comparing sacubitril with ARBs, the company used the results from the NMA analysis, presented in Section 4. The outcomes analysed in the NMA were all cause-hospitalisation, all-cause mortality and CV mortality.

In the secondary base case analysis, the all-cause mortality and all-cause hospitalisation models used the NMA results to estimate the effectiveness of sacubitril compared with candesartan. In the QoL model, the company assumed that enalapril and candesartan have an equal impact on patients QoL with regards to hospitalisation and mortality and that candesartan is equivalent to sacubitril with regards to AE rates.

For the all-cause hospitalisation model the company applied a HR of [redacted] for ARB versus ACEi, which can be interpreted as candesartan being [redacted] more effective than enalapril in preventing hospitalisations. This HR was applied to the sacubitril coefficient in the hospitalisation regression model to estimate the relative effectiveness of candesartan compared with sacubitril in preventing hospitalisations.

5.4.3 Adverse events

The company assumed that the all-cause hospitalisation model included all the relevant serious AEs. Therefore the costs and impact on patients' QoL of serious AEs were assumed to be captured through the all-cause hospitalisation model (reported in Section 5.4.2). With regards to less serious AEs, the company decided to model these independently from hospitalisation. We present these in this section.

The company reports that the AEs included were the pre-specified safety events for the PARADIGM-HF trial. These consisted on hypotension, elevated serum creatinine, elevated serum potassium, cough and angioedema which were the events likely to be associated with ACEi, ARB or neprilysin inhibitor (sacubitril) treatment.

AEs were based on the FAS population as opposed to the safety analysis set (SAF). During clarification, the ERG asked the company why the FAS population had been used when the PARADIGM-HF trial protocol specified that safety analysis was to be performed based on the safety population. The company explained that the FAS population was used in order to, "ensure consistency with the modelling of clinical and QoL outcomes…which were also based on the FAS population". Furthermore, the ERG asked the company to report the main differences in AEs across the FAS and the SAF as the FAS analysis had not been reported in the CSR of the PARADIGM-HF trial. The company provided additional details on the FAS analysis for AEs and stated that, "there are no substantial differences between the percentage of AEs in the FAS and SAF populations".

The company modelled AEs by assuming a constant probability of a specific event occurring each cycle. The probability of AEs occurring was calculated by using the total number of patients experiencing each specific event and total exposure time for each treatment arm. Annual rates were converted to monthly probabilities using the actuarial formula. Monthly probabilities used in the model are reported in Table 19.

All AE were estimated as "one-off" events each cycle, with the exception of hypotension and cough, which were assumed to last for 64.9 days and 73.3 days, respectively. This impacted the estimation of AE-related QoL, which is explored in Section 5.5.8. To note is that the company estimated the costs associated with the occurrence of all the events presented in Table 19, however, only hypotension and cough were considered for the estimation of impact on patients' QoL (Section 5.5.8 and Section 5.5.9). In the secondary base case analysis, where candesartan was compared with sacubitril, the same rates of AEs were considered in both treatment arms.

Table 19. Monthly probability of AEs based on FAS, double-blind period (reproduced from CS, pg 136, Table 56)

Event	Sacubitril valsartan (n=4187)			Enalapril (n=4212)		
	Number†	Mean annual rate	Mean monthly probability	Number†	Mean annual rate	Mean monthly probability
Hypotension	588	0.06	0.52%	388	0.04	0.35%
Elevated serum creatinine	139	0.02	0.12%	188	0.02	0.17%
Elevated serum potassium	674	0.07	0.61%	727	0.08	0.66%
Cough	474	0.05	0.42%	601	0.07	0.54%
Angioedema	19	0.00	0.02%	10	0.00	0.01%

†Absolute number of each adverse event, taken from McMurray *et al*.(2)
Abbreviations: ACEi, angiotensin-converting enzyme inhibitor.

5.4.3.1 AEs leading to permanent treatment discontinuation

The occurrence of AEs leading to treatment discontinuation was not reported in the CS. The ERG reports AEs leading to discontinuation in Table 20 and Table 21 for the run-in and double-blind period, respectively. The ERG estimated the average monthly probability of AEs leading to discontinuation occurring in both phases. To note is that this estimation was based on the SAF analysis as the occurrence of AEs during the run-in period was not provided for the FAS population. It can be noted that the monthly probability of events is consistently low across treatment arms and trial periods. However, the probability of events occurring during the run-in period was much higher than the probability of events occurring during the double-blind period. For example, the monthly probability of hypotension events occurring in the sacubitril arm during the run-in period is more than

[redacted] higher than the probability of these events occurring during the double-blind period. This issue is further discussed in Section 5.5.3.

Table 20. AEs leading to discontinuation, based on SAF, run-in period (mean follow-up 31 days for sacubitril and 19 days for enalapril)

Event	Sacubitril valsartan (n=9419)		Enalapril (n=10513)	
	Number†	Mean monthly probability	Number†	Mean monthly probability
Hypotension	[redacted]	[redacted]	[redacted]	[redacted]
Cough	[redacted]	[redacted]	[redacted]	[redacted]
Angioedema	[redacted]	[redacted]	[redacted]	[redacted]

†Absolute number of each adverse event, taken from PARADIGM-HF CSR, Table 14.3.1-1.13.a
Mean follow-up [redacted] days for sacubitril valsartan and [redacted] days for enalapril

Table 21. AEs leading to discontinuation, based on SAS, double-blind period (mean follow-up 27 months)

Event	Sacubitril valsartan (n=4203)		Enalapril (n=4229)	
	Number†	Mean monthly probability	Number†	Mean monthly probability
Hypotension	[redacted]	[redacted]	[redacted]	[redacted]
Cough	[redacted]	[redacted]	[redacted]	[redacted]
Angioedema	[redacted]	[redacted]	[redacted]	[redacted]

†Absolute number of each adverse event, taken from PARADIGM-HF CSR, Table 14.3.1-1.13
Mean follow-up: [redacted] months

5.4.4 Mortality

In this section the ERG focuses on the company's estimation of the transition probabilities between the alive and the dead states. Mortality data captured in the PARADIGM-HF trial looked at all-cause mortality, CV mortality and non-CV mortality. The company decided to use the all-cause mortality data from the trial to develop an all-cause mortality model for the economic analysis. The company report that as sacubitril was not associated with a significant difference in non-CV mortality compared with enalapril an alternative analysis was run where CV mortality from the PARADIGM-HF trial was used in combination with non-CV mortality taken from UK life tables (described in Section 5.4.4.1). However the company reported that this approach was less conservative as it generated more optimistic survival curves and lower ICERs. The strengths and limitations of these alternative modelling approaches were reported by the company and are presented in Table 22.

Table 22.Strengths and limitations of mortality approaches (reproduced from CS, pg 128, Table 51)

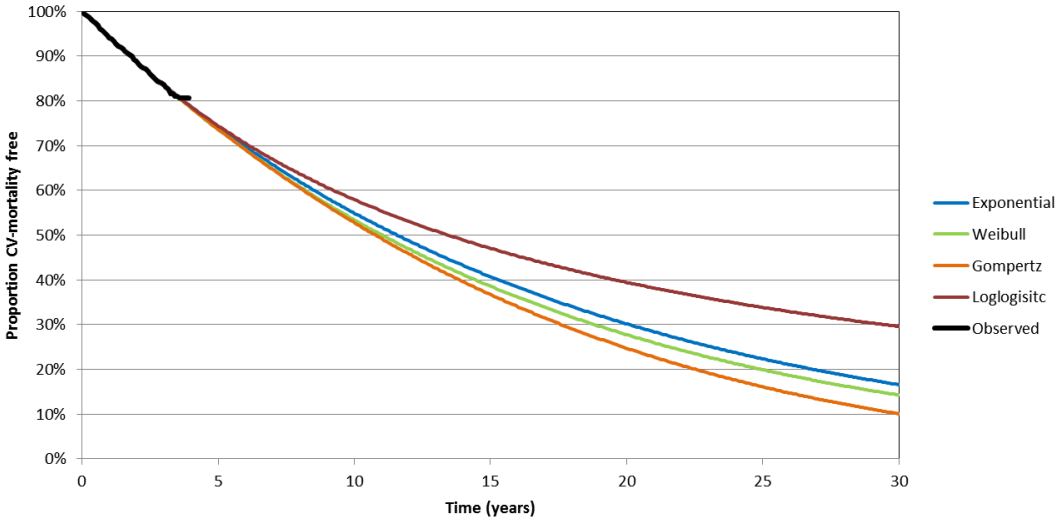
	Strengths	Limitation

Base case analysis – All-cause mortality	• Clear application of data from the PARADIGM-HF trial in the cost-effectiveness model • Fewer data sources required to model mortality • Non-CV mortality is sourced from a HFrEF population	• Exclusion of patients from trial with presence of other disease with life expectancy < 5 years may lead to lower rates of non-CV mortality • Rates of non-CV mortality are not statistically significantly different between sacubitril valsartan and ACEi enalapril • All-cause mortality is a secondary endpoint of the trial
Alternative mortality analysis – CV mortality	• CV mortality is the key driver of mortality benefit in the PARADIGM-HF trial's patient population • CV mortality is a component of the composite primary endpoint • This approach aligns with the approach taken in TA267 • Life-tables will reflect local non-CV mortality rates	• Introducing uncertainty in model by combining RCT data and life tables • No reliable estimates of non-CV mortality are available in HF patients, which is likely to underestimate mortality
Abbreviations: CV, cardiovascular; RCT, randomised controlled trial		

The company conducted survival analysis in order to estimate the mortality benefits associated with sacubitril in the model. The proportional hazard (PH) assumption was tested through visual inspection of log cumulative hazard plots, which the company considered to present parallel lines. The company also reported the cumulative hazard and stated that analysis of this resulted in the confirmation of linear trends thus the risk of all-cause mortality appeared to be relatively constant over the observed study period. The log-cumulative and cumulative hazard plots can be found in the CS, page 129.

A Gompertz distribution was used to fit the PARADIGM-HF trial's mortality data. Other parametric distributions were assessed for their goodness of fit. The company looked at the exponential, Weibull, generalised gamma, log-logistic and lognormal distributions, additionally to the Gompertz. The Akaike Information Criteria (AIC) and Bayesian Information Criterion (BIC) were used to assess the best model fit. Upon inspection of the AIC and the BIC the company considered that these were insufficient to draw a conclusion on the best distribution to use as the values were similar, with the exception of the lognormal which was deemed to perform worse than other distributions. Therefore external validation of the different fitted survival curves was undertaken by company's clinical experts. The curves reported by the company are reproduced in Figure 5 and Figure 6. To note is that the curves seem to model the proportion of patients free of CV-mortality. The company selected the Gompertz distribution as it was considered that this model provided the shortest survival times and the most conservative estimate of the mortality benefit.

Figure 5.Company's extrapolated curves, sacubitril (CS, Appendix 8.14)



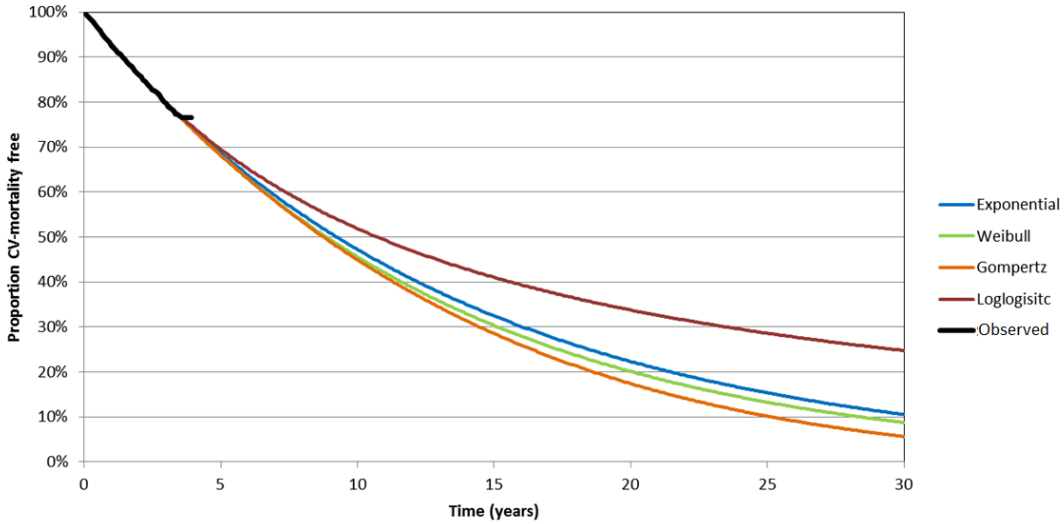


Figure 6. Company's extrapolated curves, sacubitril (CS, Appendix 8.14)

Predicted all-cause mortality was determined by the treatment received by the patient (sacubitril or enalapril) and patients' baseline characteristics, taken from the PARADIGM-HF trial. The mortality model was run using the FAS population of the PARADIGM-HF trial and the model outputs provided daily hazard rates. These were used to model the probability of patients dying in the initial period of the economic analysis but also permitted extrapolation beyond the end of the PARADIGM-HF trial.

Baseline variables considered for selection included the ones listed for the hospitalisation model (Section 5.4.2). Clinical experts advising the company noted that background medications frequently

act as markers of disease severity and it was considered that inclusion of these variables would produce non-intuitive estimates of mortality effects. The company recognised this as a limitation of the approach adopted, but explained that it was retained on the basis that it would improve predictive performance of the model. The company reported that tests of interaction between subgroups suggested no difference in treatment effect between subgroups for the primary end point and death from CV causes from the PARADIGM-HF trial. Final selection of covariates used in the model was based on the same stepwise process described for all-cause hospitalisation (Section 5.4.2)

The predictive model for all-cause mortality is presented in Table 23. The predicted HR for sacubitril is 0.85 (95% CI: 0.77 to 0.94; p=0.002). To note is that unlike the predicted rate of hospitalisation, which was constant over time, the mortality hazard varies each cycle as the mortality model is based on survival analysis, while the hospitalisation model is based on a multivariable regression analysis. Even though time was not included as a covariate in the base case model, the company reports that the effect of time on mortality was assessed by including a time-varying sacubitril covariate (including a time and sacubitril interaction term) in the model. The company states that there was no evidence found supporting that the treatment effect for sacubitril varies over time. The company reports a HR for interaction of 1.00 with a p-value of 0.989 however the model including the time-varying covariate was not provided by the company.

The final model of all-cause mortality exhibited a concordance measure of 68% (95% CI: 67% to 70%). The company reported this was in line with the results presented in TA267.(57)

Table 23.Gompertz regression model for all-cause mortality (reproduced from CS, pg 135, Table 55)

Mortality	HR	Coef.	SE	z	P>z	95% CI	
Sacubitril valsartan	0.851	-0.161	0.051	-3.15	0.002	-0.261	-0.061
Age†	0.903	-0.102	0.016	-6.30	0.000	-0.134	-0.070
Age^2*	1.001	0.001	0.000	6.86	0.000	0.001	0.001
Female	0.681	-0.384	0.069	-5.52	0.000	-0.520	-0.247
Region							
Latin America	1.719	0.542	0.127	4.28	0.000	0.294	0.790
Western Europe	1.139	0.130	0.112	1.17	0.243	-0.088	0.349
Central Europe	1.439	0.364	0.114	3.18	0.001	0.140	0.588
Asia-Pacific	0.820	-0.199	0.298	-0.67	0.505	-0.784	0.386
Race							
Black	1.343	0.295	0.130	2.27	0.023	0.040	0.550
Asian	2.045	0.715	0.283	2.52	0.012	0.160	1.271
Other	1.091	0.087	0.110	0.79	0.430	-0.129	0.302
NYHA III/IV	1.239	0.214	0.061	3.52	0.000	0.095	0.334
Ejection fraction†	0.987	-0.014	0.004	-3.25	0.001	-0.022	-0.005
Heart rate†	1.006	0.006	0.002	2.62	0.009	0.001	0.010

Mortality	HR	Coef.	SE	z	P>z	95% CI	
(log) eGFR†	0.796	-0.228	0.095	-2.39	0.017	-0.415	-0.041
(log) NT-proBNP†	1.478	0.391	0.027	14.34	0.000	0.337	0.444
Sodium†	0.969	-0.031	0.009	-3.50	0.000	-0.049	-0.014
QRS duration	1.002	0.002	0.001	3.07	0.002	0.001	0.003
Diabetes	1.230	0.207	0.054	3.83	0.000	0.101	0.313
BB use	0.749	-0.289	0.088	-3.28	0.001	-0.461	-0.116
Time since diagnosis of HF							
1-5 years	1.227	0.204	0.067	3.03	0.002	0.072	0.336
> 5 years	1.338	0.291	0.072	4.02	0.000	0.149	0.434
Ischaemic disease	1.171	0.158	0.057	2.80	0.005	0.047	0.269
Prior stroke	1.182	0.168	0.083	2.03	0.043	0.005	0.330
Prior HF hosp.	1.165	0.153	0.055	2.76	0.006	0.044	0.261
Baseline EQ-5D	0.587	-0.532	0.115	-4.61	0.000	-0.758	-0.306
Constant	-	-12.840	0.579	-22.17	0.000	-13.976	-11.705
Gamma	-	0.000	0.000	4.57	0.000	0.000	0.001

†Variable centred on mean
* Age exhibited a non-linear effect, and therefore a quadratic transformation was included.
Abbreviations: BB, beta blocker; CI, confidence interval; coef, coefficient; eGFR, estimated glomerular filtration rate; HF, heart failure; hosp., hospitalisation; HR, hazard ratio; NT-proBNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association; SE, standard error.

5.4.4.1 CV mortality – alternative mortality analysis

The company reports that in the PARADIGM-HF trial sacubitril was not associated with a significant difference in non-CV mortality compared with enalapril thus an alternative analysis was run where CV mortality death from the trial was used in combination with non-CV mortality taken from UK life tables.

It is stated in the CS that extrapolation, distribution and covariate selection for the CV mortality model followed the same approach as for all-cause mortality. A Gompertz model was also selected to estimate CV mortality. The predictive model for CV mortality is presented in Table 24. The predicted HR for sacubitril is 0.81 (95% CI: 0.72 to 0.90; p<0.001).

The final model of CV mortality exhibited a concordance measure of 70% (95% CI: 68% to 71%). The company reported this was in line with the results presented in TA267.(57)

Table 24.Gompertz regression model for CV mortality (reproduced from CS Appendix, pg 154, Table 129)

Mortality	HR	Coef.	SE	z	P>z	95% CI	
Sacubitril valsartan	0.81	-0.216	0.0570	-3.79	0.000	-0.328	-0.104
Age†	0.91	-0.092	0.0180	-5.13	0.000	-0.128	-0.057
Age^2	1.00	0.001	0.0001	5.35	0.000	0.000	0.001
Female	0.70	-0.357	0.0766	-4.67	0.000	-0.508	-0.207
Region							

Mortality	HR	Coef.	SE	z	P>z	95% CI	
Latin America	1.87	0.625	0.1455	4.3	0.000	0.340	0.910
Western Europe	1.18	0.168	0.1307	1.28	0.200	-0.089	0.424
Central Europe	1.70	0.529	0.1319	4.01	0.000	0.270	0.787
Asia-Pacific	0.83	-0.187	0.3172	-0.59	0.556	-0.809	0.435
Race							
Black	1.50	0.409	0.1440	2.84	0.005	0.126	0.691
Asian	2.62	0.962	0.2989	3.22	0.001	0.377	1.548
Other	1.18	0.168	0.1226	1.37	0.169	-0.072	0.409
NYHA III/IV	1.34	0.296	0.0669	4.42	0.000	0.165	0.427
Ejection fraction†	0.98	-0.017	0.0046	-3.6	0.000	-0.026	-0.008
(log) eGFR†	0.79	-0.238	0.1054	-2.26	0.024	-0.444	-0.031
(log) NT-proBNP†	1.56	0.443	0.0299	14.84	0.000	0.385	0.502
Sodium†	0.97	-0.027	0.0099	-2.69	0.007	-0.046	-0.007
QRS duration	1.00	0.002	0.0007	3.04	0.002	0.001	0.003
Diabetes	1.26	0.229	0.0599	3.82	0.000	0.111	0.346
BB use	0.73	-0.320	0.0964	-3.32	0.001	-0.509	-0.131
Time since diagnosis of HF							
1-5 years	1.23	0.210	0.0748	2.8	0.005	0.063	0.356
> 5 years	1.41	0.344	0.0805	4.28	0.000	0.186	0.502
Ischaemic disease	1.17	0.156	0.0626	2.48	0.013	0.033	0.278
Prior HF hosp.	1.17	0.159	0.0617	2.57	0.010	0.038	0.280
Baseline EQ-5D	0.57	-0.563	0.1275	-4.42	0.000	-0.813	-0.313
_cons	0.00	-12.665	0.6477	-19.55	0.000	-13.934	-11.395
/gamma	1.00	0.000	0.0001	2.56	0.010	0.000	0.000

†Variable centred on mean
Abbreviations: BB, beta blocker; CI, confidence interval; Coef., coefficient; CV, cardiovascular; eGFR, estimated glomerular filtration rate; HF, heart failure; hosp., hospitalisation; HR, hazard ratio; NT-proBNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association; SE, standard error

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5.4.4.2 Secondary base case analysis

In the secondary base case analysis, the all-cause mortality and all-cause hospitalisation models used the NMA results to estimate the effectiveness of sacubitril compared with candesartan. For the all-cause mortality model the company applied a HR of 1.05 for ARB versus ACEi, which can be interpreted as enalapril being 5% more effective than candesartan in preventing all-cause mortality. This HR was applied to the sacubitril coefficient in the mortality survival model to estimate the relative effectiveness of candesartan compared with sacubitril in preventing all-cause deaths.

For the CV mortality model the company applied a HR of 1.03 for ARB versus ACEi, which can be interpreted as enalapril being 3% more effective than candesartan in preventing CV mortality. This HR was applied to the sacubitril coefficient in the mortality model to estimate the relative effectiveness of candesartan compared with sacubitril in preventing CV deaths.

5.4.5 Health-related quality of life

This section outlines the systematic review carried out by the company to identify health-related quality of life (QoL) data. It also describes how QoL is included and evaluated in the economic analysis; the data sources identified and used and finally the methods used to translate patients' QoL into quality-adjusted life years (QALYs) in the economic model.

The main source of evidence for the estimation of QoL within the economic model is the EQ-5D data collected in the PARADIGM-HF trial. QoL was modelled by applying utility scores derived from fitting a linear mixed-effects model on patient-level EQ-5D trial data (Section 5.4.5.2). The methods used to estimate QALY gain in the economic model are reported from Section 5.4.5.2 onwards. The ERG critiques the submitted evidence in Section 5.5.8.

5.4.5.1 Systematic literature review for health-related QoL

A systematic literature review to identify evidence sources for health-related QoL relevant to the decision problem was performed by the company. The main focus of the search was to identify studies reporting EQ-5D health state utility values relating to patients with chronic HF.

As reported in Section 5.4.4 of the CS, the following databases were searched using OVID:

- MEDLINE® and Ovid MEDLINE In-Process & Other Non-Indexed Citations, 1946 to present;
- EMBASE, 1980 to present;
- Econlit, 1969 to present;
- Cochrane library, from inception to present, searching the following databases:
    - EBM (evidence-based medicine) Reviews – Cochrane Central Register of Controlled Trials;
    - EBM Reviews – Health Technology Assessment;
    - EBM Reviews – Cochrane Database of Systematic Reviews;
    - EBM Reviews – Database of Abstracts of Reviews of Effects;
    - EBM Reviews – NHS Economic Evaluation Database.

Additionally electronic searches were supplemented by hand searching the following sources: primary sources of utilities used in economic evaluations; company databases; Research Papers in Economics

(RePEc); the EQ-5D website, the CEA (Cost-Effectiveness Analysis) Registry; proceedings from the ISPOR (International Society for Pharmacoeconomics and Outcomes Research), ESC (European Society of Cardiology) Heart Failure, HFSA (Heart Failure Society of America) conferences and meetings; NICE technology appraisals; and SMC (Scottish Medical Consortium) advice.

The details of the literature review were not reported in the main submission but in Appendix 10, Section 8.10 of the CS; the searches performed on the electronic databases were detailed in Section 8.10.4 of the appendix. The search was performed on the 21st of November 2014, and updated on the 11th of May 2015. The PICOS criteria of the search are reported in Table 25.

Table 25. PICOS criteria for the health-related quality of life search (CS Appendix 10; Section 8.10.3)

Criteria	Description
Population	Adult patients with chronic HF, regardless of age, gender, and race
Interventions	Not restricted by any particular intervention
Comparators	Not restricted by any particular comparator
Outcomes	• Euro-QoL (EQ-5D), HUI2, HUI3, AQoL, AQoL 2, SF-6D, 15D, QWB • Directly-elicited utility scores (TTO, SG) • Mapping algorithms from disease specific to generic HSUV instruments, e.g. the EQ-5D. • A HRQoL outcome was prioritised according to NICE preferences: according to NICE guidance, the preferred HRQoL outcome is EQ-5D, weighted with UK general population preference weights. This was considered the gold standard of evidence throughout the review. The identified utilities was extracted in a staged approach, with initial quality assessment of articles reporting HSUVs, and thereafter full data extraction for those articles providing the most relevant utility estimates.
Study design	The type of study design was not limited. As it was expected that health state utility values will be reported in RCTs, observational studies as well as other cost-effectiveness evaluations such as HTAs and economic evaluations. Any such study reporting relevant, non-treatment-specific HRQoL data was included.
Restrictions	Studies of patient populations from the OECD countries were included in the first instance. If there were more than 25 includable full text publications and 20 conference abstracts across all these countries narrower selection criteria to identify the most relevant citations based on EQ-5D with UK general population preference weights, and chronic HF disease severity were applied.
Publication date	Not limited by date.
Languages	Non-English publications (if any) were excluded. English abstracts of foreign publications (if any) were included.
Exclusion criteria	
Population	Patients without chronic HF or mixed populations in which utility values for chronic HF patients are not reported separately.
Other	Studies reporting only non-HSUV outcomes (e.g., clinical, economic evaluations, costs) will not be included in this review.

Abbreviations in table: AQol, Assessment of Qualify of Life; EQ-5D, European Quality of Life 5 Dimensions; HF, heart failure; HRQoL, health-related quality of life; HSUV, health-state utility value; HTA, health technology assessment; HUI, Health Utilities Index; NICE, National Institute for Health and Care Excellence; OECD, Organisation for Economic Co-operation and Development; PICOS, Population, Interventions, Comparators, Outcomes and Study design; QWB, Quality of Well-Being; RCT, randomized clinical trial; SF-6D, Short Form 6-Dimensions; SG, standard gamble; TTO, time-trade-off; UK, United Kingdom.

A total of 47 publications were included, of which only one was identified in the updated search. Among these, 19 studies (18 full publications and 1 abstract) met the NICE reference case while 28 studies (22 full publications, 4 abstracts and 2 posters) did not. The identified studies were assessed by a single analyst to ascertain they met the pre-defined inclusion and exclusion criteria. The included studies were data extracted and are summarised in Table 26. The systematic review found that most studies summarised utility scores by NYHA class, which was not considered in the economic evaluation.

The ERG finds that the search strategy was appropriate and identified relevant sources of data. These however were not used in the economic model or in the company's scenario analyses.

Table 26. Studies identified in the search for health-related quality of life (CS Appendix 10; Table 123)

Study and Country	Population detail (patients, age (mean±SD), NYHA class, EF)	Intervention (s) and sample size(N)	Elicitation technique	Valuation	Health states	Utility score, Mean (SD) (SE) (95% CI)
Austin 2008(9) UK	• HF patients recruited from hospital outpatient clinic, medical wards and general practice in the UK • Age >60 years • NYHA class II-III • LVEF <40%	SC, N=55 vs Cardiac rehabilitation, N=57	EQ-5D completed by patients	NR†	HF patients: Baseline (SC)	0.66 (0.23) (NR) (NR)
					HF patients: Post-treatment 5 years (SC)	0.60 (0.34) (NR) (NR)
					HF patients: Baseline (cardiac rehabilitation)	0.69 (0.23) (NR) (NR)
					HF patients: Post-treatment 5 years (cardiac rehabilitation)	0.61 (0.32) (NR) (NR)
Calvert 2005(71) Multicentre	• HF patients from multicentre RCT CARE-HF in comparison with representative sample of UK population • Age 65.3±10 years • NYHA III-IV • LVEF ≤35%‡	NR¶¶, N=813 (CARE-HF), N=NR (UK general population)	EQ-5D completed by patients	UK general population values, method of valuation, TTO	HF patients: UK general population	0.86 (NR) (NR) (0.85 - 0.87)
					HF Patients: CARE-HF population	0.60 (NR) (NR) (0.58 - 0.62)
Clarke 2014(72) UK	• HF patient data from BTDB in the UK • Age 44 years (42.7 – 45.3)‡‡ • NYHA I-IV • EF NR	MM, N=307 vs LVAD, N=235	EQ-5D data determined using NYHA scores from BTDB	NR†	HF patients: MM (patients on inotropes), survival-12 months 29%	0.55 (NR) (0.023) (NR)
					HF patients: Post-LVAD, survival-12 months 71%	0.74 (NR) (0.075) (NR)
					HF patients: Post-HT, survival-24 months 75%	0.83 (NR) (0.005) (NR)
Cleland 2009(73)c Multicentre	• HF patients from multicentre RCT CARE-HF • Age 65 years • NYHA III-IV • LVEF ≤35%	MT alone vs CRT, N=404 (all patients)	EQ-5D completed by patients	UK general population values, method of valuation, TTO	HF patients: Baseline (MT)	0.6 (NR) (NR) (0.57 - 0.63)
					HF patients: Post-treatment 3 months (MT)	0.61 (NR) (NR) (0.59 - 0.64)
					HF patients: Post-treatment 18 months (MT)	0.51 (NR) (NR) (0.48 - 0.54)
					HF patients: End of study ≥2	0.43 (NR) (NR) (0.39 -

Study and Country	Population detail (patients, age (mean±SD), NYHA class, EF)	Intervention (s) and sample size(N)	Elicitation technique	Valuation	Health states	Utility score, Mean (SD) (SE) (95% CI)
					years (MT)	0.46)
					HF patients: Baseline (CRT)	0.6 (NR) (NR) (0.58 - 0.63)
					HF patients: Post-treatment 3 months (CRT)	0.69 (NR) (NR) (0.66 - 0.72)
					HF patients: Post-treatment 18 months (CRT)	0.61 (NR) (NR) (0.58 - 0.64)
					HF patients: End of study ≥2 years (CRT)	0.56 (NR) (NR) (0.52 - 0.59)
Eurich 2006(74) USA and Canada	• HF patients recruited from outpatient departments in USA and Canada • Age 60±13 years • NYHA I-IV • LVEF <40%	Intervention: NR, N=298	EQ-5D completed by patients	UK general population values, method of valuation, TTO	HF patients: Overall baseline score	0.66 (0.26) (NR) (NR)
					HF patients: Baseline, improving two NYHA classes	0.75 (0.19) (NR) (NR)
					HF patients: Post-treatment 6 week, improving two NYHA class	0.79 (0.14) (NR) (NR)
					HF patients: Baseline, improving one NYHA class	0.68 (0.25) (NR) (NR)
					HF patients: Post-treatment 6 week, improving one NYHA class	0.70 (0.24) (NR) (NR)
					HF patients: Baseline, no change in NYHA class	0.66 (0.27) (NR) (NR)
					HF patients: Post-treatment 6 week, no change in NYHA class	0.71 (0.22) (NR) (NR)
					HF patients: Baseline, deteriorating one NYHA class	0.65 (0.27) (NR) (NR)
					HF patients: Post-treatment 6 week, deteriorating one NYHA	0.65 (0.25) (NR) (NR)

Study and Country	Population detail (patients, age (mean±SD), NYHA class, EF)	Intervention (s) and sample size(N)	Elicitation technique	Valuation	Health states	Utility score, Mean (SD) (SE) (95% CI)
					class	
Göhler 2009(75) Multicentre	• Subset of CHF patients from multicentre trial EPHESUS • Age 64±12 years • NYHA NR • LVEF 32%	Eplerenone vs Placebo, N=1,395 (all patients)	EQ-5D completed by patients	Population values based on subject's specific region of origin United States (31%), Western Europe (52%), Latin America (14%), method of valuation, TTO	CHF patients: NYHA class I	0.855 (NR) (NR) (0.845 – 0.864
					CHF patients: NYHA class II	0.771 (NR) (NR) (0.761 – 0.781)
					CHF patients: NYHA class III	0.673 (NR) (NR) (0.665 – 0.690)
					CHF patients: NYHA class IV	0.532 (NR) (NR) (0.480 – 0.584)
					CHF patients: No of rehospitalisation (n=0)	0.812 (NR) (NR) (0.802–0.821)
					CHF patients: No of rehospitalisation (n=1)	0.787 (NR) (NR) (0.774–0.799)
					CHF patients: No of rehospitalisation (n=2)	0.769 (NR) (NR) (0.751–0.787)
					CHF patients: No of rehospitalisation (n≥3)	0.746 (NR) (NR) (0.727–0.765)
Griffiths 2014(56) Multicentre	• HF patients from multicentre trial SHIFT • Age ≥18 years • NYHA II-IV • LVEF ≤35%§	SC vs ivabradine, N=5313 (all patients)	EQ-5D completed by patients	UK general population values, method of valuation, NR	CHF patients: NYHA class I, no hospitalisation	0.82 (NR) (NR) (NR)
					CHF patients: NYHA class II, no hospitalisation	0.74 (NR) (NR) (NR)
					CHF patients: NYHA class III, no hospitalisation	0.64 (NR) (NR) (NR)
					CHF patients: NYHA class IV, no hospitalisation	0.46 (NR) (NR) (NR)
					CHF patients: NYHA class I, hospitalisation	-0.04 (NR) (NR) (NR)
					CHF patients: NYHA class II, hospitalisation	-0.07 (NR) (NR) (NR)

Study and Country	Population detail (patients, age (mean±SD), NYHA class, EF)	Intervention (s) and sample size(N)	Elicitation technique	Valuation	Health states	Utility score, Mean (SD) (SE) (95% CI)
					CHF patients: NYHA class III, hospitalisation	-0.10 (NR) (NR) (NR)
					CHF patients: NYHA class IV, hospitalisation	-0.29 (NR) (NR) (NR)
					CHF patients: Ivabradine therapy (reduction in hospitalisation)	0.01 (NR) (NR) (NR)
Holland 2007(76) UK	• HF patients recruited from general hospital inpatient in the UK • Age 76.4±9.5 years (usual care), 77.6±9.0 years (pharmacist care) • NYHA I-IV • EF NR	Usual care, N=143 vs Pharmacist care, N=148	EQ-5D completed by patients	NR†	HF patients: Baseline (usual care)	0.57 (0.34) (NR) (NR)
					HF patients: Post-treatment, 3 months (usual care)	0.51 (0.37) (NR) (NR)
					HF patients: Post-treatment, 6 months (usual care)	0.52 (0.34) (NR) (NR)
					HF patients: Baseline (pharmacist care)	0.58 (0.32) (NR) (NR)
					HF patients: Post-treatment 3 months (pharmacist care)	0.54 (0.33) (NR) (NR)
					HF patients: Post-treatment 6 months (pharmacist care)	0.58 (0.29) (NR) (NR)
Iqbal 2010(77) UK	• HF patients recruited from hospital outpatient clinics and cardiology wards (at discharge) in the UK • Age 71±1 years • NYHA I-IV • EF NR	Intervention: NR N=179	EQ-5D completed by patients	UK general population values, method of valuation, NR	CHF patients	0.57 (0.03) (NR) (NR)
Jolly 2009(78) UK	• HF patients from BRUM-CHF UK study • Age 70±12.5 years (specialist nurse care), 65.9±12.5 years (exercise program and specialist nurse care) • NYHA ≤III • LVEF ≤40%	Specialist nurse care alone, N=85 vs Exercise program and specialist	EQ-5D completed by patients	NR†	HF patients: Baseline (specialist nurse care)	0.696 (0.26) (NR) (NR)
					HF patients: Post-treatment 6 months (specialist nurse care)	0.617 (0.32) (NR) (NR)
					HF patients: Post-treatment 12	0.691 (0.28) (NR) (NR)

Study and Country	Population detail (patients, age (mean±SD), NYHA class, EF)	Intervention (s) and sample size(N)	Elicitation technique	Valuation	Health states	Utility score, Mean (SD) (SE) (95% CI)
		nurse care, N=84			months (specialist nurse care)	
					HF patients: Baseline (exercise program and specialist nurse care)	0.675 (0.25) (NR) (NR)
					HF patients: Post-treatment 6 months (exercise program and specialist nurse care)	0.663 (0.24) (NR) (NR)
					HF patients: Post-treatment 12 months (exercise program and specialist nurse care)	0.679 (0.21) (NR) (NR)
Kontodimopoulos 2011(79) Greece	• CHF patients recruited from inpatient (elective cardiac surgery) hospital in Greece. • Age 65.80±10.59 years • NYHA NR • EF 51.88% (mean)	Elective cardiac surgery, N=251	EQ-5D & SF-6D completed by patients	UK general population values, method of valuation TTO (EQ-5D) and SG (SF-6D)	CHF patients: SF-6D	0.710 (0.136) (NR) (0.693 – 0.727)
					CHF patients: EQ-5D	0.703 (0.303) (NR) (0.665 – 0.741)
Kraai 2013(80) Netherlands	• HF patients recruited from outpatient HF clinic in the Netherlands • Age 70±9.4 years • NYHA I–IV • LVEF 33% (mean)	NR, N=100	EQ-5D & TTO completed by patients	UK general population values, method of valuation, NR	HF patients: EQ-5D (no further detail reported)	0.68 (0.26) (NR) (NR)
					HF patients: TTO (no further detail reported)	0.77 (0.26) (NR) (NR)
Nafees 2014(81) UK	• CHF patients and cardiologists (no further detail reported)	Intervention: NR, N=10(CHF patients), N=5(Cardiologists)	Interview (Concept Elicitation for developing health states) completed by CHF patients and cardiologists	UK general population values method of valuation, TTO	CHF patients: Reduced EF, NYHA class II	0.86 (0.19) (NR) (NR)
					CHF patients: Reduced EF, NYHA class III	0.60 (0.23) (NR) (NR)
					CHF patients: Reduced EF, NYHA class IV	0.28 (0.41) (NR) (NR)
					CHF patients: Preserved EF, NYHA class II	0.83 (0.24) (NR) (NR)
					CHF patients Preserved EF, NYHA class III	0.55 (0.28) (NR) (NR)

Study and Country	Population detail (patients, age (mean±SD), NYHA class, EF)	Intervention (s) and sample size(N)	Elicitation technique	Valuation	Health states	Utility score, Mean (SD) (SE) (95% CI)
					CHF patients Preserved EF, NYHA class IV	0.27 (0.35) (NR) (NR)
Peters 2014(82) UK	• HF patients from a cohort survey conducted by general practitioner clinics in the UK • Age between ≥18 and ≥85 years • NYHA NR • EF NR	Intervention: NR, N=137	EQ-5D completed by patients	UK general population values, method of valuation, NR	HF patients: Baseline	0.64 (NR) (NR)(0.59 – 0.69)
					HF patients: one year follow-up	0.64 (NR) (NR)(0.59 – 0.69)
Pulikottil-Jacob 2014(83) UK	• HF patient data from BTDB in the UK • Age 40.8±14.4 years (HeartMate II), 47.7±12.0 years (HeartWare) • NYHA NR • EF NR	HeartMate II VAD, N=82 vs HeartWare VAD, N=125	EQ-5D data determined using NYHA scores from BTDB	NR†	HF patients: Post-implantation (HeartMate II VAD)	0.73 (NR) (0.008) (NR) (NR)
					HF patients: Post-implantation (HeartWare VAD)	0.75 (NR) (0.006) (NR) (NR)
					HF patients: Post-HT, average NYHA (recorded at 3, 12 and 24 month assessments used to determine utility scores)	0.83 (NR) (0.005) (NR) (NR)
Spiraki 2008(84) Greece	• HF patients recruited from cardiology inpatient in Greece • Age ≥35yrs and ≥74 years • NYHA NR • EF NR	NR, N=49	EQ-5D completed by patients	UK general population values, method of valuation, NR	HF patients: Patient admission (phase A)	0.544 (NR) (NR) (NR)
					HF patients: Patients discharged from the hospital (phase B)	0.616 (NR) (NR) (NR)
					HF patients: One month post discharge date (phase C)	0.671 (NR) (NR) (NR)
Thylen 2014(85) Sweden	• HF patients recruited from Swedish ICD and pacemaker registry • Age 65.9±11.5 years • NYHA NR • EF NR	ICD, N=3067	EQ-5D completed by patients	UK tariff for EQ-5D	HF patients: ICD recipients	0.82 (0.21) (NR) (NR)
Yao 2007(86) Multicentre	• HF patients from multicentre RCT CARE-HF • Age 66 median years (MT alone), 67 median years (MT + CRT +/- ICD)††	MT alone vs MT plus CRT with and without ICD	EQ-5D completed by patients	NR§§	HF patients: NYHA class I (independent of intervention)	0.815 (NR) (NR) (0.781 - 0.850)
					HF patients: NYHA class II (independent of intervention)	0.720 (NR) (NR) (0.693 - 0.749)

Study and Country	Population detail (patients, age (mean±SD), NYHA class, EF)	Intervention (s) and sample size(N)	Elicitation technique	Valuation	Health states	Utility score, Mean (SD) (SE) (95% CI)
	• NYHA III-IV • LVEF ≤35%	N=813 (all patients)			HF patients: NYHA class III (independent of intervention)	0.590 (NR) (NR) (0.551 - 0.629)
					HF patients: NYHA class IV (independent of intervention)	0.508 (NR) (NR) (0.412 - 0.605)
Zhang 2010(87) Multicentre	• HF patients from multicentre EPHESUS trial • Age 63.3±11.5 years (Eplerenone), age 63.8±11.7 years (Placebo) • NYHA NR • LVEF ≤40%	Eplerenone, N=2113 vs Placebo, N=2152	EQ-5D completed by patients	NR	HF patients: Baseline (Eplerenone)	0.645 (NR) (NR) (NR)
					HF patients: Post-treatment 6 months (Eplerenone)	0.768 (NR) (NR) (NR)
					HF patients: Post-treatment 1 year (Eplerenone)	0.799 (NR) (NR) (NR)
					HF patients: Baseline (placebo)	0.657 (NR) (NR) (NR)
					HF patients: Post-treatment 6 months (placebo)	0.775 (NR) (NR) (NR)
					HF patients: Post-treatment 1 year (placebo)	0.645 (NR) (NR) (NR)

Abbreviations in table: BRUM-CHF, Birmingham Rehabilitation Uptake Maximisation for patients with Congestive Heart Failure; BTDB, Blood and Transplant Data Base; CARE-HF, Cardiac Resynchronisation in Heart Failure; CHF, Chronic Heart Failure; CI, confidence interval. CRT, Cardiac Resynchronization Therapy; ECMO, Extracorporeal Membrane Oxygenation; EF, Ejection fraction; EPHESUS, Eplerenone Post-Acute Myocardial Infarction Heart failure Efficacy and Survival Study; ESHF, End stage heart failure; HF, Heart Failure; HUI2, Health Utilities Index Mark2; HT, Heart Transplant; ICD, Implantable Cardioverter defibrillator; LVAD, Left Ventricular Assist Device; LVEF, Left Ventricular Ejection Fraction; MM, Medical Management; MT, Medical therapy; NA, Not Applicable; NR, Not Reported; NYHA, New York Health Association; OPT, Optimum pharmacologic therapy; RCT, Randomised Clinical Trial; SF-36, Short form-36; SG, Standard gamble; SC, Standard Care; SBRSA, Smith Beecham Retired Service Association; SHIFT, Systolic Heart failure treatment with the If inhibitor ivabradine Trial; SD, Standard Deviation; TTO, Time Trade-Off; UK, United Kingdom; VAD, Ventricular Assist Device

† Population used for valuation of health states is not reported in these studies, it is assumed that the study used a UK tariff as the patient population (in whole or in part) were recruited from the UK; ‡ Representative UK general population details are not reported in the study; § Patient characteristics obtained from – Swedberg *et al.* 2012(88); ¶ Study reported as a conference abstract; †† Patient characteristics (age) obtained from Cleland *et al.* 2005(89); ‡‡ Age mean (95% Confidence Interval); §§ Population used for valuation of health states is not reported in the study, it is assumed that the study uses a UK tariff as the study is a cost-effectiveness analysis based on UK perspective; ¶¶ Study did not report intervention, patient enrolled in the study were already receiving OPT.

Note: the ERG corrected the table as an error was found in the CS for the study by Eurich *et al*.(74)

5.4.5.2 Overview of QoL within the economic analysis

The company used a linear mixed regression model based on EQ-5D trial data to predict the utility scores for patients in the economic model. Since the economic model did not explicitly include mutually exclusive health states (other than the alive and the dead states), mean utility values over time were calculated for each patient profile (or average cohort). The predictive QoL model took into account:

- Patient baseline characteristics (including EQ-5D index values at baseline);
- The treatment received (i.e. sacubitril or ACEi);
- Time elapsed since beginning of the model;
- Hospitalisation and AEs which were accounted for by including utility decrements based on the average event rate by treatment arm.

The AEs considered in the QoL model were cough and hypertension as the CS (Section 5.4.7) reported that elevated serum potassium and serum creatinine were assumed to have no impact on QoL, and that too few angioedema events were observed to make inference regarding the effects on QoL. Hospitalisation and the AEs experienced (i.e. cough and hypertension) were expressed as function of the treatment received. Event-related disutilities were applied at the time of occurrence of events for simplicity, even though the time-frame for event occurrence was up to 90 days. The mean utility scores predicted by the QoL regression are reported in Table 27. To note is that the values reported below incorporate the ERG corrections made to the QoL analysis and reported in Section 5.5.9.5. The company assumed the utility scores to decrease linearly with time at a rate of -0.008 per year based on the statistical analysis performed.

Table 27.Mean predicted utility scores over time by treatment

Year	Sacubitril valsartan	Enalapril
0	0.79	0.78
10	0.72	0.71
20	0.64	0.63
30	0.56	0.55
Note: the utility scores reported in the table are the half-cycle utility scores for the first and second cycles of the year (or the last cycle for year 30). These are calculated as per the ERG correction of the error found in the utility score estimation (see Section 5.5.9.5).		

5.4.5.3 Analysis of health-related QoL trial data

The PARADIGM-HF trial included several secondary and exploratory objectives aimed at evaluating differential QoL effects between the treatments. The two most relevant exploratory outcomes are:

- To compare the effects of sacubitril valsartan and enalapril on improving health-related QoL, assessed by total score and individual scores of the sub-domains from the Kansas City Cardiomyopathy Questionnaire (KCCQ) and by the total score of the EuroQol [EQ-5D] for health status);

- To compare the effects of sacubitril valsartan and enalapril on the clinical composite score (assessed by NYHA classification and patient global assessment) at 8 months.

EQ-5D data in the trial were collected at the following time points:

- Baseline (i.e. end of run-in, visit 5 of 777);

- Pre-planned visits 9, 10, 11, 14 and 17, respectively at 4, 8, 12, 24 and 36 months;

- End of the study (visit 778), scheduled upon the decision to close the study.(90)

The company considered that the use of the utility values derived from the trial has several advantages over using utility values identified in the published literature. More precisely:

- EQ-5D data could be derived from the same population as the clinical efficacy data;

- Changes in EQ-5D over time could be considered;

- Utility decrements associated with hospitalisation and AEs could be incorporated;

- Significant differences associated with sacubitril could be incorporated;

- Baseline characteristics of individuals from the PARADIGM-HF trial could be used to predict EQ-5D scores;

- EQ-5D index scores elicited in the PARADIGM-HF trial were from the period 2009 to 2014 thus reasonably current.

In Section 5.4.2 the CS reports that the patients' responses, summarised by the EQ-5D 3-level index, were converted to utility values using the UK tariff as presented by Dolan, which uses a time-trade-off (TTO) methodology to elicit preferences from the general population.(91, 92) The justification for not using the KCCQ clinical assessment score in the economic evaluation was that it is not a preference-based measure (CS, Section 5.4.2).

The baseline EQ-5D and KCCQ values were supplied to the ERG in a short supporting document summarising the details of a commissioned analysis of the EQ-5D data (91) and in the appendix tables

of the PARADIGM-HF CSR (as part of the evidence requested in the clarification stage).(90) The EQ-5D commissioned analysis reports that at baseline [redacted] ([redacted]%) and [redacted] ([redacted]%) patients had complete EQ-5D index data in the enalapril and sacubitril arms, respectively. The mean EQ-5D values at baseline were [redacted] (SD [redacted]) for both arms. The distribution of the EQ-5D index data is [redacted] (Figure 7). About [redacted] of the total population had a [redacted] utility score at baseline while around [redacted] had a score less than [redacted] and [redacted] of the patients had a score equal to [redacted]. The left tail was influential in the estimation of the mean, as the trimmed mean (with a tail trimming proportion of 5%) was [redacted], equal to the median of the distribution. A description of these data was not included in the CS or in the EQ-5D analysis document. There was no justification as to why a proportion of patients in the trial would have such a low quality of life at baseline (considered worse than death). In Section 5.4.6 of the CS it is stated that, "the utility values identified in in the literature search were broadly consistent with baseline utility values in PARADIGM-HF". However no comparison was reported. The histogram of the utility data at baseline is reported in Figure 7.

Figure 7. Distribution of the EQ-5D index data (TTO). Source: Novartis, reproduced by the ERG

A two-sample *t* test was performed to compare the two distribution means and [redacted] (p value = [redacted]). The validity of this conclusion is further discussed in Section 5.5.8. The EQ-5D TTO scores by treatment arm (except for the mean values) were not reported in any of the documents provided by the company.

The company supplied the values of the mean KCCQ clinical summary score as part of the supplementary EQ-5D analysis document, showing [redacted] in the KCCQ scores at baseline (mean ± SD: [redacted] and [redacted] respectively for sacubitril and enalapril; p-value=[redacted]). The ERG notes that [redacted], as showed by the *t* tests performed by the ERG using the data reported in Section 14 of the CSR, Table 14.2-3.20. These are reported in Table 28.

Table 28. Comparison of KCCQ scores at baseline

KCCQ dimension	Sacubitril valsartan			Enalapril			Difference			
	N	Mean	SD	N	Mean	SD	Mean	SE	*t*	p-value
Physical limitation	[redacted]									
Symptom stability	[redacted]									
Symptom frequency	[redacted]									
Symptom burden	[redacted]									
Total symptom score	[redacted]									
Self-efficacy	[redacted]									
Quality of life	[redacted]									
Social limitation	[redacted]									
Overall summary score	[redacted]									
Clinical summary score	[redacted]									

* statistical significance

Source: ERG calculations based on KCCQ data reported in PARAIDMG-HF CSR, Table 14.2-3.20.

Abbreviations used in table: KCCQ, Kansas City Cardiomyopathy Questionnaire; SD, standard deviation; SE, standard error.

The mean changes from baseline in the utility scores (EQ-5D valuated using UK tariffs) are reported in Table 29. The utility scores declined over time at a slightly different rate for the two treatments, as shown in Figure 8. The observed time effect was tested in the statistical modelling of the utility scores.

Table 29. Changes from baseline, EQ-5D TTO data (CS; Table 59)

Month	Sacubitril valsartan			Enalapril			Difference			
	N	CFB	SE	N	CFB	SE	Mean difference	95% LB	95% UB	P value

Month	Sacubitril valsartan			Enalapril			Difference			
4	[redacted]									
8	[redacted]									
12	[redacted]									
24	[redacted]									
36	[redacted]									
Abbreviations in table: CFB, change from baseline; LB, lower bound; SE, standard error; UB, upper bound.										

[redacted]

The PARADIGM-HF trial also collected EQ-5D data using the visual analogue scale (VAS) method. However the EQ-5D VAS change from baseline [redacted] compared to the mean change from baseline in the EQ-5D TTO scores (Figure 9). It is clear from the comparison between Figure 8 and Figure 9 that the two measures [redacted]

[redacted] While the two measuring methods cannot be compared quantitatively and the VAS scores are regarded as weaker evidence, they can be compared qualitatively.(93) [redacted].

[redacted] The implications of this are further discussed in Section 5.5.8.

[redacted]

[redacted]

[redacted]

5.4.5.4 QoL modelling approach

QoL in the economic analysis was not specific to health states in the model (because there were no health states explicitly included in the model except for the alive and death states). In Appendix 12, Section 8.12 of the CS, the company reports that the model structure was designed to reflect that of the ivabradine model in NICE TA267, however the economic model in TA267 included the four NYHA classes as the basis for health states, and associated different utility scores to each class in the model.(57) In the current submission the company preferred modelling utility scores directly without

attaching them to model health states. The following reasons were reported in to justify the chosen modelling approach:

- The chosen approach results in lower utilities at later time points; as such the QALY gains associated with extended survival are reduced, producing a more plausible scenario and resulting in a higher cost per QALY associated with sacubitril;
- The chosen approach removes the step of 'mapping' to NYHA, which introduces additional uncertainty into the model not readily characterised within sensitivity analysis;
- The parameters associated with a mixed model are on the scale of EQ-5D, and are therefore arguably more intuitive and easier to subject to checks of face validity than those associated with a multinomial logistic regression;
- Removing the NYHA statistical model is associated with a considerable reduction in the number of parameters used, resulting in a more parsimonious model.

A longitudinal analysis was performed by fitting a repeated measures linear mixed-effects model to the utility score data. Baseline characteristics considered as potential covariates for the model included the ones reported in Section 5.4.2.1 of the ERG report (Table 17). Section 5.4.11 of the CS reports the selection process carried out to be similar to the one used for the mortality and hospitalisation regression, but performed manually by an analyst.

Four different models were presented in the CS, varying the assumptions regarding the effects on QoL of treatment, interaction between treatment and time, and recent hospitalisation and occurrence of adverse events. The models varied in the set of selected covariates only, as the presented models were all linear mixed models with individual-level random effects. A brief description of the models and the main results are reported in Table 30.

Table 30. Alternative models for the longitudinal analysis of utility scores (CS; Table 60)

Variable	**Model 1**	**Model 2**	**Model 3**	**Model 4**
	Baseline characteristics and time	Baseline characteristics, time and treatment	Baseline characteristics, time, treatment, treatment x time interaction	Baseline characteristics, time, treatment, hospitalisation and adverse event effects
Time (years)	-0.008***	-0.008***	-0.009***	-0.008***
Sacubitril valsartan		0.011***	0.008*	0.011***
Sacubitril valsartan*Time			0.003	
Hosp. previous 30 days				-0.105***
Hosp. previous 30-90 days				-0.054***
Cough				-0.028***

Variable	Model 1	Model 2	Model 3	Model 4
	Baseline characteristics and time	Baseline characteristics, time and treatment	Baseline characteristics, time, treatment, treatment x time interaction	Baseline characteristics, time, treatment, hospitalisation and adverse event effects
Hypotension				-0.029***
p-value for sacubitril valsartan effect	NA	<0.001***	0.0219*	<0.001***
Implied annual change				
ACEi	-0.008	-0.008	-0.009	-0.008
Sacubitril valsartan			-0.006	
p-value for comparison of slopes	NA	NA	0.1318	NA
n	34,208	34,208	34,208	34,208
AIC	-23604	-23615	-23615	-24153

* p< 0.1; ** p< 0.01; *** p<0.001.

Abbreviations in table: ACEi, angiotensin-converting enzyme inhibitor; AIC, Akaike information criterion; Hosp., hospitalisation; NA, not available.

The model chosen for the analysis (model 4 in Table 30) had the lowest AIC among the four options presented therefore was considered the best fit to the data by the company. All the included covariates had a non-null effect (at a significance level of α=0.05) on the dependent variable. An alternative model (model 3 in Table 30) tested for the interaction between the effects of time and treatment on the utility scores. The interaction was found to be non-statistically different from zero at a significance level of α=0.05. However the interaction between time and treatment was only tested by using model 2 as a basis (thus building model 3) as such it did not consider the effects of adverse events and hospitalisation on quality of life (considered inly in model 4).

The final QoL model used to predict the utility scores included the effect of treatment, time, hospitalisation in the previous 30 and 30 to 90 days, occurrence of cough and hypertension and controlled for baseline age, gender, region, NYHA class, heart rate, NT-proBNP, sodium, BMI, diabetes, duration of heart failure, ischaemic aetiology, previous stroke, current smoker status and EQ-5D-derived utility score at baseline. The regression coefficients for the model used to predict the utility scores in the economic evaluation are reported in Table 31.

In Section 5.4.13 of the CS it is reported that the key assumptions regarding utility are the following:

- Existence of a small but significant treatment effect on EQ-5D even after controlling for the effects of hospitalisations and adverse events. This implies that patients on sacubitril experience an improvement in their QoL besides the improvement related to the decrease in mortality, hospitalisation and AEs. This was assumed to persist for the duration of the time horizon;

- There is a decline in EQ-5D decline from randomisation. The utility scores were assumed to decline at a constant rate over the modelled time horizon (i.e. 30 years). The decline rate was not dependent on baseline characteristics, and the implied annual change was estimated to be -0.008;

- The detrimental effect of the entire duration of hospitalisation and AEs managed in the outpatient setting (i.e. cough, hypertension) on QoL was applied in the model cycle in which the patient experienced the event:

    - Hospitalisation was assumed to be associated with a decrement of -0.105 during days 0 to 30, and -0.054 during days 30 to 90;

    - The utility decrement for hypotension and cough were associated with reductions in QoL equal to -0.028 and -0.029 over an average duration of 64.9 and 73.3 days respectively;

- The effect on QoL of serious adverse events requiring hospitalisation was assumed to be captured in the utility decrements associated with hospitalisation.

Table 31. Coefficients of the mixed model with individual-level random effects for utility scores (CS; Table 61)

Covariate	Coefficient	SE	P value	95% CI	
Sacubitril valsartan	0.011	0.003	0.001	0.004	0.017
Age†	-0.001	0.000	0.000	-0.001	0.000
Female	-0.031	0.004	0.000	-0.039	-0.023
Region					
Latin America	0.041	0.007	0.000	0.027	0.055
Western Europe	0.013	0.007	0.063	-0.001	0.026
Central Europe	0.000	0.007	0.969	-0.014	0.013
Asia-Pacific	0.041	0.008	0.000	0.026	0.056
NYHA classification					
II (vs. I)	-0.009	0.008	0.224	-0.024	0.006
III (vs. I)	-0.051	0.008	0.000	-0.067	-0.034
IV (vs. I)	-0.092	0.021	0.000	-0.132	-0.051
Heart rate†	0.000	0.000	0.049	-0.001	0.000
(log) NT-proBNP†	-0.009	0.002	0.000	-0.013	-0.006
Sodium†	0.001	0.001	0.071	0.000	0.002
BMI*	-0.002	0.000	0.000	-0.003	-0.001
Diabetes	-0.014	0.003	0.000	-0.021	-0.007
Time since diagnosis of HF					
1-5 years	-0.017	0.004	0.000	-0.024	-0.009
> 5 years	-0.023	0.004	0.000	-0.031	-0.014
Ischaemic aetiology	-0.007	0.003	0.033	-0.014	-0.001

Covariate	Coefficient	SE	P value	95% CI	
Prior stroke	-0.012	0.006	0.039	-0.023	-0.001
Current smoker	-0.013	0.005	0.005	-0.022	-0.004
Baseline EQ-5D†	0.488	0.008	0.000	0.473	0.504
Hosp. 0 – 30 days	-0.105	0.006	0.000	-0.116	-0.094
Hosp. 30 – 90 days	-0.054	0.004	0.000	-0.062	-0.045
AE – cough	-0.028	0.007	0.000	-0.041	-0.015
AE – hypotension	-0.029	0.006	0.000	-0.042	-0.017
Time (years)	-0.008	0.001	0.000	-0.010	-0.006
Constant	0.822	0.010	0.000	0.802	0.843

Abbreviations in table: AE, adverse event; BMI, body mass index; CI, confidence interval; EQ-5D, European Quality of Life 5 dimensions; HF, heart failure; Hosp., hospitalisation; NT-proBNP, N-terminal of the prohormone brain natriuretic peptide; NYHA, New York Heart Association (functional classification); SE, standard error.

†Variable centred on the mean.

*Variable centred on the mean; no reported erroneously in the CS, Table 61

Note: a repeated row appearing in Table 61 of the company submission has been removed by the ERG.

5.4.6 Resources and costs

In this section the ERG outlines the systematic review carried out by the company to identify resource use and cost evidence in HF for use within the economic model. The assumptions and estimates used in the economic model submitted by the company are detailed in the following subsections, while the ERG critique is reported in Section 5.5.9.

The company's model included costs associated with HF from the perspective of the NHS and Personal Social Services (PSS), according to the NICE reference case.(5) Resource use and costs considered in the model consist on:

- Intervention and comparator's costs (including background therapies), described in Section 5.4.6.3;
- Treatment initiation costs, described in Section 5.4.6.4;
- Hospitalisation costs, described in Section 5.4.6.5;
- HF management costs, described in Section 5.4.6.6;
- AE costs, described in Section 5.4.6.7;
- Other costs, described in Section 5.4.6.8.

The sources for the resource use and cost data are summarised in Table 32 by cost category.

Table 32. Resource use and cost data sources by cost category

Cost category	Resource use source(s)	Cost source(s)	Modelling choice
Intervention and comparator costs, primary therapy	Average doses of PARADIGM-HF trial(2)	BNF(94), Novartis	Monthly costs applied to all alive patients depending on treatment
Background therapy costs	Treatment regimens at baseline in the PARADIGM-HF trial(2), Bermingham *et al.*(95), BNF(94)	BNF(94), Drugs.com(96)	Monthly costs applied to all alive patients, independent of treatment and time
Hospitalisation costs	Physician-reported hospitalisation causes in the PARADIGM-HF trial(2), NHS National Schedule of Reference Costs(97)	NHS National Schedule of Reference Costs(97)	Average cost per event independent of time and patient characteristics. Applied to all patients based on average hospitalisation rates by therapy
HF management	CPRD data analysis(98)	PSSRU(99), NHS National Schedule of Reference Costs(97)	Monthly cost applied to all alive patients, independent of treatment, time and patient characteristics
AE costs	Clinical expert opinion, Novartis	PSSRU(99), NHS National Schedule of Reference Costs(97), BNF(94)	Average cost per event independent of time and patient characteristics. Applied to all patients based on average event rates by therapy
Abbreviations in table: AE, adverse events; BNF, British National Formulary; CPRD, Clinical Practice Research Datalink; HF, heart failure; NHS, National Health Service; PSSRU, Personal Social Services Research Unit.			

5.4.6.1 Systematic review for resource use and costs

The company performed a systematic literature review to identify publicly available sources for resource use and cost data in chronic HF. Two separate searches were conducted, for direct and indirect costs respectively. The search for the direct cost review was performed on the 5th of June 2015; the search for the indirect cost review was first performed on the 3rd of July 2014 and updated on the 2nd of June 2015. No language limits were applied. Additional studies were identified by hand searching conference proceedings and the reference list of previous trials and systematic reviews.

As reported in Appendix 11, Section 8.11 of the CS, the company searched the following electronic databases: MEDLINE® and MEDLINE® In Process & Other Non-Indexed Citations (1946 to present), Embase (1980 to present), NHS EED (from inception to present) and Econlit (1969 to present). The Cochrane Central Register of Controlled Trials, the Cochrane Database of Systematic Reviews, the Database of Abstracts of Reviews of Effects (DARE), and the Health Technology Assessment Database were included in the search for indirect costs but not for direct costs.

No studies were identified in the indirect cost searches. The search strategy for direct costs was designed to identify UK resource use and cost data sources (e.g. health care expenditure, pharmacological and hospitalisation costs) in patients with chronic HF. Outcomes of interest were

direct costs, number of hospitalisations and resource use (i.e. medicines, diagnostics). No exclusion criteria, language or data restriction were applied. Two reviewers assessed independently the inclusion of identified studies according to the inclusion criteria, with discrepancies resolved by a third party. Six studies were identified in the systematic search and two in the hand search, for a total of eight studies. A brief summary of the selected publications are reported in Appendix 11, Section 8.11.8 of the CS.

Two studies (Wynn *et al.*(100) and CIBIS Investigators(101)) reported cost data from RCTs; one evaluated bisoprolol in France, the UK and Germany while the other evaluated the use of ivabradine in the UK. McMurray *et al.*(102) described a retrospective study of case records in Scotland, reporting length of hospitalisation data for the 1980 and 1990's; Stewart *et al.*(103) estimated direct costs expenditure in 1995 using Scottish data to estimate UK prevalence, resource utilisation and cost data for chronic HF patients. Kadam *et al.*(104) and Doos *et al.*(105) both analysed patient data from 53 general practices in Stoke-on-Trent using a database linkage methodology. Parameshwar *et al.*(106) reported an analysis based on 1992 patient data taken from the Hillingdon hospital district general hospital, however direct costs were not reported and hospitalisation data were very limited. McMurray *et al.*(102) used the data reported by Parameshwar *et al.*(106) to estimate the annual number of HF hospitalisations.

Studies already identified in the cost-effectiveness search (described in Section 5.3) were not reported in the resource use and costs literature review in Appendix 11 of the CS, Section 8.11.8. It is unclear whether these were checked for data sources relevant to this search.

Even though relevant studies were identified through the systematic searches, the company commissioned an analysis of the Clinical Practice Research Datalink (CPRD) dataset which is described in the next subsection.(98)

5.4.6.2 CPRD data analysis

The company commissioned a database linkage analysis, designed as a cohort study. The goal of the study was to characterise the HF burden of illness in the UK in terms of demographic and clinical characteristics of patients; resource use (inpatient and outpatient) and cost for HF patients; treatment patterns (medications and devices), adherence and persistence with drug therapy. The study covered the period of 1st of January 2008 to 31st of December 2011 and included patients eligible for linkage to the HES (Hospital Episode Statistics) and ONS (Office for National Statistics) databases.(98) The version used for the analysis was the November 2014 build of the CPRD dataset. The subject inclusion criteria included patients who:

- Had an HF diagnosis before 1st of January or during the identification period (1st of January 2009 to 31st of December 2010) and were alive on the 1st of January 2009. The index date was defined as the date of the first recorded evidence of diagnosis of HF during the identification period;

- Were aged at least 18 years old at index date;

- Were male or female;

- Had a minimum of one year of up-to-standard registration prior to their index event;

- Had HF events within his/her up-to-standard follow-up period;

- Had a minimum of one year of follow-up from the index date, unless dead;

- Had at least one health contact (specifically GP visits, other cardiology visit, A&E or hospital visit) between the index date and the end of the follow-up period;

- Were eligible for linkage in both HES and ONS.

The CPRD analysis was used as the main source for resource use in HF management in the base case model rather than the literature identified in the systematic reviews. The company justified this choice with the following reasons:

- The CPRD dataset covers the English NHS, and so better reflects the population considered by NICE than studies considering resource use outside of England, or within smaller subpopulations;

- The CPRD analysis is reasonably current (study period: 1 January 2008 to 31 December 2011), while a number of alternative studies are based on data from the 1990s;

- Bespoke data tables considering resource use excluding hospitalisation and pharmacological therapies are available from CPRD analysis as is necessary in order to avoid double counting.

The ERG agrees with the company that real-world data from CPRD is more robust and more reflective of the UK population than literature studies. However the ERG is concerned with the appropriateness of the use of the CPRD data to estimate the resource use for the patient profiles observed in the trial as there seem to be differences in the population observed in the CPRD analysis and the one analysed in the PARADIGM-HF trial. This issue is explored in Section 5.5.9 and Section 5.6.2.

5.4.6.3 Intervention and comparator's costs

In their base case analysis the company estimates the daily cost of sacubitril and enalapril based on the average observed drug doses in the PARADIGM-HF trial.

Standard care and background therapies are defined in Section 5.2.4 of the CS. The company states that the majority of patients who receive an ACEi as first-line therapy (or ARB for those who are intolerant to ACEi) might also receive additional standard care therapies including BB (recommended for all patients) and AA (recommended for patients who remain symptomatic). Therefore, patients in the sacubitril and enalapril (or candesartan) arms of the model also received the standard care therapies.

The observed proportions of patients in the PARADIGM-HF trial receiving BB and AA at baseline (93.00% and 55.61% respectively) were similar to the UK data reported by the British Society for Heart Failure for the treatment of patients with left ventricular systolic disease (LVSD) at discharge (82% and 49% respectively).(1, 90) Based on this similarity, data from the PARADIGM-HF trial were used to define the proportion of patients receiving each drug at baseline. Drug regimens (i.e. the distribution of patients receiving each drug) were assumed not to change over time, irrespective of ageing population and mortality. The proportion of patients on background therapies observed in the trial and applied in the economic model is reported in Table 33. Drug regimens were also assumed not to depend on patient characteristics or the occurrence of events such as adverse events or hospitalisations, and to have no impact on the efficacy outcomes or incidence of hospitalisation or adverse events.

Table 33. Proportion of patients receiving background therapies

Therapy	Proportion of patients	Source
Beta blockers	93.00%	PARADIGM-HF trial(90)
Aldosterone antagonists	55.61%	PARADIGM-HF trial(90)
Digoxin	30.23%	PARADIGM-HF trial(90)
Lipid lowering medications	56.30%	PARADIGM-HF trial(90)
Diuretics	80.22%	PARADIGM-HF trial(90)
Aspirin	51.78%	PARADIGM-HF trial(90)
Anticoagulants	31.97%	PARADIGM-HF trial(90)
ADP antagonists	15.00%	PARADIGM-HF trial(90)
Abbreviations in table: ADP, adenosine diphosphate.		

The daily dose for sacubitril and enalapril in the model was assumed equal to the observed mean dose in the PARADIGM-HF trial, respectively 375 and 18.9 milligrams. (2) (39) (39) (39) (39) (39) (McMurray, Packer et al. 2014) The daily doses for other therapies were based on the British National Formulary (BNF)(94), with the exception of aspirin and warfarin. The CS did not report how the daily

doses for aspirin and warfarin were calculated. In the economic analysis, the daily dose of aspirin was referenced from Bermingham *et al.*, but it was not clearly explained (see Section 5.5.9.1).(95) The daily dose of warfarin (5 mg) was referenced from drugs.com, but it was not clearly explained in the CS (see Section 5.5.9.1).(96) The daily doses used in the model and the daily costs for each intervention are reported in Table 34.

The daily cost of sacubitril based on the pre-specified target dose of 200 mg BID is expected to be the same as that of the observed dose in the trial (375 mg daily) as sacubitril has a flat pricing structure. The different costs per pack were reported in Section 2.3 of the CS and are reported in Table 35 below. The daily cost of sacubitril was set to £3.27, resulting in a monthly cost of £99.53 per patient. The costs of the other primary and background therapies were derived from the British National Formulary.(94)

Table 34. Daily costs of primary and background therapies

Intervention	Daily cost[§]	Daily dose	Source
Sacubitril valsartan[†]	£3.27	375 mg	PARADIGM-HF(2)
Enalapril[†]	£0.07	18.9 mg	PARADIGM-HF(2)
Ramipril	£0.09	Two 5 mg tabs	BNF(94)
Perindopril	£0.05	One 4 mg tab	BNF(94)
Lisinopril	£0.11	One 20 mg tab, one 10 mg tab and one 5 mg tab	BNF(94)
Losartan	£0.10	One 100 mg tab and one 50 mg tab	BNF(94)
Candesartan	£0.08	One 32 mg tab	BNF(94)
Valsartan	£1.32	Two 160 mg tabs	BNF(94)
Carvedilol[†]	£0.11	Two 25 mg tabs	BNF(94)
Bisoprolol	£0.04	One 10 mg tab	BNF(94)
Spironolactone*	£0.07	One 50 mg tab	BNF(94)
Digoxin[†]	£0.05	One 62.5 µg or 125 µg tab	BNF(94)
Atorvastatin[†]	£0.05	One 20 mg tab	BNF(94)
Simvastatin	£0.07	One 80 mg tab	BNF(94)
Furosemide[†]	£0.03	One 20 mg or 40 mg tab	BNF(94)
Aspirin[†]	£0.03	One 75 mg tab	Bermingham *et al*.(95)
Warfarin[†]	£0.04	One 5 mg tab	Drugs.com(96)
Clopidogrel[†]	£0.07	One 75 mg tab	BNF(94)

Abbreviations in table: BNF, British National Formulary; mg, milligram; µg, microgram.
[†]Cost used in the base case
[§]Using list prices all taken from BNF other than sacubitril valsartan

Table 35. Acquisition cost scheme of sacubitril valsartan

Tablet size	Tablets per pack	Acquisition cost	Cost per tablet
50 mg	28	£45.78	£1.635
100 mg	28	£45.78	£1.635
100 mg	56	£91.56	£1.635

Tablet size	Tablets per pack	Acquisition cost	Cost per tablet
200 mg	56	£91.56	£1.635

5.4.6.4 Treatment initiation costs

No additional monitoring, laboratory tests or visits were assumed for patients initiating therapy with sacubitril compared to ACEis or ARBs. This is because all of these drugs were assumed to require the same resource use for up-titration at the beginning of therapy.

5.4.6.5 Hospitalisation costs

The hospitalisation costs were based on the NHS National Schedule of Reference Costs 2013–2014.(97) The distribution of hospitalisation types and procedures (surgical, interventional and medical management) were assumed equal to the ones observed in the PARADIGM-HF trial.(2)

The average hospitalisation cost was calculated as a multilevel weighted average. At the first level, it was defined as the weighted average of hospitalisation types (surgical procedure, intervention procedure or medical management), with weights given by the respective frequencies observed in the trial. The second-level average was calculated as the weighted average of the type of procedure (i.e. the type of procedure within each hospitalisation type, for example, within medical management procedures there were cases of pneumonia, stroke, renal failure, etc.), again with weights given by the respective frequencies observed in the trial. At the third and bottom level, each type of procedure was weighted according to NHS activity, i.e. the number of occurrences of each Healthcare Resource Group (HRG) code (for example, within pneumonia cases, patients can have lobar, atypical or viral pneumonia, with different critical care scores). The resulting final weighted average was then multiplied by the HRG code cost for each type of NHS activity. The resulting average cost for each hospitalisation event was £2,866.35. The cost of a hospitalisation event was assumed equal for all treatment arms, constant over time and invariant to patient characteristics. This cost was also varied in scenario analyses.

The company divided the hospitalisation types in three distinct categories, and associated a proportion to each category based on the PARADIGM-HF trial data, as reported in Table 36. The hospitalisation type was further broken down by type of procedure, as reported in Appendix 13, Section 8.13 of the CS. Within each type of procedure, physician-reported diagnoses in the trial were mapped to the HRG codes deemed most appropriate. The HRG codes associated with each diagnosis are reported in Table 37, Table 38 and Table 39 respectively for hospitalisations for surgical procedures, interventional procedures and medical management.

Table 36. Proportion of hospitalisations by type in PARADIGM-HF (CS, Table 64)

Hospitalisation type	Proportion of hospitalisations
Surgical procedures	3%
Interventional procedures	7%
Medical management	91%
Source: Novartis(90)	

Table 37. HRG codes for surgical procedures (CS, Appendix 13, Table 125)

Hospitalisation	PARADIGM-HF frequency	HRG code(s)	NHS activity	Unit cost
Coronary artery bypass grafting	[redacted]	EA14A	416	£15,121
		EA14B	1390	£10,741
		EA14C	3426	£9,144
		EA14D	3285	£8,716
		EA16A	753	£12,613
		EA16B	979	£10,904
		EA16C	2030	£9,565
		EA16D	2083	£8,632
		EA51A	880	£16,174
		EA51B	766	£13,141
		EA51C	1003	£11,876
		EA51D	674	£10,242
Mitral valve repair/ mitral valve replacement/ other valve surgery	[redacted]	EA17A	405	£13,632
		EA17B	501	£10,802
		EA17C	987	£9,961
		EA17D	1202	£9,013
Other cardiac surgery	[redacted]	EA03A	1321	£6,540
		EA03B	1335	£4,999
		EA03C	3160	£3,548
		EA03D	9315	£2,658
		EA03E	20315	£1,403
		EA05A	1180	£6,910
		EA05B	2991	£4,572
		EA05C	7533	£3,363
		EA05D	7938	£2,846
		EA12A	571	£17,104
		EA12B	1028	£14,902
		EA12C	2324	£13,999
		EA12D	3289	£9,930
		EA29A	604	£7,735
		EA29B	2402	£5,317
		EA29C	6161	£4,555
		EA39A	545	£5,821
		EA39B	703	£3,592
		EA39C	658	£2,129
Left ventricular aneurysmectomy	[redacted]	YQ01A	320	£11,269
		YQ01B	283	£7,240
		YQ02Z	172	£10,531
		YQ03A	683	£8,366
		YQ03B	1,439	£5,561
		YR01Z	186	£21,616
		YR02Z	258	£16,241
		YR03Z	1,869	£11,181
		YR04Z	1,850	£10,759
Ventricular assist device	[redacted]	EA43Z	157	£70,225
Heart transplantation	[redacted]	EA02Z	189	£43,515
Abbreviations in table: HRG, Healthcare Resource Group; NHS, National Health Service.				

Table 38. HRG codes for interventional procedures (CS, Appendix 13, Table 126)

Hospitalisation	PARADIGM-HF frequency	HRG code(s)	NHS activity	Unit cost
Implantable cardioverter defibrillator	[redacted]	EA12A	571	£17,104
		EA12B	1028	£14,902
		EA12C	2324	£13,999
		EA12D	3289	£9,930
Cardiac pacemaker (biventricular, defibrillating CRT-D)	[redacted]	EA56A	991	£17,142
		EA56B	1189	£15,578
		EA56C	790	£14,102
Cardiac pacemaker (biventricular, non-defibrillating CRT-D)	[redacted]	EA07A	370	£8,855
		EA07B	1132	£6,146
		EA07C	1516	£4,713
Cardiac pacemaker (conventional)	[redacted]	EA39A	545	£5,821
		EA39B	703	£3,592
		EA39C	658	£2,129
		EA03A	1321	£6,540
		EA03B	1335	£4,999
		EA03C	3160	£3,548
		EA03D	9315	£2,658
		EA03E	20315	£1,403
		EA05A	1180	£6,910
		EA05B	2991	£4,572
		EA05C	7533	£3,363
		EA05D	7938	£2,846
Coronary angioplasty	[redacted]	EA49A	899	£7,528
		EA49B	1265	£4,643
		EA49C	4371	£3,630
		EA49D	8244	£3,106
Percutaneous coronary intervention (multiple)	[redacted]	EA31A	1273	£6,780
		EA31B	3468	£4,282
		EA31C	19948	£3,029
		EA31D	30165	£2,533
Percutaneous coronary intervention (single)	[redacted]	EA31A	1273	£6,780
		EA31B	3468	£4,282
		EA31C	19948	£3,029
		EA31D	30165	£2,533

Abbreviations in table: CRT-D, cardiac resynchronization therapy device; HRG, Healthcare Resource Group; NHS, National Health Service.

Table 39. HRG codes for medical management (CS, Appendix 13, Table 127)

Hospitalisation	PARADIGM-HF frequency	HRG code(s)	NHS activity	Unit cost
Cardiac failure/ cardiac failure congestive/ cardiac failure chronic/ cardiac failure acute/ dyspnoea	[redacted]	EB03A	5678	£4,015
		EB03B	21285	£3,151
		EB03C	33895	£2,217
		EB03D	49820	£1,597
		EB03E	12307	£1,184
Pneumonia	[redacted]	DZ11D	5428	£4,817
		DZ11E	26905	£3,753
		DZ11F	60092	£2,666
		DZ11G	97494	£1,927
		DZ11H	103460	£1,433
		DZ11J	49864	£1,000
Atrial fibrillation/ ventricular tachycardia	[redacted]	EB07A	2672	£3,057
		EB07B	9466	£2,086
		EB07C	22832	£1,409
		EB07D	50382	£993
		EB07E	88775	£673

Hospitalisation	PARADIGM-HF frequency	HRG code(s)	NHS activity	Unit cost
Cerebrovascular accident	[redacted]	AA22C	663	£8,478
		AA22D	1567	£4,923
		AA22E	3013	£3,507
		AA22F	5507	£2,412
		AA22G	13202	£1,687
Angina pectoris/ angina unstable	[redacted]	EB13A	2872	£1,744
		EB13B	13778	£1,113
		EB13C	38913	£765
		EB13D	26482	£604
Myocardial infarction/ acute myocardial infarction	[redacted]	EB10A	5010	£3,353
		EB10B	12834	£2,448
		EB10C	21600	£1,739
		EB10D	30780	£1,357
		EB10E	25604	£1,036
Syncope	[redacted]	EB08A	2060	£2,548
		EB08B	8344	£1,653
		EB08C	20559	£1,163
		EB08D	40228	£855
		EB08E	50781	£571
Coronary artery disease	[redacted]	EA31A	1,273	£6,780
		EA31B	3,468	£4,282
		EA31C	19,948	£3,029
		EA31D	30,165	£2,533
Non-cardiac chest pain	[redacted]	EB12A	5060	£1,058
		EB12B	74932	£647
		EB12C	210306	£454
Chronic obstructive pulmonary disease	[redacted]	DZ21A	89592	£456
		DZ21L	269	£3,261
		DZ21M	1519	£3,379
		DZ21N	3422	£2,331
		DZ21P	2407	£2,074
		DZ21Q	1691	£3,794
		DZ21R	7072	£2,916
		DZ21S	18192	£2,237
		DZ21T	38769	£1,810
		DZ21U	44135	£1,495
Ischaemic stroke	[redacted]	AA35A	2,829	£8,858
		AA35B	7,511	£7,145
		AA35C	15,671	£5,169
		AA35D	28,755	£3,566
		AA35E	46,153	£2,489
		AA35F	41,484	£1,833
Renal failure acute	[redacted]	LA07H	951	£6,471
		LA07J	2748	£4,964
		LA07K	2351	£3,653
		LA07L	2711	£3,105
		LA07M	12341	£2,325
		LA07N	28487	£1,717
		LA07P	22170	£1,253
Congestive cardiomyopathy/ hypotension	[redacted]	EB14A	2,724	£4,019
		EB14B	10,175	£2,766
		EB14C	15,690	£1,907
		EB14D	20,719	£1,469
		EB14E	16,405	£910
Transient ischaemic attack	[redacted]	AA29C	1332	£2,605
		AA29D	3214	£1,386
		AA29E	9035	£971
		AA29F	16899	£715
Urinary tract infection	[redacted]	LA04H	742	£8,135
		LA04J	1803	£6,161
		LA04K	3442	£4,708

Hospitalisation	PARADIGM-HF frequency	HRG code(s)	NHS activity	Unit cost
		LA04L	4073	£3,350
		LA04M	2866	£2,335
		LA04N	2557	£4,247
		LA04P	28475	£2,949
		LA04Q	88689	£1,929
		LA04R	65128	£1,351
		LA04S	61466	£930
Anaemia	[redacted]	SA03G	1331	£1,836
		SA03H	1951	£623
		SA04G	1160	£2,913
		SA04H	2648	£1,840
		SA04J	7400	£1,159
		SA04K	15865	£688
		SA04L	18570	£443
		SA05G	622	£2,099
		SA05H	635	£1,313
		SA05J	810	£749
Abbreviations in table: HRG, Healthcare Resource Group; NHS, National Health Service.				

5.4.6.6 HF management costs

The company included the costs associated with HF management in their economic analysis. These costs are related with patients' HF condition and therefore are not dependant on the type of treatment received (even though a patient living for longer periods of time incurs more HF management costs). Estimates of the background medical resource use were obtained from an analysis of the CPRD database commissioned by the company.(98) The company preferred not using resource data from the PARADIGM-HF trial because it considered these data to be protocol-driven, while the CPRD database analysis was reported to reflect more appropriately UK's clinical practice. Estimates of mean annual resource use extracted from the CPRD analysis were used for accident and emergency department (A&E) referrals, general practitioner (GP) visits and outpatient contacts (GP, cardiologist and other physician visits). Resource use and unit costs used for estimating HF management costs are reported in Table 40. Unit costs were taken from the NHS National Schedule of Reference Costs 2013–2014 or from the PSSRU 2014 report.(97, 99)

Table 40. Background medical resource use

Resource category	Specific resource	Mean annual use	Source of resource use	Unit cost	Source of unit costs
A&E visits	GP emergency visits	[redacted]	CPRD data analysis(98)	£35.00	PSSRU 2014(99)
	A&E referrals	[redacted]	CPRD data analysis(98)	£124.00*	NHS National Schedule of Reference Costs 2013–2014(97)
Outpatient office physician visits	GP visits	[redacted]	CPRD data analysis(98)	£35.00	PSSRU 2014(99)
	Cardiologist visits	[redacted]	CPRD data analysis(98)	£130.86	NHS National Schedule of

Resource category	Specific resource	Mean annual use	Source of resource use	Unit cost	Source of unit costs
					Reference Costs 2013–2014(97)
	Other physician visits	[redacted]	CPRD data analysis(98)	£35.00	PSSRU 2014(99)
Other GP visits or contacts	GP home visits	[redacted]	CPRD data analysis(98)	£35.00	PSSRU 2014(99)
	GP hospital visits	[redacted]	CPRD data analysis(98)	£35.00	PSSRU 2014(99)
	GP nursing home visits	[redacted]	CPRD data analysis(98)	£35.00	PSSRU 2014(99)
	GP residential home visits	[redacted]**	CPRD data analysis(98)	£35.00	PSSRU 2014(99)
	GP phone calls to patient	[redacted]	CPRD data analysis(98)	£35.00	PSSRU 2014(99)
	GP visits with third parties	[redacted]**	CPRD data analysis(98)	£35.00	PSSRU 2014(99)

Abbreviations in table: A&E, accident and emergency (department); CPRD, Clinical Practice Research Datalink; GP, general practitioner; NHS, National Health Service, PSSRU, Personal Social Services Research Unit.

Source: adapted from CS, Table 66.

* The value of the cost of A&E referrals in Table 66 of the CS was £123.67, while £124.00 was included in the model.

**Values used in the company's economic model. The CS reported [redacted] annual GP residential home visits and [redacted] annual GP visits with third parties.

As reported in Table 41, patients were assumed to have a total of [redacted] annual GP or other physician visits ([redacted] per month per patient on average), [redacted] annual cardiologist visits (i.[redacted] years), [redacted] A&E referrals (i.e. 1 every [redacted] patient years). The company estimated an average monthly cost of £[redacted] per patient per month, constant over time and not dependent on patient characteristics and occurrence of events such as adverse events or hospitalisation.

5.4.6.7 AE costs

AEs included in the economic analysis are based on the FAS population in the PARADIGM-HF trial and are reported in Section 5.3.1 of the CS and in Section 5.4.3 of this report. As described in Section 5.4.3, AE managed in an inpatient setting were not included explicitly in the economic analysis, but were considered to be already included in the costs of hospitalisation. The AEs managed in the outpatient setting, and selected for inclusion in the model, were associated with one-off costs based on the resource use required to manage them. The company reports that the resource use associated with the management of AEs was based on UK clinical expert opinion. The resource use and cost associated with the included adverse events are reported in Table 41.

Table 41. Cost and resource use associated with AEs

Event	Resource use	Resource cost	Source of cost	Total cost
Hypotension	2 GP visits	£35.00	PSSRU(99)	£70.00

Event	Resource use	Resource cost	Source of cost	Total cost
Cough	2 GP visits	£35.00	PSSRU(99)	£73.00
	Blood test	£3.00	NHS National Schedule of Reference Costs 2013-2014(97)	
Elevated serum creatinine	2 GP visits	£35.00	PSSRU(99)	£73.00
	Blood test	£3.00	NHS National Schedule of Reference Costs 2013-2014(97)	
Elevated serum potassium	2 GP visits	£35.00	PSSRU(99)	£73.00
	Blood test	£3.00	NHS National Schedule of Reference Costs 2013-2014(97)	
Angioedema, mild (60% of cases)	2 cardiologist outpatient visits	£130.86	NHS National Schedule of Reference Costs 2013-2014(97)	£262.28
	Antihistamine treatment (Cetirizine 10 mg for 14 days)	£0.04 per day	BNF(94)	
Angioedema, severe (40% of cases)	A&E visit	£123.67	NHS National Schedule of Reference Costs 2013-2014(97)	£160.52
	GP visit	£35.00	PSSRU(99)	
	Glucocorticoid treatment (Prednisolone 40 mg for 5 days)	£0.37 per day	BNF(94)	
Source: adapted from CS, Table 69. ResResource use was based from clinical expert opinion. Abbreviations in table: A&E, accident and emergency (department); BNF, British National Formulary; GP, general practitioner; mg, milligram; NHS, National Health Service; PSSRU, Personal Social Services Research Unit.				

5.4.6.8 Other costs

Patients in the dead health state did not incur any costs. Terminal care costs were not considered in the economic model.

5.4.7 Discounting

An annual discount rate of 3.5% was applied to the both cost and health effects, in accordance to the NICE reference case.(5) The discount rates were varied for both costs and health effects to values of 1.5% and 6% in scenario analyses as reported in Section 5.8.8.2 of the CS.

5.4.8 Sensitivity analysis

The company carried out a series of sensitivity analyses to test the robustness of model results to changes in model parameters. Specifically, the company presented result of deterministic analysis,

including scenario and subgroup analysis, and probabilistic sensitivity analyses. The results of these analyses are provided in Section 5.6.2.

5.4.9 Model validation

In their submission, the company reports that validation was assessed using two primary criteria, internal (verification) and external consistency (validation). The company reports that internal verification of calculations was performed by the primary modeller and then checked by a second modeller who peer reviewed calculations. The economic model was reported to have been examined by two modellers external to the model development process (external peer review). Verification was assessed by using the following techniques:

- Face validity: testing that the model met expectations based on simple calculations;
- Model behaviour: testing whether varying model inputs had the expected directional effect;
- Internal consistency: model outputs were compared against the PARADIGM-HF trial;
- Cell-by-cell checks of calculations: manual inspection of formulae;
- Use of logical scenario checks and the rebuilding of important parts of the model;
- A complete cross-check of inputs, sources, and supporting documentation.

The company stated that external consistency was assessed by comparing the results of the analysis against published results (cross validation). The ivabradine standard care arm in the model used in TA267 was the chosen source for comparing the model outputs in the enalapril arm of the model, even though the company acknowledged the fact that patient populations in PARADIGM-HF and SHIfT (ivabradine pivotal trial) are not directly comparable. (57) Results of the cross validation undertaken by the company are reported in Table 42.

The company explained that compared with the ivabradine model, the company's model predicted costs for the enalapril arm are 41% higher. The additional costs predicted were considered to be attributable to differences in the estimation of follow-up costs and also by differences in predicted survival. Estimated QALYs are 12% higher and life-years are 7% higher in the company's model, which was deemed to reflect the more severe patient population considered in the SHIfT study. For example, in the PARADIGM-HF trial, 25% of subjects had NYHA III/IV, whereas the corresponding proportion in SHIfT was 52%. It was also noted that the ivabradine model predicted slightly poorer survival at Year 5, and that this difference grows to 5% (in absolute terms) at Year 10.(57) The

company considered that, given the differences in data, model design and approaches to the estimation of costs, the extent to which the models aligned was reasonable.

The company also compared model results with the CPRD data. However this was done in the form of scenario analysis, as previously reported in Section 5.4.8.

Table 42. Cross validation of model with ivabradine standard care arm (reproduced from CS, pg 194, Table 101)

Technologies	Standard care ivabradine model‡	ACEi arm in sacubitril valsartan model	Absolute difference	Relative difference
Technology cost†	£642	£691	£49	8%
Follow-up costs	£1,803	£5,106	£3,303	183%
Hospitalisation	£7,001	£7,489	£488	7%
Total costs	**£9,446**	£13,286	£3,840	41%
QALYs	3.99	4.46	0.47	12%
Life-years	5.61	6.03	0.42	7%
Survival Year 5	59%	60%	1%	1%
Survival Year 10	22%	27%	5%	23%

† Therapy titration and drug costs; ‡ As reported in manufacturer submission to NICE (57)
Abbreviations: ACEi, angiotensin converting enzyme inhibitor; QALY, quality-adjusted life year.

Despite the validation procedures reported by the company, the ERG found a few inconstancies in the model inputs and identified problems with the estimation of QALYs in the economic model.

5.5 Critique of the company's economic evaluation

5.5.1 NICE reference case checklist

Table 43 and Table 44 summarise the ERG's quality assessment of the company's economic evaluation. Table 43 summarises the ERGs appraisal of the company's economic evaluation against the requirements set out in the NICE reference case checklist for the base case analysis, with reference to the NICE scope(5) outlined in Section 3 and Table 44 summarises the assessment of the quality of the company's *de novo* economic model using the Philips checklist.(107)

Table 43. NICE reference case checklist for the base case analysis

Attribute	Reference case	Does the *de novo* economic evaluation match the reference case?
Decision problem	The scope developed by NICE	Yes, however some patients experienced an improvement in their NYHA classification between screening and randomisation which led to the inclusion of NYHA class I patients at baseline. NYHA class I was not considered in the NICE scope.
Comparator(s)	Alternative therapies routinely used in the NHS	Yes, however standard care in the economic model was based on drug use in the PARADIGM-HF trial, and did not include therapy with beta blocker and aldosterone antagonist for all patients but only for

		93% and 56% of patients, respectively.
Perspective costs	NHS and Personal Social Services	Yes.
Perspective benefits	All health effects on individuals	Yes.
Form of economic evaluation	Cost-utility analysis	Yes.
Time horizon	Sufficient to capture differences in costs and outcomes	Yes.
Synthesis of evidence on outcomes	Systematic review	Yes, a systematic review was carried out. The ERG notes that the synthesis of the clinical data was carried out through a NMA described in Section 4. The ERG also notes that the results of the utility and cost systematic reviews were not used in the economic analysis.
Outcome measure	Quality adjusted life years	Yes.
Health states for QALY	Described using a standardised and validated instrument	Yes.
Benefit valuation	Time-trade off or standard gamble	Yes, TTO (and additional VAS analysis).
Source of preference data for valuation of changes in health-related QoL	Representative sample of the public	Yes, PARADIGM-HF trial patients but not restricted geographically.
Discount rate	An annual rate of 3.5% on both costs and health effects	Yes.
Equity	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes.
Sensitivity analysis	Probabilistic sensitivity analysis	No. Sensitivity analyses, both deterministic and probabilistic, did not include key parameters for the assessment of the generalisability of model results. The PSA did not incorporate stochastic variation in baseline characteristics, resulting in an underestimation of the uncertainty. The ERG also has concerns about the scenario and subgroup analyses assessing the generalisability of the results. These issues are discussed in Section 5.6.2.

Abbreviations used in the table: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; ERG, evidence review group; NHS, National Health System; NICE, National Institute for Health and Care Excellence; NMA, network meta-analysis; NYHA, New York Heart Association; PSA, probabilistic sensitivity analysis; QoL, quality of life; QALYs, quality-adjusted life yeas; TTO, time trade-off; VKA, vitamin k agonist; WTP, willingness to pay.

Table 44. Philips checklist(107)

Dimension of quality	Comments
Structure	
S1: Statement of decision problem/objective	Clearly stated.
S2: Statement of scope/perspective	Clearly stated (UK NHS and PSS) and consistent with the scope.
S3: Rationale for structure	The company stated that expert opinion was obtained to validate the model structure. The modelling approach was based from previous economic studies in HF (i.e. TA267).
S4: Structural assumptions	The chosen structure is appropriate however it implies that disease progression is not explicitly modelled.
S5: Strategies/ comparators	The company considered enalapril and candesartan as comparators.
S6: Model type	Appropriate; cost-utility analysis.
S7: Time horizon	A life time horizon (30 years) is long enough to capture the costs and consequences associated with treatment.
S8: Disease states/pathways	The health states considered by the company are appropriate. However disease progression was not explicitly modelled.
S9: Cycle length	Appropriate. A half-cycle correction was applied, which was considered appropriate; however the ERG found and corrected an issue in the half-cycle calculations.
Data	
D1: Data identification	The company's literature searches for cost-effectiveness analyses, resource use and costs were only briefly described in appendixes of the CS. The ERG notes the following: It is not clear if studies identified in the cost-effectiveness searches were double-checked for utility, resource use and cost data; Studies out of the scope of the searches (e.g. publication date) were used in the CS (i.e. Berg *et al.(8)*). Studies identified in the searches were not used to inform analyses and comparisons, with the exception of the ivabradine submission (TA267).(57) The company commissioned an analysis to identify population characteristics, resource use, costs and treatment patterns of HF patients in the UK from appropriate sources. The company failed to identify severe discrepancies between the trial population and the population resulting from the commissioned analysis. The data integration in the analysis suffered from these differences in the populations from which different data were obtained.
D2: Pre-model data analysis	Pre-model data analysis was performed for some aspects of the economic evaluation however the ERG believes these are not sufficient to explore methodological uncertainty in the model.
D2a: Baseline data	Baseline data were taken from the PARADIGM-HF trial. The ERG has substantial issues with the generalisability of the trial population when compared to HF patients in the UK. The company tried to address this issue partially, however the ERG does not believe the company has succeeded in doing so.
D2b: Treatment effects	Treatment effectiveness within the model was implemented through transition probabilities between the alive and the dead states (i.e. mortality) and also through the probability of hospitalisation which patients experience while in the alive state. Treatment effectiveness was also included in the model through an improvement in HFrEF symptoms, which impacted on patients' QoL. The company used the hospitalisation, mortality and QoL models to predict the within-trial period in the analysis, as well as the extrapolated period. The company used the FAS population to undertake their economic analysis. The ERG has several issues with the lack of generalisability of the trial population and the potential impact of these on the effectiveness of sacubitril when assessed in the context of the UK's clinical practice.

D2c: Costs	Pharmacological resource use is based on PARADIGM-HF trial data, while CPRD analysis results are used to inform medical resource use. The costs are appropriately sourced from the latest BNF and PSSRU publications available; however the ERG notes some minor inconsistencies in the values used and dose assumptions made in the model. Hospitalisation costs are based on hospitalisation causes observed in the PARADIGM-HF trial population and mapped to the appropriate HRG codes. NHS Reference Costs data were used to weight the frequency of the HRG codes to produce an average cost estimate.
D2d: Quality of life weights (utilities)	The economic model uses utility scores which are estimated based on a regression analysis of the PARADIGM-HF trial data. The ERG identified a few issues in the estimation of QoL in the model. These issues are further explored in Section 5.5.8.
D3: Data incorporation	The scarcity of analyses investigating the impact of using alternative assumptions and data sources for resource use and quality of life result in the model underestimates the amount of uncertainty associated with the model predictions.
Assessment of uncertainty	
D4a: Methodological	The company used alternative methodologies to model mortality in the economic analysis. These consisted in using all-cause mortality or CV-specific mortality form the PARADIGM-HF trial. Different parametric curves were also provided as alternatives to the Gompertz distribution used to model all-cause (or CV) mortality in the model. The distributions considered were the Weibull, exponential and lognormal distributions. The company's decision to use a Gompertz distribution was based on this distribution presenting the most plausible (i.e shortest) survival time. The ERG believes that the company should have presented different modelling options, such as spline models. No other approach outside parametric curves was tried, and this might have produced suboptimal results. No alternative models were tested for the longitudinal analysis of QoL data, even though the data suggests other model specifications would have been more appropriate.
D4b: Structural	Structural scenario analysis was explored by means of a scenario analysis considering treatment discontinuation. A supplementary analysis based on associating utility scores to patients' NYHA classes and including NYHA progression in the model was supplied to the ERG as part of the clarification responses.
D4c: Heterogeneity	Heterogeneity across PARADIGM-HF patients was assessed as part of the company's subgroup analyses.
D4d: Parameter	Parametric uncertainty was assessed in univariate deterministic and multivariate PSA. However the impact of varying baseline characteristics on the model outcomes was not assessed properly.
Consistency	
C1: Internal consistency	The model is generally sound with no obvious mathematical inconsistencies.
C2: External consistency	The company stated that external consistency was assessed by comparing the results of the analysis against results of the ivabradine standard care arm in the model used in TA267.(57) Nonetheless, the ERG is concerned with the fact that: • Mortality predicted by the model is very different from mortality predictions in NICE CG108; • Life expectancy in the model is considerably different from the UK Life Tables. Nonetheless, the ERG believes that the model is a good predictor of the trial outcomes, therefore the issues enumerated above relate to the lack of

	representativeness of the trial outcomes and not with the economic model.

Abbreviations used in table: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BNF, British National Formulary; CPRD, Clinical Practice Research Datalink; CS, company's submission; CV, cardiovascular; ERG, evidence review group; HF, heart failure; HRG, health-related group; NHS, National Health System; NICE, National Institute for Health and Care Excellence; NMA, network meta-analysis; NYHA, New York Heart Association; PSA, probabilistic sensitivity analysis; PSS, Personal Social Services; PSSRU, Personal Social Services Research Unit; QoL, quality of life; QALYs, quality-adjusted life yeas; TA, Technology Appraisal; TTO, time trade-off; VKA, vitamin k agonist; WTP, willingness to pay.

5.5.2 Modelling approach and model structure

In this section the ERG discusses the modelling approach used by the company, the different health states considered, the cycle length and time horizon of the economic model and finally the perspective and discounting used in the analysis.

5.5.2.1 Modelling approach

The company's base case analysis used individual patient-level data from the PARADIGM-HF trial. Each treatment arm in the model was run using individual patient characteristics each time and was run the same number of times as the number of patients included in the analysis (8,399 patients). As the 8,399 patients were used to run both the sacubitril and the enalapril arms, the model was effectively run for 16,798 patients. At the i^{th} model run, a cohort with the same baseline profile of the i^{th} patient was assumed to enter the model, and the outcomes were calculated deterministically. The overall model outcomes were obtained by averaging the results obtained from the 8,399 patient-based cohorts, by treatment arm.

The company made the model flexible, allowing the user to run the model as a cohort Markov model where average patient characteristics of the PARADIGM-HF trial population were used as model inputs. The company states that the cohort approach does not account for non-linearities within the model and is therefore considered less accurate. It is also reported that model results were consistent across both approaches and therefore the cohort approach was only used for analyses in which the use of the patient-level approach was deemed impractical.

The approach undertaken by the company has been previously used in other economic analysis in CV conditions, where patient-level data were used to evaluate a Markov model deterministically (e.g. Griffiths *et al.*(56)). However the choice between patient-level and cohort models should be well substantiated. The company states that the cohort approach does not account for non-linearities within the model; however there is no justification as to why subgroup analysis couldn't have overcome this issue. Equally there is no mention to the extent to which the mentioned non-linearities affect model outcomes.

When patients' characteristics (e.g. age) are different across the modelled population, and these have a non-linear relationship with the model outcomes (e.g. costs and QALYs), estimating the model outcomes for a cohort of patients using average characteristics might provide a biased estimate of the average outcome across the entire population. However subgroup analysis may be used to overcome this issue in cohort models provided the outcomes within those subgroups are expected to be reasonably homogeneous.(108) Nonetheless the use of subgroup analysis and model averaging to address patient heterogeneity might become problematic when the number of categories required to define groups with homogeneous outcomes becomes large, either due to the presence of continuous variables requiring granular categorisation or due to the presence of many interacting factors.(108) Assessment of the modelling approach taken by the company suggests that:

- Some of the patients' characteristics in the PARADIGM-HF trial appear to have a non-linear relationship with model outcomes. More precisely, age was modelled using a quadratic transformation in the mortality and hospitalisation models and the natural logarithm of proBNP and eGFR was taken in the same models. Nonetheless, the impact of age on mortality and hospitalisation could potentially have been addressed through subgroup analysis in a single-cohort approach, while proBNP and eGFR are likely to have been modelled with a logarithm likelihood due to the fact that these variables cannot assume negative values and thus need to be truncated at 0.

- If there is only one prognostic factor (age) requiring subgroup analysis in order to define groups with homogeneous outcomes, this would be relatively straightforward from a modelling point of view.

Taking these issues in consideration it seems that the need for a patient-level approach is not completely justifiable in this case. The ERG believes that the company should have provided more details and a clear justification as to why this approach was preferred to a cohort model. Furthermore the fact that results across the patient-level and the cohort approach produce similar model outcomes might suggest that the cohort approach would have sufficed in this case.

One of the disadvantages of the patient-level approach undertaken by the company is the added computational burden to the analysis. For example, the PSA in the Excel model takes 7 days to run, which made it impractical for the ERG to re-run the PSA using the patient-level approach.

5.5.2.2 Health states included in the economic model

Patients start the model in the alive state, where they can receive sacubitril or enalapril in the main base case analysis and sacubitril or candesartan in the secondary base case analysis. The company's anticipated positioning of sacubitril in the HFrEF pathway is first-line treatment nonetheless the

model population is not reflective of newly diagnosed HFrEF as 78% and 23% of patients had received ACEi or ARB treatment, respectively, for at least 4 weeks before the randomisation period and also 70% of patients had been diagnosed for over 1 year. Therefore, even though the assumption that patients receive sacubitril at the beginning of the model is reasonable, the model population does not reflect a situation where sacubitril is given as a first-line treatment (this is further discussed in Section 5.5.3). Patients are assumed to remain in their original treatment arm for the rest of the economic analysis (this assumption was varied in scenario analysis) thus assuming a lifelong treatment effect. Clinical opinion sought by the ERG confirmed this is a reasonable assumption.

While in the alive health state, patients can be hospitalised, suffer a treatment-related AE (for example hypotension, cough or angioedema) and can also experience changes in their QoL due to different causes such as improvement in overall symptoms or worsening of their chronic condition due to disease progression. Given that hospitalisation, AE and changes in QoL events were not captured through explicit health states in the Markov model, patients remain in the alive state until dead. The justification to exclude these events as explicit health states in the Markov model was not provided by the company and it was only referred that the model submitted to NICE as part of TA267 had a similar structure.(57) While it may appear that the decision to model these events as simple proportions of the alive population does not seem to have any additional implications, it does prevent further transitions to be considered from any of these events. For example, mortality can only be applied to patients in the alive health state, which prevents the explicit use of an increased risk of death for patients who have been hospitalised. Arguably, since the trial captured all-cause mortality (CV and non-CV deaths together), when patients move from the alive to the dead state all the possible causes of death are being considered, nevertheless in a more aggregate (and therefore less explicit and transparent) manner.

The company decided not to include a NYHA health state (even as an implicit health state) but instead modelled an EQ-5D health state implicitly within the alive state in the model to capture changes in QoL over time (other than the ones caused by hospitalisation and AE). This approach departs from the one taken in TA267 where a NYHA implicit heath state was modelled within the alive state.(57)

At any point in the model patients in the alive health state can die, moving to the absorbing state of all-cause death. This is further explored in Section 5.5.7.

5.5.2.3 Cycle length

The cycle length in the economic model is 1 month (considered as 30.4 days). A half-cycle correction was applied, which is appropriate, however the ERG found a mistake in the half-cycle correction calculations in the QALY estimation. This issue is further explored in Section 5.5.8. Clinical opinion sought by the ERG informed that 1 month is a reasonable time-frame to capture all the relevant

changes in QoL, costs and disease progression for HFrEF patients. Furthermore, monthly cycles have been used before in economic models of HF (for example TA267(57)).

5.5.2.4 Time horizon

The time horizon considered in the economic model was lifetime (the model was run for 360 cycles, the equivalent to 30 years). A hundred percent of enalapril patients are dead 18 years after the beginning of the model (so when patients are around 81 years old) while sacubitril patients are all virtually dead about 19 years after beginning of the model (by when patients are 82 years old).

5.5.2.5 Perspective and discounting

The company adopted an NHS and personal social services (PSS) perspective for the analysis, and applied a discount rate of 3.5% for costs and outcomes beyond the first year of the model. The ERG considers this to be appropriate and in line with the NICE reference case.

In conclusion, the ERG has some issues regarding the modelling approach undertaken by the company since:

- The ERG believes that the company should have provided more details and a clear justification as to why a patient-level approach was preferred to a cohort model;
- The results across the patient-level and the cohort approach produce similar model outcomes which might suggest that the cohort approach would have sufficed.

5.5.3 Population

5.5.3.1 Population considered in the economic analysis versus the NICE final scope

The population considered by the company for this STA comprised people with symptomatic HF (NYHA II–IV) with reduced LVEF, referred to as patients with HFrEF.

Subgroup analysis included results by different age groups, region, baseline characteristics such as LVEF, NYHA class, SBP, eGFR, NT-proBNP, diabetes, hypertension, prior use of ACEi, prior use of ARB, use of BB, use of AA, time since diagnoses (in years), ischaemic aetiology, AF and prior hospitalisation. Nonetheless, the NICE final scope did not specify any subgroups of interest hence the company presented analysis beyond what was specified in the NICE scope.

The population considered by the company is largely in adherence with requirements of the NICE final scope for this STA. The company limited the population to people with symptomatic HF (NYHA II–IV) with reduced LVEF, while the final scope issued by NICE defined the population as people with chronic HF (NYHA II–IV) with systolic dysfunction.

5.5.3.2 Generalisability of modelled population

The model population characteristics were based on the PARADIGM-HF trial population. The baseline patient characteristics used in the model are presented in Table 45 and are based on FAS population. Patients' baseline characteristics were used as covariates in the regression models used to estimate mortality, hospitalisation and QoL in the economic analysis (Section 5.5.8, Section 5.5.5 and Section 5.5.9, respectively).

Table 45. Baseline population in the economic model – all treatment arms

Parameter	**Mean values used in the model (N= 8399)**
Age	63.80
Female	21.81%
Region - North America	7.17%
Region - Latin America	17.06%
Region - Western Europe	24.42%
Region - Central Europe	33.65%
Region - Asia-Pacific	17.70%
Race - white	66.01%
Race - black	5.10%
Race - Asian	17.97%
Race - other	10.93%
NYHA class I	4.63%
NYHA class II	70.63%
NYHA class III	24.03%
NYHA class IV	0.71%
NYHA class III/IV	24.74%
LVEF (%)	29.49
LVEF > median	46.25%
SBP (mmHg)	121.38
SBP > median	45.27%
Heart rate (bpm)	72.35
eGFR (mL/min/1.73m2)	67.70
eGFR ≥ 60 mL/min/1.73m2	63.56%
NT-proBNP (pg/mL)	2891.04
NT-proBNP > median	48.22%
Sodium (mmol/L)	141.46
Potassium (mmol/L)	4.51
QRS duration (ms)	117.36
BMI (kg/m2)	28.16
Diabetes	34.61%
Hypertension	70.72%
Prior ACEi use	77.77%
Prior ARB use	22.53%
BB use	93.00%
AA use	55.61%

Digoxin use	30.23%
Lipid lowering medication use	56.30%
Allopurinol use	4.83%
≤ 1 year since HF diagnosis	30.04%
1-5 years since HF diagnosis	38.48%
> 5 years since HF diagnosis	31.48%
Ischaemic aetiology	59.96%
Prior stroke	8.63%
Prior atrial fibrillation/ flutter	36.80%
Prior angina	0.40%
Prior cancer	4.31%
Current smoker	14.38%
Prior HF hospitalisation	62.79%
EQ-5D	0.78
Abbreviations used in the table: AA, aldosterone antagonists; ACEi, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin receptor blocker; BB, beta blocker; BMI, body mass index; eGFR, estimated glomerular filtration rate; EQ-5D, European Quality of life 5-Dimensions; HF, heart failure; LVEF, left ventricular ejection fraction; NT-proBNP, N terminal pro-brain natriuretic peptide; NYHA, New York Heart Association; SBP, systolic blood pressure.	

Clinical opinion given to the ERG indicated that the study population broadly reflects a typical HF trial population. However, when compared to patients seen in clinical practice, the typical HF trial patient is usually healthier than the average HF patient at diagnosis. The ERG believes that the following population characteristics in the PARADIGM-HF trial warrant further assessment:

- Mean age at baseline;
- Previous HF treatment received and time from diagnosis;
- Tolerability of sacubitril;
- Region;
- Device use at baseline.

Mean age at baseline

The average age of patients in the PARADIGM-HF trial is 64 years. Clinical opinion sought by the ERG informed that this reflects a younger population than the average UK HFrEF population, which on average, is between 76 years (males) and 80 years (females) old.(1) This means that the PARADIGM-HF trial (and therefore the model) population is, on average, over 10 years younger than the typical UK HFrEF population. This presents a major challenge in terms of the replicability and representativeness of the modelled population, especially when considering the life expectancy of newly diagnosed HFrEF patients. According to NICE Clinical Guideline (CG) 108, "heart failure has a poor prognosis: 30-40% of patients diagnosed with heart failure die within a year – but thereafter the mortality is less than 10% per year".(6) Therefore the amount of time for which patients live (and collect costs and benefits) after HFrEF diagnosis is crucial for the assessment of the cost-effectiveness

of sacubitril. This also means that the starting age of patients in the economic analysis is key. To better exemplify this issue, the ERG produced Figure 11 and Figure 12 where the survival curves show a combination of CV mortality (according to NICE CG 108 and assuming that in the first year after diagnosis patients have a 35% probability of dying, 10% in the second and third year, 9% in the fourth and fifth year, 8% in the sixth year, 7% in the seventh year and 6% thereafter) and of non-CV mortality (age-dependant mortality taken from the UK Life Tables 2013(109)) for two economic analysis, one where patients enter the model at 64 years and the other at 75 years. Using only these assumptions it can be observed that starting an economic model at 64 years instead of 75 years of age produces considerable survival gains over time. The difference between the areas under the survival curves (which can be seen in Figure 12) is quite large. For example, 15 years after the beginning of the model (so when patients are 77 years old or 90 years old respectively), survival is nearly halved for the 90 year old patients. This means that 15 years after the beginning of the economic analysis, we could have nearly twice the survival benefits purely due to the difference in the starting age of the analysis. This issue is further explored in the mortality section of this report (Section 5.5.8) where the ERG analyses the impact of the starting age of the economic analysis in the company's model.

Figure 11.Survival curves at different starting ages

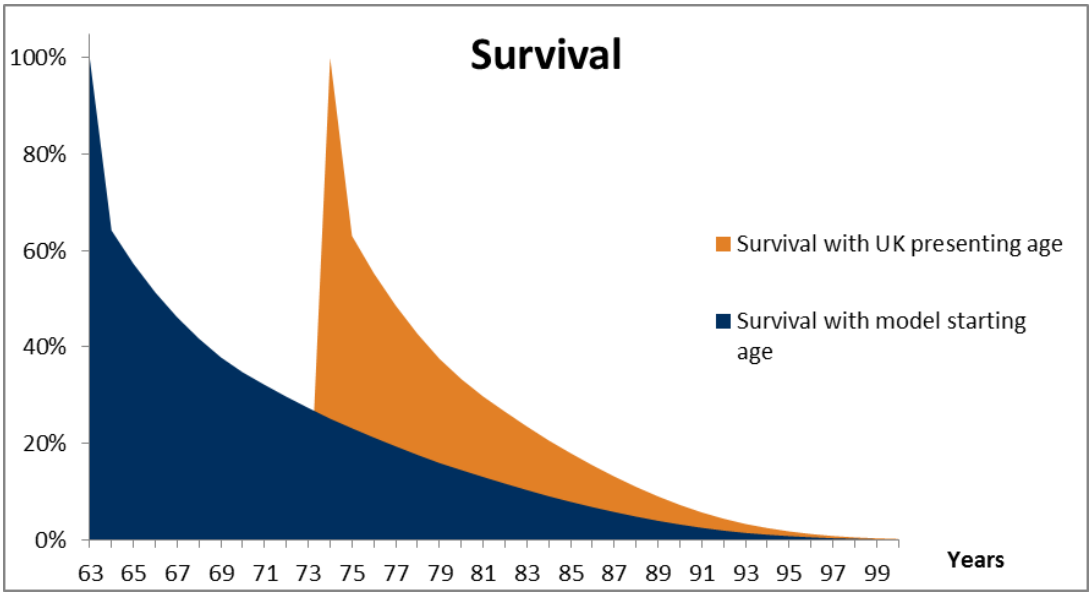
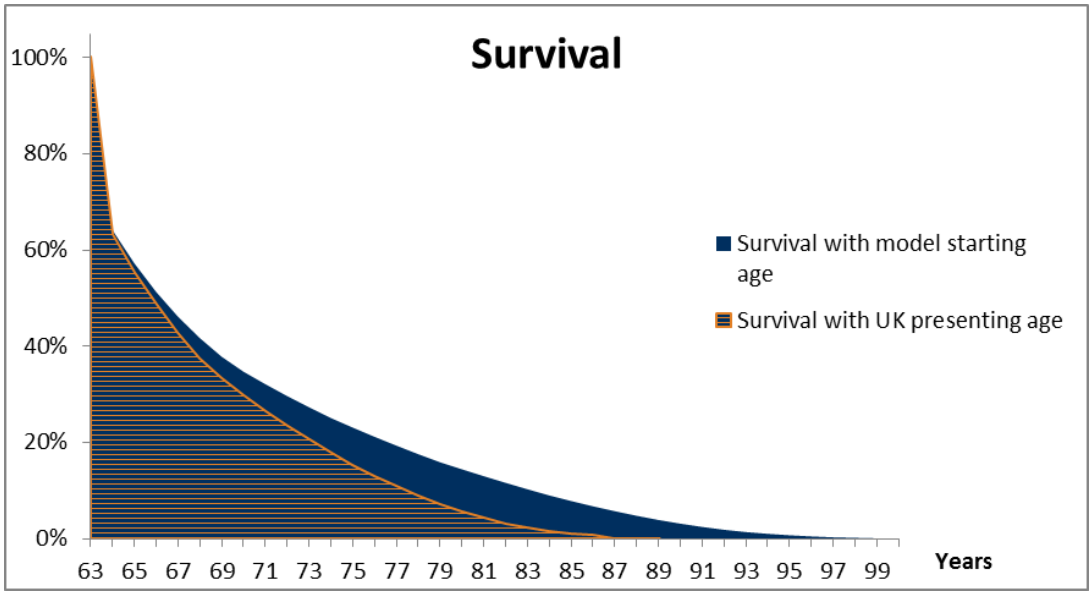


Figure 12.Survival curves at different starting ages (superimposed)



Previous HF treatment received and time from diagnosis

The company's anticipated positioning of sacubitril in the HFrEF pathway is as a first-line treatment in newly diagnosed patients. Nonetheless the model population is not reflective of newly diagnosed HFrEF patients as 78% and 23% of patients had received ACEi or ARB treatment, respectively, for at least 4 weeks before randomisation and 70% of patients had been diagnosed for over 1 year at baseline (and 31% had been diagnosed more than 5 years ago). Therefore the model population does not accurately reflect an HFrEF population for whom sacubitril would be given as a first-line treatment. Clinical opinion sought by the ERG indicated that based on the trial design, population and outcomes, the available evidence(in the ERG's clinical experts' views) only supports sacubitril as a second-line treatment option, given to HFrEF patients who are still symptomatic despite being on an ACEi drug therapy.

The ERG's clinical experts' anticipated positioning of sacubitril matches the trial design and the trial population much more closely than the use of sacubitril as a first-line treatment for newly diagnosed patients, for whom there is no available robust evidence on the effectiveness of sacubitril. To note is that the trial (and therefore the model) population reflects a chronic, stable and symptomatic (95% of patients in the NYHA class II–IV) HFrEF population that has been on ACEi (or ARB) treatment for at least 1 month.

The company also presented the TITRATION study as supporting evidence for the use of sacubitril in treatment-naïve patients.(110) However, only 6.6% of patients in TITRATION were treatment-naïve (i.e had not received ACEi or ARBs in the previous 4 weeks). In the TITRATION CSR the company acknowledges that the small number of naïve patients included in the analysis is not robust enough to draw conclusions about this group of patients.(47) Furthermore, the TITRATION study did not look at the same effectiveness outcomes as PARADIGM-HF as the latter investigated the safety and

tolerability of initiating and up-titrating sacubitril but it did look at the evolution of the NYHA in patients (including treatment-naïve patients) across treatment arms. This outcome was not fully reported in the TITRATION CSR therefore the ERG requested that the company provided it during clarification. The company only provided the evolution of NYHA for sacubitril patients (total patients and treatment-naïve patients) and did not provide the results for the enalapril arm. Therefore the additional data provided by the company is of limited value given that it does not allow a comparison between treatment arms with respect to this outcome.

Tolerability of sacubitril

In order to analyse the tolerability of valsartan, the ERG makes several comparisons across the PARADIGM-HF trial and the company's commissioned analysis of the CPRD dataset. The CPRD analysis was undertaken with the goal of characterising the burden of illness of HF in the UK in terms of demographic and clinical characteristics of patients, resource use (inpatient and outpatient), treatment patterns (medications and devices), adherence and persistence with drug therapy. Further details on the company's CPRD analysis and its use in the economic model are provided in Section 5.4.6 of this report.

To note is that the CPRD data analysis included HF patients with substantially different characteristics from the PARADIGM-HF population (Section 5.4.6). [redacted] of the CPRD patients had confirmed left ventricular dysfunction even though all patients included were HF patients. CPRD patients also presented the average co-morbidities expected for an older population [redacted] such as cancer, diabetes, kidney disease, etc. While the CPRD population presented with serious co-morbidities, one of the PARADIGM-HF inclusion criteria was that patients could not have any co-morbidities associated with a life expectancy of less than 5 years. Therefore the PARADIGM-HF population is not only younger but healthier than the CPRD population, nonetheless the CPRD population can potentially be considered more reflective of the typically presenting HF population in the UK.

The PARADIGM-HF trial included a pre-randomisation run-in phase where all patients included in the study received enalapril (10mg BID) for two weeks followed by a two-week period of sacubitril at 100mg BID which was then increased to 200mg BID for another 2 weeks (i.e. sacubitril was given for 4 weeks before randomisation). During the run-in phase [redacted] of patients in PARADIGM-HF discontinued enalapril (mean follow-up [redacted] days) while [redacted] of patients receiving sacubitril valsartan discontinued the drug (mean follow up [redacted] days). To note is that enalapril patients were already receiving an ACEi (or an ARB) for at least 4 weeks and most likely for over 1 year (70% of patients). During the randomisation phase of the trial (mean follow-up period of [redacted] years), there were 32% of discontinuations in the enalapril arm and 28% of discontinuations in the sacubitril arm of the trial.

Clinical opinion sought by the ERG noted that the discontinuation rates observed in the PARADIGM-HF trial are lower than what would be expected in clinical practice, especially with regards to valsartan (given in combination with sacubitril) and that there are no reasons to expect sacubitril valsartan would present higher tolerability than valsartan given alone. As previously mentioned in Section 4 the target dose of valsartan in the trial (in combination with sacubitril) was 160mg BID which is the maximum dose allowed for valsartan. However it seems to be uncommon for patients to tolerate such high doses of valsartan in clinical practice. According to the ERG's clinical experts' opinion the higher valsartan tolerability in PARADIGM-HF might be related to a pre-selection of patients during the run-in phase of the trial. Additionally, the study eligibility criteria set by the PARADIGM-HF protocol defined the minimum tolerable dose of valsartan to be 160mg, which seems to be higher than the average dose tolerated by patients in clinical practice. As an example, analysis of the CPRD data presented by the company shows that the average dose of valsartan tolerated by patients ([redacted]. As for enalapril, the inclusion criterion for this drug was set to be 10mg as the minimum tolerable daily dose, which seems to be lower than the average dose tolerated by patients in clinical practice. Analysis of the CPRD data presented by the company shows that the average dose of enalapril[redacted]. Therefore, while the CPRD data shows that the average dose of valsartan tolerated by patients is [redacted] lower than the minimum tolerable dose of valsartan set in the eligibility criteria of the PARADIGM-HF protocol (106mg), the average dose of enalapril tolerated by patients reported in the CPRD ([redacted]) is higher than the minimum tolerable dose of elaparil set in the eligibility criteria (10mg) of the trial. This issue is further discussed in Section 5.5.4.

Taking this in consideration, it seems that the trial (and therefore the model) population presents a higher tolerability to the intervention drugs, especially valsartan (given in combination with sacubitril) than the typical HFrEF population. This has an impact on the observed discontinuation of study drugs, which is likely to be higher in UK clinical practice than it is in the trial.

The ERG produced Table 46 which presents a summary of the discontinuation rates in the PARADIGM-HF trial and in the CPRD analysis. The ERG estimated the proportion of patients discontinuing study drugs in the run-in phase and in the randomisation phase of the trial by considering all causes for discontinuation (i.e. AEs, protocol deviations, administrative problems, lost to follow-up, death, etc.). To note is that discontinuations in the enalapril run-in (and randomisation) stages need to be interpreted with caution as these patients had been on ACEi or ARB treatment for at least 1 month, and most likely (70% of patients) for over 1 year. The same is true for valsartan (in combination with sacubitril) patients, given that 23% of patients had received an ARB at baseline.

Looking at Table 46 it can be observed that [redacted]. During the run-in phase of the trial [redacted] of patients in PARADIGM-HF had discontinued enalapril (mean follow-up [redacted] days), while [redacted] of patients receiving sacubitril valsartan discontinued the study drug (mean follow-up [redacted] days). Nonetheless, it should be noted that the tolerability in the CPRD dataset and in the trial are in respect of different drug doses. The average dose of the drugs tolerated by patients during the run-in period is not available in the PARADIGM-HF CSR, but given that the target dose for the run-in period was 10mg BID for enalapril and 100mg BID for sacubitril (followed by 200mg BID), it is likely that patients who were receiving ACEi before the start of the run-in period (and who might not have been receiving enalapril, but instead other ACEi) had to adjust to the new study drug and to a higher drug dose, leading to a peak in discontinuations even for patients who were tolerating ACEi before. The same applies to ARBs (i.e. to valsartan).

Comparing the 1 year discontinuation rates in the CPRD patients with the [redacted] discontinuation rates in PARADIGM-HF it is apparent that the trial discontinuation is substantially lower than the CPRD discontinuation (even when the trial follow-up period is twice as much as the CPRD follow-up is). When the 1 year discontinuation rates for valsartan-naïve patients, [redacted], are compared with the 28% discontinuation in the trial after a mean follow-up of [redacted] years, the difference is even bigger, with CPRD data presenting much higher discontinuation rates. In terms of discontinuation after the initial 90 days of treatment for CPRD naïve patients, around [redacted] discontinued enalapril [redacted] valsartan-naïve patients had discontinued study drug by then.

To also note is that according to the CPRD data for treatment-naïve patients, valsartan presents higher discontinuation rates than enalapril in the long-term [redacted].

Table 46. Discontinuation in the PARADIGM-HF trial and in the CPRD data analysis

Drug	**PARADIGM- HF run-in phase (mean follow-up of [redacted] for sacubitril and [redacted] for enalapril)**	**CPRD data – 90 days, all patients**	**CPRD data – 90 days, naïve patients**	**PARADIGM- HF randomisation phase, mean follow-up period of [redacted]**	**CPRD data, 1 year, all patients**	**CPRD data, 1 year, naïve patients**
Enalapril	[redacted]	[redacted]	[redacted]	**31.96%**	[redacted]	[redacted]

Valsartan (with sacubitril in PARADIGM-HF)	[redacted]	[redacted]	[redacted]	**28.08%**	[redacted]	[redacted]
Candesartan	n/a	[redacted]	[redacted]	n/a	[redacted]	[redacted]
Ramipril	n/a	[redacted]	[redacted]	n/a	[redacted]	[redacted]
Abbreviations used in table: CPRD, Clinical Practice Research Datalink.						

In summary, the tolerability (or discontinuation) of study drugs is likely to be substantially overestimated (or underestimated in the case of discontinuations) in the trial and as such, in the economic model. Different factors are likely to have contributed to an increased tolerability to study drugs in PARADIGM-HF when compared to clinical practice:

- Around 78% of patients were receiving ACEi at baseline;
- Around 23% of patients were receiving ARBs at baseline;
- Around 70% of trial patients had been diagnosed with HFrEF for over 1 year;
- The minimum tolerability inclusion criterion in the PARADIGM-HF protocol defined a minimum tolerable dose of valsartan (160mg daily) which appears to be higher than the average dose tolerated by patients in UK clinical practice;
- The minimum tolerability inclusion criterion in the PARADIGM-HF protocol defined a minimum tolerable dose of enalapril (10mg daily) which appears to be lower than the average dose tolerated by patients in UK clinical practice;
- The fact that trial patients didn't have any serious co-morbidities (the ones expected to be observed in the typically presenting HFrEF patient) and that death is included as a reason for discontinuation in both the trial and the CPRD data analysis.

As the base case economic model did not consider drug discontinuation, the company undertook a scenario analysis including drug discontinuation. Sacubitril patients were assumed to have a monthly discontinuation rate of 0.64% (the equivalent to an annual probability of discontinuation of 7.40% if we assume a constant rate) while 0.71% of enalapril patients were assumed to discontinue drug treatment every month (the equivalent to an annual probability of discontinuation of 8.24% if assuming a constant rate). This is further explored in Section 5.6.2.

Region

Around 24% of patients in PARADIGM-HF were from Western Europe. Countries included in this category were Belgium, Denmark, Finland, France, Germany, Iceland, Italy, Netherlands, Portugal, Spain, Sweden, Israel and South Africa.

Clinical expert opinion sought by the ERG informed that HF can have different causes across different geographical regions. It was also noted that the place of care is likely to have an effect on the use of medical devices, as for example it is more likely to see implants in Western Europe and North America than Latin America. The ERG's clinical experts also advised that differences in mortality across North America, Western Europe and the UK could be expected given that the UK has previously used fewer ICDs than the rest of Europe or North America. Nonetheless, it was also noted that with the 2014 NICE device guidelines, ICD implants were expected to catch up in the UK.

The company undertook subgroup analysis by region. The results of the analysis are presented in Section 5.6.2.

Device use at baseline

The use of cardiac resynchronisation therapy (CRT), cardiac resynchronisation therapy-defibrillator (CRT-D), cardiac resynchronisation therapy pacemaker (CRT-P) and implantable cardioverter defibrillator (ICD) at baseline was reported in the PARADIGM-HF CSR but not in the CS.

The ERG's clinical experts mentioned that the use of devices at baseline is an important prognostic factor for HFrEF patients and that subgroup analyses by device use should have been carried out by the company. The ERG wanted to explore this issue further by requesting these data from the company at the clarification stage, however NICE declined the ERG's request.

Opinion provided by the ERG's clinical experts was that the device use observed at baseline (Table 47) was lower than what would be expected for the typically presenting HFrEF patient within UK clinical practice.

Table 47. Device use at baseline in PARADIGM-HF

[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]		

In conclusion, the ERG is concerned with the generalisability of the modelled population, more particularly with the following issues:

- The modelled population is, on average, 10 years younger than the typical HFrEF population in the UK. The starting age in the economic model is expected to have an impact on the analysis, which is discussed in the mortality section of this report (Section 5.5.8).

- The model population does not reflect an HFrEF population for whom sacubitril could be given as a first-line treatment in newly diagnosed patients. About 78% and 23% of patients had received ACEi or ARB treatment, respectively before randomisation and 70% of patients had been diagnosed for over 1 year at baseline (and 31% had been diagnosed more than 5 years ago). Clinical opinion sought by the ERG indicated that based on the trial design, population and outcomes, the available evidence only supports the use of sacubitril in clinical practice as a second-line treatment option, given to HFrEF patients who are still symptomatic despite being on an ACEi drug therapy. The trial (and therefore the model) population reflects a chronic, stable and symptomatic (95% of patients in the NYHA class II–IV) HFrEF population who has been on ACEi (or ARB) treatment for at least 1 month.

- The tolerability of study drugs is likely to be substantially overestimated (or underestimated in the case of discontinuations) in the trial and therefore in the economic model. Different factors are likely to have contributed to an increased tolerability to valsartan in PARADIGM-HF when compared to UK clinical practice, especially the chosen minimum tolerable dose of 160mg per day as an inclusion criterion in the trial.

- Opinion provided by the ERG's clinical experts advised that the device use observed at baseline in PARADIGM-HF was lower than what would be expected in UK clinical practice.

The ERG's clinical experts mentioned that the use of devices at baseline is an important prognostic factor for HFrEF and that is should have been included in a subgroup analysis.

Finally the ERG would like to note that because the PARADIGM-HF patients are symptomatic patients, despite having been treated with ARBs and ACEi, the impact of continuing these patients on ACEi is likely to be a misrepresentation compared to what would happen in treatment-naïve patients. Given that, in principle, the ACEi treatment regimen is not effective in improving these patients' HFrEF symptoms, keeping them on the same treatment regimen is unlikely to show any improvements. This has an impact on the observed effectiveness of sacubitril, which might be overrepresented in the trial population when compared to treatment-naïve patients. This argument adds to the issue raised by the ERG that the PARADIGM-HF trial and the economic model presented by the company build the evidence base for patients receiving sacubitril as second-line treatment. However, the trial and the economic analysis herein presented should be interpreted with caution when making extrapolations to the effectiveness of sacubitril as a first-line treatment option. Finally, the ERG notes the potential bias arising from the early stop observed in the PARADIGM-HF trial, when the data observed might have been a "random high" effect, favouring sacubitril (Section 4.3 of the ERG report).

5.5.4 Interventions and comparators

5.5.4.1 Comparison with the NICE scope

The NICE final scope for this submission considered sacubitril valsartan in combination with standard care (including treatment with a BB and an AA).(3)

The CS reports that the application for the UK marketing authorisation of sacubitril was submitted on 16th December 2014. It is also stated that the CHMP has granted accelerated assessment to sacubitril and that an EMA decision regarding marketing authorization is expected in December 2015. The expected indication for sacubitril is to reduce the risk of CV mortality and morbidity in adult patients with symptomatic HF and reduced ejection fraction. It is also mentioned that in July 2015, the US FDA approved sacubitril for the treatment of HF.

The company states that the recommended starting dose for sacubitril is 100mg BID. A starting dose of 50mg BID is recommended for patients not currently taking any ACEi or an ARB, or on low doses of these agents. The dose is meant to be doubled every 2–4 weeks to the target of 200mg BID, as tolerated by the patient. It is also reported [redacted] The comparators included in the scope were as follows:

- ACEi in combination with standard care (treatment with a BB and an AA);
- ARB in combination with standard care (treatment with a BB and an AA), for whom treatment with ACEi is unsuitable.

The intervention drug considered in the economic model matches the NICE final scope.(3) With regards to the comparators included in the economic analysis:

- The ACEi considered in the economic analysis was enalapril. The inclusion of enalapril is appropriate and consistent with the NICE final scope even though clinical opinion sought by the ERG advised that ramipril is the most commonly used ACEi in the UK. Ramipril was considered in the company's scenario analysis.(3)
- The ARB considered in the economic analysis was candesartan, which appears to be appropriate.
- Standard of care considered in the economic analysis included BB, AA for both intervention and comparator arms of the model, which is appropriate. Nonetheless, according to the ERG's clinical experts' opinion, the proportion of patients receiving AA was considered to be lower than what would be expected in clinical practice.
- In addition to standard care, the company also included background therapies in both treatment and comparator arms of the model. This included digoxin, lipid lowering medications, diuretics, aspirin, anticoagulants and ADP antagonists. This reflects the PARADIGM-HF treatment regimen and was considered to be reflective of UK clinical practice according to the expert opinion provided to the ERG.

5.5.4.2 Modelled treatment regimens

The treatment regimens modelled for sacubitril and the included comparators are outlined in Table 48. Table 49 shows the background therapies modelled together with treatment and comparator drugs. The ERG notes that while the enalapril dose used in the model was based on the average dose observed in the PARADIGM-HF trial, the modelled dose of sacubitril was based on the drug target dose (even though the company reports that the modelled dose of sacubitril was the average daily dose of 375mg observed in the trial).

Overall the ERG believes that the choice of drug doses to be used in the economic model was not consistent across therapies. For example, sacubitril was based on its target doses while enalapril was based on the observed dose in the PARADIGM-HF trial. There were also inconsistencies in the chosen drug doses modelled for the background therapies. This is further reviewed in the discussion of cost estimation in the economic model (Section 5.5.9).

Table 48. Intervention and comparators modelled in the company's economic analysis

Therapy	Treatment duration	Modelled dose
Intervention		
Sacubitril valsartan	Lifetime	Sacubitril at a dose of 200mg BID, as per EMA filing*
Comparators		
Enalapril	Lifetime	18.9mg per day as per the mean dose observed in PARADIGM-HF trial
Candesartan	Lifetime	32mg taken as a one 32mg tab once daily
* The company reported that the modelled dose was 375mg as observed in the PARADIGM-HF trial, however the daily dose of sacubitril used in the model is 400mg. Abbreviations used in table: BID, bis in die; EMA, European Medicine Agency; mg, milligram.		

Table 49. Background therapies modelled in the company's economic analysis

Therapy	Modelled dose	Proportion of patients receiving therapy (based on PARADIGM-HF baseline treatment regimens)
BB (carvedilol)	25mg twice daily	93.00%
AA (spironolactone)	50mg once daily	55.61%
Digoxin	Either 62.5µg or 125µg tab once daily	30.23%
Lipid lowering drug (atorvastatin)	20 mg once daily	56.30%
Diuretics (furosemide)	One 20 mg or 40 mg tab once daily	80.22%
Aspirin	75mg once daily	51.78%
Warfarin	5mg once daily	31.97%
ADP antagonists (clopidogrel)	75mg once daily	15.00%
Abbreviations in table: AA, aldosterone antagonist; ADP, adenosine diphosphate; BB, beta blocker; mg, milligrams; µg, micrograms		

ACEi therapies modelled

The ACEi included in the economic model was enalapril. Clinical opinion provided to the ERG advised that while enalapril is the most commonly used ACEi in HF trials, it is not the most commonly used ACEi in UK clinical practice. Ramipril is the most frequently used ACEi in the UK with enalapril being prescribed to around 20% of HFrEF patients. Analysis of the CPRD data commissioned by the company also confirmed that ramipril is the most commonly used ACEi in the UK (98). One of the clinical experts advising the ERG explained that ramipril has advantages over enalapril as it appears to be better tolerated by patients and is usually given as a daily dose regimen, which helps with drug compliance. Nonetheless, comparison of enalapril and ramipril discontinuation

rates in the long-term using the CPRD data (Table 46, Section 5.5.3.2) seems to show relatively similar compliance. It was also mentioned to the ERG that a class effect can be assumed within ACEi (as assumed by the company). It should also be noted that given the expected ACEi class effect, cheaper ACEis would be expected to be more frequently used in clinical practice. The company has conducted a scenario analysis where the cost of ramipril was assumed in the model (combined with enalapril effectiveness), however the ERG found some problems in the company's scenario analysis. This is further explored in Section 5.5.9 and in Section 5.6.2.

ARB therapies modelled

The ARB included in the economic analysis was candesartan. Clinical expert opinion sought by the ERG advised that candesartan and losartan are the most commonly used ARBs in UK clinical practice.

Standard of care and background therapies modelled

Clinical expert opinion sought by the ERG advised that the therapies included in the standard of care and background regimens are generally representative of UK clinical practice, with the exception of AA. Around 60% of patients were using AA therapy at baseline in PARADIGM-HF however the ERG's clinical experts advised that about 75% of HFrEF patients receive this drug in the UK.

Treatment duration

In the PARADIGM-HF trial, sacubitril and enalapril were given until drug discontinuation or end of study period (average follow-up study period was [redacted]). In their base case economic analysis, the company assumed that sacubitril (and its comparators) are received until death. Clinical opinion sought by the ERG advised that for patients who can tolerate sacubitril the drug is likely to be taken for the rest of the patients' lives.

Scenario analysis was undertaken by the company to reflect treatment discontinuation (where patients discontinuing their original treatment switch to a different drug) and also to simulate a cessation of sacubitril effectiveness after 5 and 10 years of drug therapy. This is further explored in Section 5.6.2. Clinical opinion provided to the ERG advised that it is reasonable to assume that the sacubitril relative effectiveness will be maintained for as long as the patient is alive and receiving the drug.

The dose of sacubitril

The modelled dose of sacubitril was 400mg per day, as per the target dose of the drug in the PARADIGM-HF trial (Table 50). As previously mentioned in Section 5.5.3 the target dose of valsartan (in combination with sacubitril) in the trial was 160mg BID which is the maximum dose allowed for valsartan monotherapy (i.e. 320mg). The daily average dose of sacubitril observed in the trial was 375mg. According to clinical expert opinion provided to the ERG it is uncommon for

patients to tolerate such high dose of valsartan in UK clinical practice. One of the possible reasons for the increased tolerance to higher valsartan doses in the trial might be related to the minimum tolerability criteria set by the PARADIGM-HF protocol, which defined the minimum tolerable dose of valsartan to be 160mg daily as an eligibility criterion (Figure 13). It seems that the minimum tolerable dose of valsartan set by the PARADIGM-HF trial protocol (160mg) is likely to be higher than the average tolerated dose by patients in clinical practice. Analysis of the CPRD data presented by the company, and reported in Figure 14 below, shows that within the pre-index period of the analysis, i.e. one year prior to evidence of recorded HF diagnosis, the average daily dose of valsartan tolerated by patients was [redacted], which increased to [redacted] during the follow-up period (which consisted on the period from HF diagnosis till end of study period – 4 years, death or last health contact).

Furthermore, and as discussed in Section 5.5.3.2, the ERG has other reasons to believe that the tolerability to the observed dose of valsartan (in combination with sacubitril) in the PARADIGM-HF trial is unlikely to represent the typical valsartan tolerability (and therefore average dose of valsartan received) in clinical practice. Considering that clinical opinion provided to the ERG advised that there is no reason to expect valsartan given with sacubitril to present higher tolerability than valsartan given alone, caution should be taken when interpreting the effectiveness outcomes in the PARADIGM-HF trial as it is difficult to understand how the trial could inform the effectiveness of sacubitril if given at a lower mean dose of valsartan (for example, such as 106mg). Even though there is a small discrepancy between the average enalapril dose observed in the trial and the 4-year CPRD data analysis (dose in CPRD is [redacted]), this is substantially smaller than the discrepancy in values observed for valsartan (dose in CPRD is[redacted]).

Finally, it should be noted that the dose of candesartan modelled in the economic analysis (32mg daily) seems to be quite dissimilar to the average dose of candesartan reported in the CPRD analysis, which is around [redacted] per day during the follow-up period. Clinical opinion sought by the ERG advised that the observed daily mean dose of candesartan in UK clinical practice is around 16mg.

The dose of enalapril

The minimum tolerable dose of enalapril specified in the PARADIGM-HF inclusion criteria protocol was 10mg daily. This dose seems to be lower than the average dose tolerated by patients. Analysis of the CPRD data presented by the company shows that within the pre-index period of the analysis, the average daily dose of enalapril tolerated by patients was [redacted], which decreased to [redacted] over the follow-up period. This compares to an observed average daily dose of 18.9mg in the PARADIGM-HF trial (Table 50).

Even though there is a small discrepancy between the average dose observed in the trial and the 4-year CPRD data analysis for enalapril (13% lower in CPRD), this is substantially smaller than the discrepancy in values observed for valsartan.

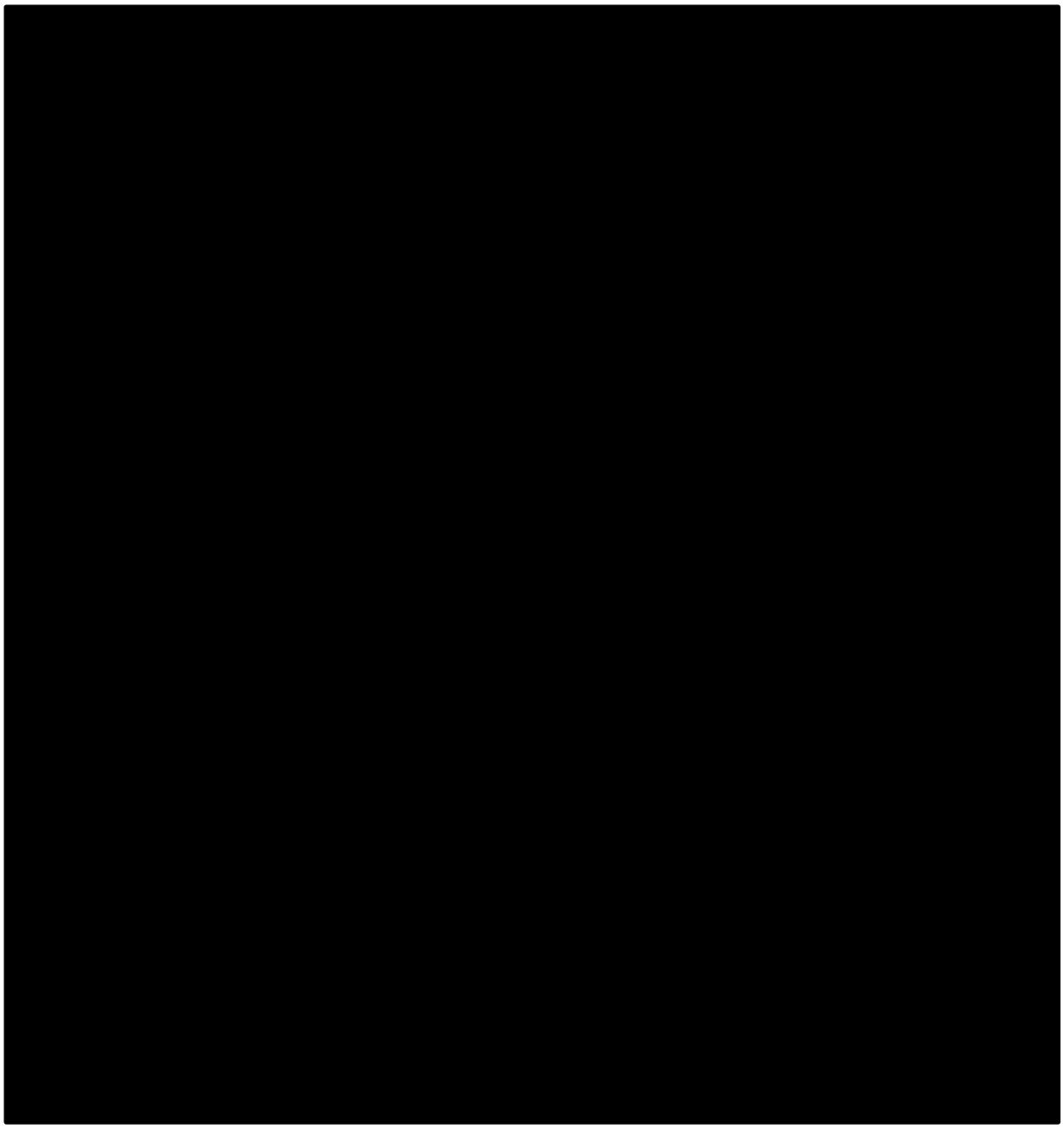
Table 50. Sacubitril and enalapril dose summary, safety analysis set (reproduced from CSR, pg 138, Table 12-3)

Dose	Sacubitril N=4201	Enalapril N=4228
Mean daily dose per patient in mg (SD)	374.86 (62.426)	18.88 (2.885)
Mean daily target dose per patient in mg	400.00	20.00
Abbreviations: mg, milligrams; SD, standard deviation		

Figure 13. Minimum required pre-study daily doses of commonly prescribed ACEi and ARBs (PARADIGM-HF protocol, page 34, Table 4-1).

ACEIs	Minimum dose	ARBs	Minimum dose
Enalapril	10 mg	Candesartan	16 mg
Benazepril	20 mg	Eprosartan	400 mg
Captopril	100 mg	Irbesartan	150 mg
Cilazapril	2.5 mg	Losartan	50 mg
Fosinopril	20 mg	Olmesartan	10 mg
Lisinopril	10 mg	Telmisartan	40 mg
Moexipril	7.5 mg	Valsartan	160 mg
Perindopril	4 mg		
Quinapril	20 mg		
Ramipril	5 mg		
Trandolapril	2 mg		
Zofenopril	30 mg		

Figure 14. Drug dose achieved during pre-index and follow-up periods for subjects with left ventricular disorder, company's CPRD data analysis, n=8,646



In conclusion, the ERG believes that the modelled treatment regimens broadly reflect the PARADIGM-HF trial, even though there was some inconsistency in the chosen treatment doses. However the ERG is concerned with the representativeness of the modelled treatment regimens, more specifically with regards to the dose of valsartan (in combination with sacubitril) given to patients. The ERG has reasons to believe that the tolerability to the observed dose of valsartan (in combination with sacubitril) in the PARADIGM-HF trial is unlikely to accurately represent valsartan tolerability (and therefore average dose of valsartan received) in UK clinical practice. Therefore, caution should be taken when interpreting the effectiveness outcomes in the PARADIGM-HF trial as it is difficult to understand how the trial could inform the effectiveness of sacubitril if given at a lower mean dose of valsartan (for example, such as 106mg). Even though there is a small discrepancy between the

average enalapril dose observed in the trial and the 4-year CPRD data analysis, this is substantially smaller than the discrepancy in values observed for valsartan.

5.5.5 Treatment effectiveness

In this section the ERG focus on the probability of hospitalisation estimated within the different arms of the economic model. The mortality section (Section 5.4.7) critiques the company's estimation of the transition probabilities between the alive and the dead states and finally Section 5.5.6 covers the estimated QoL within the model.

Hospitalisation data captured in the PARADIGM-HF trial looked at all-cause hospitalisation, HF, other CV and non-CV related hospitalisations. The company decided to develop an all-cause hospitalisation regression model. The ERG believes that the following issues are worth further discussion:

- Use of all-cause hospitalisation data versus CV hospitalisation data from the PARADIGM-HF trial (Section 5.5.5.1);
- Use of estimated data for the within trial period (Section 5.5.5.2);
- Modelling approach (Section 5.5.5.3);
- Starting age in the model (Section 5.5.5.4);
- Model predicted outcomes (Section 5.5.5.5);
- Comparison with ARBs (Section 5.5.5.6).

5.5.5.1 All cause hospitalisation versus CV-related hospitalisation

The company decided to build an all-cause mortality model given that a statistically significant reduction in all-cause hospitalisation, HF, CV and non-CV hospitalisation was observed in the trial. To note is that sacubitril-related hospitalisation in the PARADIGM-HF trial was only modestly lower than enalapril-related hospitalisation (Table 51).

Even though there was a statistical significant reduction for all analysed types of hospitalisation with sacubitril compared with enalapril, this does not necessarily hold true for other causes of hospitalisation which were not analysed separately in the analysis. In their all-cause hospitalisation model, the company assumed that sacubitril reduces hospitalisation equally for any cause however as it can be observed from Table 51, it does not appear to be the same for all causes and this could impact the cost of hospitalisation. However, given the small variation in the differential across

different reasons for hospitalisation the ERG does not believe this assumption to be a major issue in the economic analysis.

Furthermore, because all-cause hospitalisation included the more serious AEs managed in the hospital, the consequence of assuming equal reasons for hospitalisation admission across treatment arms is that the incidence of AEs leading to hospitalisation was effectively reduced at the same rate as hospitalisations. Given that the incidence of AEs leading to hospitalisation is unknown by the ERG, it is unclear if this assumption has any impact in the model (for example, it may be that hypotension leading to hospitalisation was higher in the sacubitril arm than in the enalapril arm of the trial).

Table 51. Total hospitalisation in the PARADIGM-HF trial

	Sacubitril (n=4187)	**Enalapril (n=4212)**	**Sacubitril monthly probability**	**Enalapril monthly probability**
HF diagnosis	20.32%	25.62%	0.75%	0.95%
Other CV diagnosis	32.60%	34.62%	1.20%	1.29%
Non-CV diagnosis	32.19%	35.99%	1.18%	1.34%
All cause	85.12%	96.23%	3.09%	3.53%

Abbreviations used in table: CV, cardiovascular; HF, heart failure.
Mean follow-up: 2.26 years in the sacubitril valsartan arm and 2.23 in the enalapril arm.
Source: Packer *et al*.(70), calculations undertaken by the ERG

5.5.5.2 Use of estimated data within the trial period

The company decided to model the within trial period (approximately 4 years) with predicted data from the hospitalisation model instead of using observed trial data. This approach is less robust as it uses estimated data instead of real data when the latter is available. Even though it would have been incompatible to use Kaplan-Meier data with the patient-level approach, the company should have provided a scenario analysis using these data and a mean cohort approach. During the clarification stage, the ERG requested that the company run their base case model using observed hospitalisation data from the PARADIGM-HF trial to model the within trial period, for a time period of 3 years (to reflect the trial period for which there are reliable data available) and for a lifetime horizon, combining observed data with extrapolated data. Results provided by the company after clarification showed relatively small variations in the final ICER. However due to time constraints, the ERG could not verify this additional analysis as the company provided the Excel model used to run the scenario analysis very late in the STA process.

5.5.5.3 Modelling approach

The company's base case analysis modelled the likelihood of a patient experiencing a hospitalisation event using a negative binomial regression model. Predicted all-cause hospitalisation rates were determined by the treatment received by the patient (sacubitril or enalapril) and patients' baseline

characteristics, taken from the PARADIGM-HF trial. As mentioned in Section 5.5.2, the company's base case analysis used individual patient-level data from the PARADIGM-HF trial however the model was made flexible, allowing the user to run the model as a cohort Markov model where average patient characteristics from the PARADIGM-HF population were used as model inputs.

The ERG identified a study conducted by Jhund *et al.* which took PARADIGM-HF data to study all-cause, CV mortality and HF hospitalisation across patients of different ages.(7) The ERG notes that the company did not mention this study in their submission, even though the study was commissioned by Novartis. The ERG now provides a brief overview of the Jhund *et al.* study statistical analysis and outcomes.(7)

Statistical analysis

The PARADIGM-HF trial population (8,399 patients) was partitioned into four mutually exclusive age categories: <55 years, 55–64 years, 65–74 years and ≥75 years. The primary outcome of the study was a composite of death from CV causes or first hospitalisation for HF. Secondary outcomes included time to death from any cause, change from baseline to 8 months in the clinical summary score on the KCCQ and others. AEs were also captured. All these outcomes were analysed for the different age groups. The effect of sacubitril compared with enalapril was examined with a Cox regression model. Age was modelled as a continuous variable and a fractional polynomial was constructed for age and entered into the model as an interaction term with treatment. The authors mention that the polynomial allowed for the possibility of a non-linear effect of treatment by age to be modelled. A logistic regression model was used to test for the presence of an interaction effect between age and treatment. The authors also examined a sex by treatment interaction and an age by treatment by sex interaction. The proportion of patients with a 5-point fall on the KCCQ questionnaire at 8 months was examined in a logistic regression model with an interaction term between age and treatment. The effect of region and differences in baseline characteristics was also analysed in sensitivity analysis as well as a region by age by treatment interaction.

Results

There were 1,624 (19.3%) patients in the <55 years' category while 2,655 (31.6%) patients were between 55 and 64 years and 2,557 (30.4%) patients were between 65 and 74 years old. There were 1,563 (18.6%) patients in the ≥75 years' category. Overall the study found that there were no significant interactions between all the variables analysed and study outcomes, except for age. Even though the HR for sacubitril compared with enalapril for the primary composite outcome, CV death, HF hospitalisation and all-cause mortality was below 1 in all the age categories, the HRs across different age categories were different and became non-statistically significant for patients above 75 years old.

Clinical expert opinion sought by the ERG confirmed that the assumption of constant hospitalisation over time is not reflective of UK clinical practice. For example, a higher proportion of interventional procedures and shorter length of stay would be expected for younger patients than for older patients. The impact of this assumption on the cost of hospitalisation is explored in Section 5.5.9. The company undertook a scenario analysis in which the baseline annual hospitalisation rate is assumed to increase by 10% of the original baseline rate each year (results are presented in Section 5.6).

5.5.5.4 Starting age in the model

The ERG believes that there are two distinct issues related with the starting age in the economic model. Firstly, there is the issue of the effectiveness of sacubitril in older people. This is particularly relevant as according to the ERG's expert opinion and CPRD data, the average UK HF patient is 75 years old (or older). Secondly there is the issue of running the economic analysis with a younger population, which (even if we assume that the effectiveness of sacubitril remains unchanged with age) lives longer and therefore accrues the benefits associated with the drug for longer. Again, the extent to which this is relevant lies in how representative the starting age (64 years old) of the modelled population is of the average UK patient, and for how long the average HF patient can potentially benefit from the effectiveness of sacubitril. The effectiveness of sacubitril in preventing hospitalisation across different age groups is now discussed, while the starting age in the economic model is discussed in the mortality section (Section 5.5.7.4).

Effectiveness of sacubitril in preventing hospitalisation across different age groups

The Jhund *et al.* study results are presented in Figure 25 and these show that for patients in the 65–74 years and ≥75 years' category, none of the hospitalisation HRs for sacubitril versus enalapril are non-statistically significant.(7) In fact, all the HRs reported for the different outcomes in the ≥75 years' category are non-statistically significant. The results of the Jhund *et al.*(7) study need careful interpretation:

1. The HRs presented in the analysis might be reflecting a trend in the effectiveness of sacubitril compared with enalapril. For example, the HF hospitalisation in the 55 to 64 years age group is 0.74 but this value changes to 0.86 in the 65 to 74 years age group. This represents a "loss" in sacubitril effectiveness by 12%. However the 95% confidence intervals are quite wide for most reported HRs and some HRs are non-statistically significant, especially in older groups;

2. It could also be argued that the different HRs presented consistently follow a similar trend and are non-statistically significantly different from one another. The difference in point estimates might be explained by other factors (such as smaller sample sizes within the subgroups, or powering calculations within subgroups).

Therefore while sacubitril appears to maintain the same direction of effect across age groups, the size of the effect is not as easily established. The authors in Jhund *et al.* conclude that the effect of sacubitril compared with enalapril was consistent across age groups even though HRs were non-statistically-significant in older groups.(7) Given that the average UK HFrEF presenting patient is 75 years or older, age is an important factor in assessing the cost-effectiveness of sacubitril.

Figure 15. Clinical outcomes in Jhund *et al.* according to age category.

	<55 years (n = 1624)		55–64 years (n = 2655)		65–74 years (n = 2557)		≥75 years (n = 1563)	
Outcome	**Enalapril (n = 786)**	**LCZ696 (n = 838)**	**Enalapril (n = 1382)**	**LCZ696 (n = 1273)**	**Enalapril (n = 1265)**	**LCZ696 (n = 1292)**	**Enalapril (n = 779)**	**LCZ696 (n = 784)**
CV death or HF hosp.								
No. rate[a]	204 13.4 (11.7, 15.3)	178 10.4 (9.0, 12.0)	352 12.5 (11.3, 13.9)	253 9.6 (8.5, 10.8)	329 12.7 (11.4, 14.2)	275 10.1 (8.9, 11.3)	232 14.8 (13.0, 16.8)	208 12.7 (11.1, 14.6)
HR[b]	0.78 (0.64, 0.96)		0.76 (0.65, 0.90)		0.80 (0.68, 0.93)		0.86 (0.72, 1.04)	
CV death								
No. rate[a]	127 7.7 (6.5, 9.2)	117 6.4 (5.4, 7.7)	199 6.4 (5.6, 7.4)	144 5.1 (4.4, 6.0)	210 7.5 (6.6, 8.6)	163 5.5 (4.8, 6.5)	157 9.2 (7.9, 10.8)	134 7.7 (6.5, 9.1)
HR[b]	0.84 (0.65, 1.08)		0.79 (0.64, 0.98)		0.74 (0.60, 0.90)		0.84 (0.67, 1.06)	
HF Hosp.								
No. rate[a]	112 7.3 (6.1, 8.8)	93 5.4 (4.4, 6.6)	223 7.9 (7.0, 9.0)	156 5.9 (45.1, 6.9)	188 7.3 (6.3, 8.4)	169 6.2 (5.3, 7.2)	135 8.6 (7.3, 10.2)	119 7.3 (6.1, 8.7)
HR[a]	0.75 (0.57, 0.98)		0.74 (0.61, 0.91)		0.86 (0.70, 1.06)		0.85 (0.66, 1.09)	
All-cause death								
No. rate[a]	148 9.0 (7.6, 10.5)	131 7.2 (6.1, 8.6)	231 7.5 (6.6, 8.5)	183 6.5 (5.6, 7.5)	251 9.0 (7.9, 10.2)	215 7.3 (6.4, 8.4)	205 12.0 (10.5, 13.8)	182 10.5 (9.0, 12.1)
HR[b]	0.80 (0.64, 1.02)		0.87 (0.72, 1.06)		0.81 (0.68, 0.97)		0.87 (0.71, 1.07)	

CV, cardiovascular; HF, heart failure; HR, hazard ratio.
[a]Rate per 100 patient-years (95% CI). [b]Hazard ratio (95% CI).

5.5.5.5 Model predicted outcomes

The number of mean hospitalisations predicted by the economic model is presented in Table 52. The values presented are the mean number of hospitalisations per patient during an average expected survival of 7.24 years for sacubitril and 7.90 years for enalapril. Table 53 presents the mean annual hospitalisations per patient predicted in the model and observed in the trial. The values are not dissimilar, indicating that the model hospitalisation predictions are in line with the mean number of hospitalisations observed in the trial.

Table 52. Mean number of hospitalisations per patient predicted by the company's model

Component	ACEi	Sacubitril valsartan	Incremental
HF hospitalisations	0.77	0.71	-0.06
Other CV hospitalisations	1.13	1.04	-0.08
All-cause hospitalisations	0.42	0.36	-0.06
Abbreviations used in table: ACEi, angiotensin-converting enzyme inhibitor; CV, cardiovascular; HF, heart failure.			

Table 53. Mean annual number of hospitalisations per patient predicted and observed

Component	ACEi (predicted)	Sacubitril valsartan (predicted)	ACEi (observed)	Sacubitril valsartan (observed)
HF hospitalisations	0.11	0.09	0.12	0.10
Other CV hospitalisations	0.16	0.13	0.17	0.16
All-cause hospitalisations	0.36	0.42	0.57	0.77
Abbreviations used in table: ACEi, angiotensin-converting enzyme inhibitor; CV, cardiovascular; HF, heart failure.				

5.5.5.6 Secondary base case analysis

In the secondary base case analysis, the all-cause hospitalisation model used the NMA results to estimate the effectiveness of sacubitril compared with candesartan. As mentioned in Section 4.3 of the report, the ERG is concerned that the core NMA population does not exactly match the PARADIGM-HF trial population and that there is wide variability in the doses of the drugs included. The NMA analysis shows all-cause hospitalisation to be similar across sacubitril and ARBs (p(better)=[redacted] for sacubitril vs [redacted] for ARBs) (CS, Table 32, page 90). The ERG also notes that the 95% credible intervals around the NMA HRs for hospitalisation indicate that the differences between ARNI vs ARBs to be non-statistically significant at the 5% significance level.

In conclusion, while sacubitril appears to maintain the same direction of effect across age groups, the size of the effect is not as easily established. The authors in Jhund *et al.* conclude that the effect of sacubitril compared with enalapril was consistent across age groups even though HRs were non-statistically-significant in older groups.(7) Given that the average UK HFrEF presenting patient is 75 years or older, age is an important factor in assessing the cost-effectiveness of sacubitril.(1)

5.5.6 Adverse events

The company assumed that all-cause hospitalisation included all the relevant serious AEs. Therefore the costs and impact on patients' QoL of serious AEs were assumed to be captured through the all-cause hospitalisation model, while the considered "less serious AEs" were modelled independently from hospitalisation. These consisted on hypotension, elevated serum creatinine, elevated serum potassium, cough and angioedema. Nonetheless, clinical expert opinion provided to the ERG explained that some of the considered "less serious AEs" can have a substantial impact on patients' QoL depending on their severity. The more severe versions of these AEs should have been included in the all-cause hospitalisation regression model however, as discussed in Section 5.5.5, some of these events were not included in the hospitalisation model.

AEs were based on the FAS population as opposed to the SAF as the company considered that this, "ensured consistency with the modelling of clinical and QoL outcomes…which were also based on the FAS population". The company also reported that, "there are no substantial differences between

the percentage of AEs in the FAS and SAF populations". The ERG reproduces the FAS analysis of AEs in Table 54 (previously reported in Section 5.4.3) for ease of reference, together with the SAF analysis (Table 55). The SAF analysis provided in the CSR only reported the total number of the events of interest for investigator-reported AEs, therefore while Table 55 presents investigator-reported AEs, Table 54 reports all AEs in the FAS analysis (the investigator-reported AEs in the FAS were not provided by the company).

The monthly probabilities of hypotension, cough and angioedema are very similar across the FAS and the SAS. However, the monthly probabilities of elevated serum creatinine and elevated serum potassium are quite different across the FAS and the SAF populations. Nonetheless, given the very small frequency of these events, the ERG is not concerned with this discrepancy.

Table 54. Monthly probability of AEs based on FAS, double-blind period (reproduced from CS, pg 136, Table 56)

Event	Sacubitril valsartan (n=4187)			Enalapril (n=4212)		
	Number†	Mean annual rate	Mean monthly probability	Number†	Mean annual rate	Mean monthly probability
Hypotension	588	0.06	0.52%	388	0.04	0.35%
Elevated serum creatinine	139	0.02	0.12%	188	0.02	0.17%
Elevated serum potassium	674	0.07	0.61%	727	0.08	0.66%
Cough	474	0.05	0.42%	601	0.07	0.54%
Angioedema	19	0.00	0.02%	10	0.00	0.01%

†Absolute number of each adverse event, taken from McMurray *et al.(2)*

Table 55. Investigator reported AEs based on SAS, double-blind period (mean follow-up 27 months)

Event	Sacubitril valsartan (n=4203)		Enalapril (n=4229)	
	Number†	Mean monthly probability	Number†	Mean monthly probability
Hypotension	[redacted]	[redacted]	[redacted]	[redacted]
Elevated serum creatinine	[redacted]	[redacted]	[redacted]	[redacted]
Elevated serum potassium	[redacted]	[redacted]	[redacted]	[redacted]
Cough	[redacted]	[redacted]	[redacted]	[redacted]
Angioedema	[redacted]	[redacted]	[redacted]	[redacted]

†Absolute number of each adverse event, taken from PARADIGM-HF CSR, Table 14.3.1-1.8

The ERG also reports the SAF analysis of AEs during the run-in period of the PARADIGM-HF trial (Table 56). Compared with the SAF analysis over the double-bind period of the trial, the mean monthly probability of events occurring is considerably higher across all events in the run-in phase.

This is unexpected, especially for enalapril, given that patients had been on ACEi treatment for at least 1 month (and most likely for over 1 year). As previously discussed in Section 5.5.3, this could be due to the fact that patients receiving ACEi before the start of the run-in period were likely to be on an ACEi at a lower drug dose, and had to adjust to a higher drug dose (and possibly a new ACEi), leading to a peak in discontinuations even for patients who were tolerating ACEi before. The same applies to ARBs (i.e. to valsartan) although to a less extent given that fewer patients were on ARBs at baseline.

Table 56. Investigator reported AEs based on SAS, run-in period (mean follow-up 31 days for sacubitril and 19 days for enalapril)

Event	Sacubitril valsartan (n=9419)		Enalapril (n=10513)	
	Number†	Mean monthly probability	Number†	Mean monthly probability
Hypotension	[redacted]	[redacted]	[redacted]	[redacted]
Elevated serum creatinine	[redacted]	[redacted]	[redacted]	[redacted]
Elevated serum potassium	[redacted]	[redacted]	[redacted]	[redacted]
Cough	[redacted]	[redacted]	[redacted]	[redacted]
Angioedema	[redacted]	[redacted]	[redacted]	[redacted]

† Absolute number of each adverse event, taken from PARADIGM-HF CSR CSR, Table 14.3.1-1.8
Mean follow-up: [redacted] days for sacubitril and [redacted] days for enalapril

Finally, all AE are estimated as "one-off" events each cycle, with the exception of hypotension and cough, which were assumed to last for 64.9 days and 73.3 days, respectively. Clinical opinion sought by the ERG advised that cough symptoms will usually persist until drug discontinuation (which is not accounted for in the economic model) and that hypotension can also last for a very prolonged period of time.

5.5.7 Mortality

Mortality data captured in the PARADIGM-HF trial included all-cause mortality, CV mortality and non-CV mortality. The company decided to develop an all-cause mortality survival model fitted with a Gompertz distribution and conducted an alternative analysis where CV mortality death from PARADIGM-HF was used (also fitted with a Gompertz model) in combination with non-CV mortality taken from UK life tables. The ERG believes that the following issues warrant further discussion:

- Use of all-cause mortality data versus CV mortality data from PARADIGM-HF (Section 5.5.7.1);
- Use of estimated data for the within trial period (Section 5.5.7.2);
- Modelling approach (Section 5.5.7.3);

- Starting age in the model (Section 5.5.7.4);
- Comparison with ARBs (Section 5.5.7.5).

The ERG would like to note that the generalisability (or lack thereof) of the modelled population impacts on the estimated mortality in the model. The fact that the PARADIGM-HF trial population was not a newly diagnosed HFrEF population (78% and 23% of patients had received ACEi or ARB treatment, respectively, before randomisation and 70% of patients had been diagnosed for over 1 year at baseline and 31% had been diagnosed more than 5 years ago) also has an impact on mortality in the model.

The ERG also notes the potential bias arising from the early stop observed in the PARADIGM-HF trial, at which point the data observed might have been a "random high" effect, favouring sacubitril (see Section 4.3).

Figure 16 shows the estimated mortality in the economic model up to year 10 using the all-cause mortality approach and the CV-mortality approach. It can be observed that at the end of year 1, less than 10% of patients in the model had died and that by the end of year 2 less than 20% of patients had died in both treatment arms. Kaplan-Meier data from the trial shows roughly the same curves (Figure 17). However, when compared to the NICE CG108 prognosis that 30% to 40% of patients diagnosed with HF die within a year (simulated by the ERG in Figure 18), the observed and predicted mortality in the CS seem substantially different (less than half).(6)

The ERG believes that mortality in the model (and in the trial) portrays a scenario representative of the use of sacubitril for established patients. This reinforces the ERG's view that the evidence presented in this submission is most applicable to the use of sacubitril as a second-line treatment option, given to HFrEF patients who are still symptomatic despite being on an ACEi drug therapy. Accordingly, the ERG would like to note that regardless of the technical issues discussed in this section, the mortality observed in the trial is not reflective of newly diagnosed HF patients.

In addition, as the PARADIGM-HF trial's patients are symptomatic, despite having been treated with ARBs and ACEi, the impact of continuing these patients on ACEi is likely to be a misrepresentation compared to what would happen in ACEi naïve patients. Given that, in principle, the ACEi treatment regimen is not effective in improving these patients' HFrEF symptoms, keeping them on the same treatment regime is unlikely to show any improvements. This has an impact on the observed effectiveness of sacubitril, which might be overrepresented in the trial population when compared to treatment-naïve patients. Therefore, the trial and the economic analysis herein presented should be interpreted with caution when making extrapolations to the effectiveness of sacubitril as a first-line treatment option. Finally, the ERG notes the potential bias arising from the early stop observed in the

PARADIGM-HF trial, at which point the data observed might have been a "random high" effect, favouring sacubitril (see Section 4.3).

The ERG did not run any additional analyses to try and replicate the mortality of newly diagnosed patients reported by the NICE CG 108 as too many assumptions would have had to be made to approximate a treatment-naïve population. More specifically the ERG would have to make assumptions regarding the effectiveness of sacubitril compared with enalapril in treatment-naïve patients over time, assume how drug treatments would be tolerated over time, and how drug discontinuations would occur in this population.(6)

Figure 16.Survival in the company's model

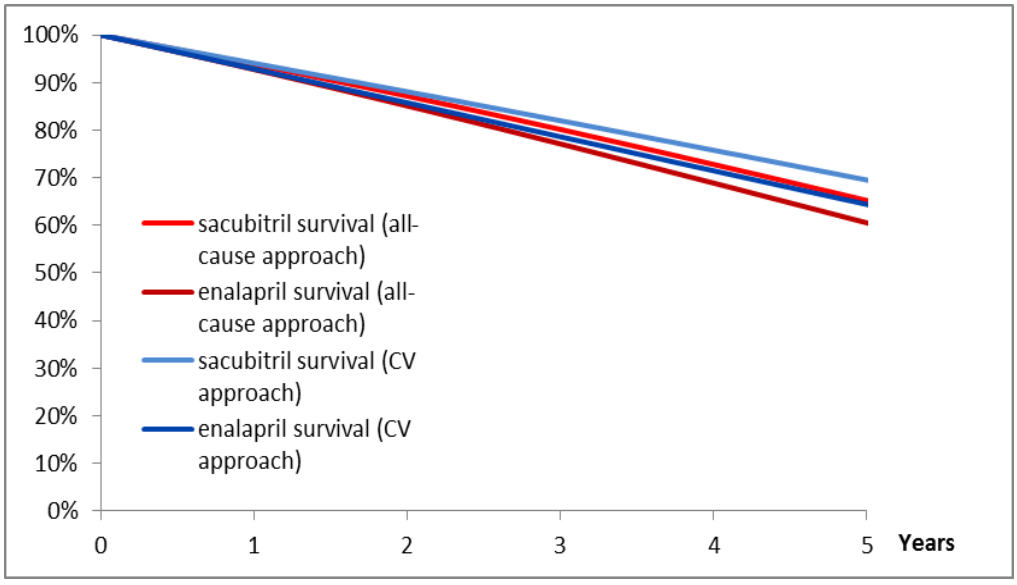


Figure 17.Kaplan-Meier curves from PARADIGM-HF

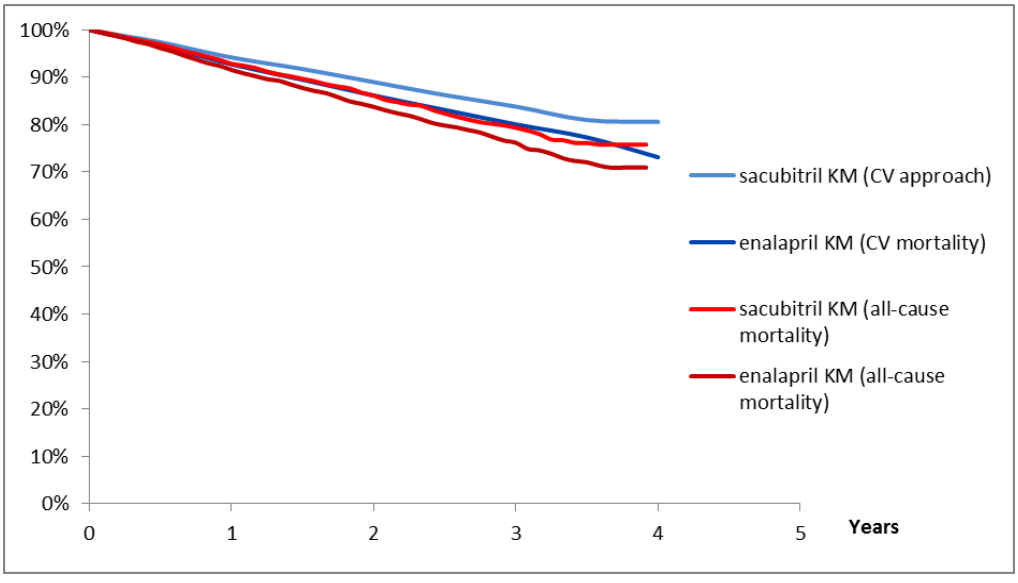
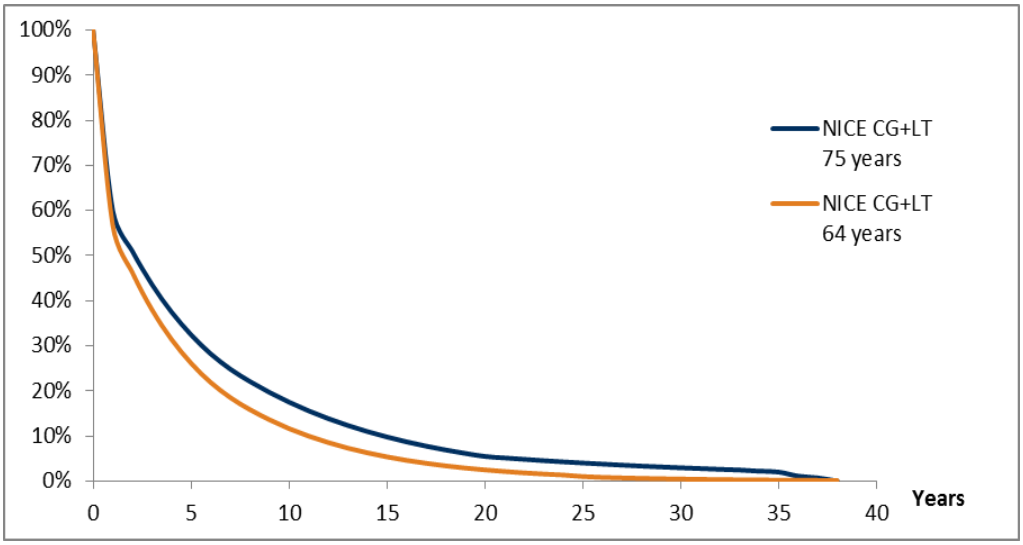
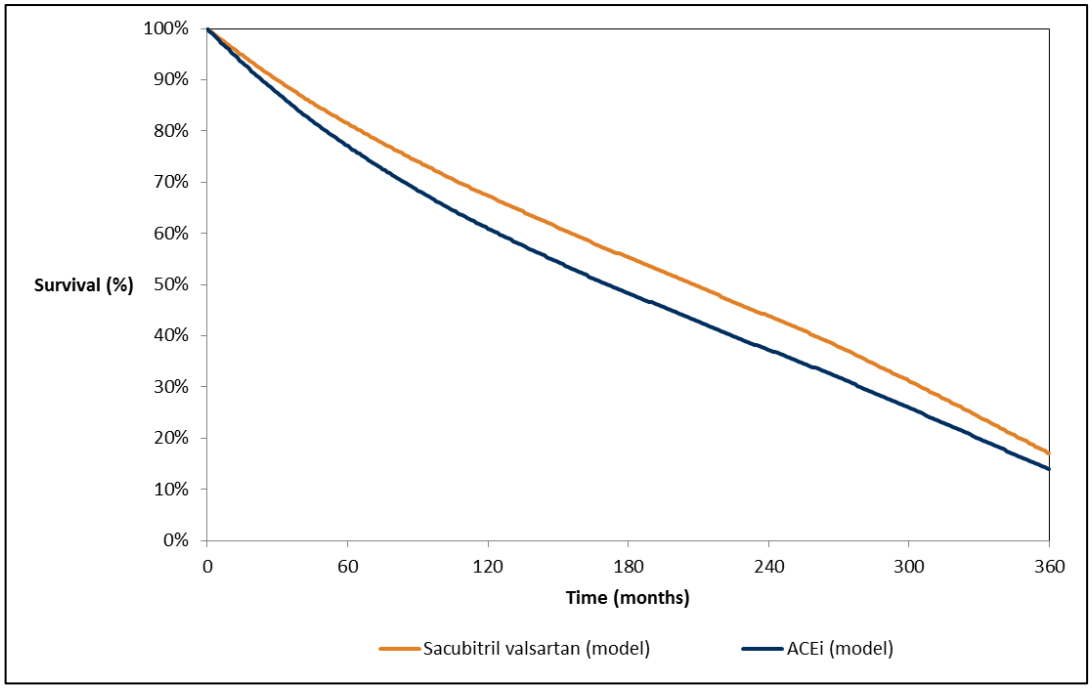


Figure 18. Survival curves produced by the ERG using NICE CG 108



To note is that upon request for clarification the company ran subgroup analysis for patients diagnosed ≤1 year. Figure 19 presents the estimated mortality in the subgroup analysis and it shows that 5 years after diagnosis (for patients diagnosed ≤1 year at baseline) less than 20% of patients have died in the enalapril and sacubitril arms of the model. Also, less than 10% of patients have died 1 year after the beginning of the analysis. Clearly this does not reflect the expected mortality for newly diagnosed patients. The ERG received the company's additional analysis late in the STA process limiting the opportunity to review the company's additional models in detail. Nonetheless, the outputs of the model in terms of mortality seem to be implausible from a clinical point of view. In particular, when analysing the tails of the survival curves presented in Figure 19, they predict that 30 years after the beginning of the economic analysis, more than 15% of patient are still alive and 94 years old.

Figure 19. Survival curves in company's additional subgroup analysis for patients diagnosed ≤1 year (cardiovascular mortality approach)



5.5.7.1 All-cause mortality versus CV mortality

The company decided to build an all-cause mortality model given that this was considered the most conservative approach (i.e the approach producing the higher ICER). The ERG believes that the CV mortality approach is likely to be more robust from a theoretical point of view since:

- Rates of non-CV mortality were not statistically significantly different between sacubitril and enalapril in the PARADIGM-HF trial;
- Reduction in CV mortality is the key benefit of sacubitril in the PARADIGM-HF trial;
- The PARADIGM-HF trial excluded patients with co-morbidities associated with life expectancy lower than 5 years, thus in theory underestimating the non-CV mortality in the trial when compared with the age-dependant non-CV mortality in the UK population;

The company acknowledged these strengths but also the limitation of a CV-model approach (for example the fact that there are no reliable estimates for non-CV mortality for HF patients). Still, there are considerable flaws in using an all-cause mortality approach as it includes the non-CV mortality observed in the trial. Non-CV mortality was higher in the sacubitril than in the enalapril arm of the model, however it was not statistically significantly different across treatments arms. Upon request for clarification the company explained that, "this could be related to the statistically significant reduction in CV deaths in the sacubitril valsartan arm compared to enalapril (which may result in a slightly

increased number of patients dying from non-CV causes in sacubitril valsartan)". Furthermore, when comparing the non-CV mortality predicted by the model with the non-CV mortality in the UK life tables, the non-CV mortality predicted by the model is higher than non-CV mortality reported in the UK life tables. This observation holds for sacubitril (Figure 20) as well as enalapril (Figure 21). This is counterintuitive given that the modelled population (i.e. the trial population) was selected so that patients presenting with co-morbidities decreasing life expectancy for less than 5 years were excluded from the trial. Thus when compared to the UK population at the same age (who not only present with HF but also with cancer, liver disease etc.) it would be expected that the non-CV mortality would be lower in the trial than in the general UK population. To note is that non-CV mortality predicted by the model is similar to non-CV mortality observed during the trial period.

The ERG requested that the company clarified why non-CV mortality in the model was higher than non-CV mortality reported in the UK life tables. The company's reply (Box 16) considered that the UK life tables underestimate non-CV mortality in the trial. However, clinical opinion sought by the ERG explained that non-CV mortality is likely to be overestimated in the trial (when compared to the UK life tables) given that the trial included a considerable proportion of patients from countries where other causes of death, such as infection, are much more prevalent than in Europe and North America.

Box 16. Company's response to differences in non-CV mortality (Company's response to clarification, B8)

"…the use of life tables may not adequately address this limitation of the all-cause mortality approach (specified in Table 51) as the life tables appear to underestimate non-CV mortality compared with the trial data…In addition, it should be noted that the deaths in the study are adjudicated while miscoding in life tables is very likely, hence, the comparison between these two datasets should be interpreted carefully… No reliable estimates of non-CV mortality are available in HF patients; this was highlighted in Table 51 as a limitation to the CV mortality approach using life tables…"

Figure 20. Sacubitril survival (all-cause and CV mortality, observed and estimated)

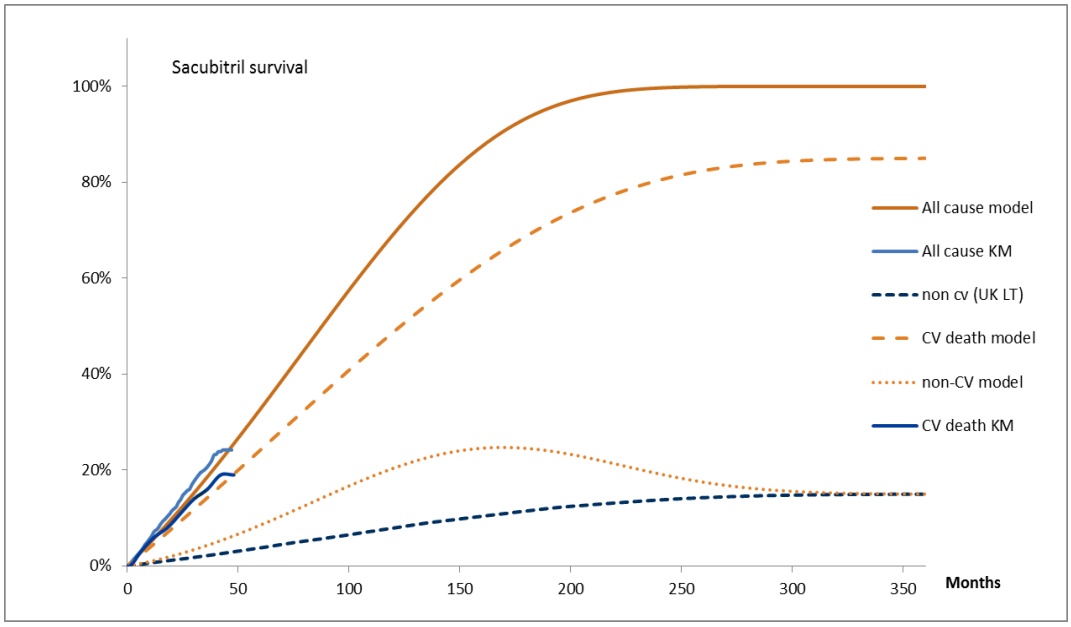
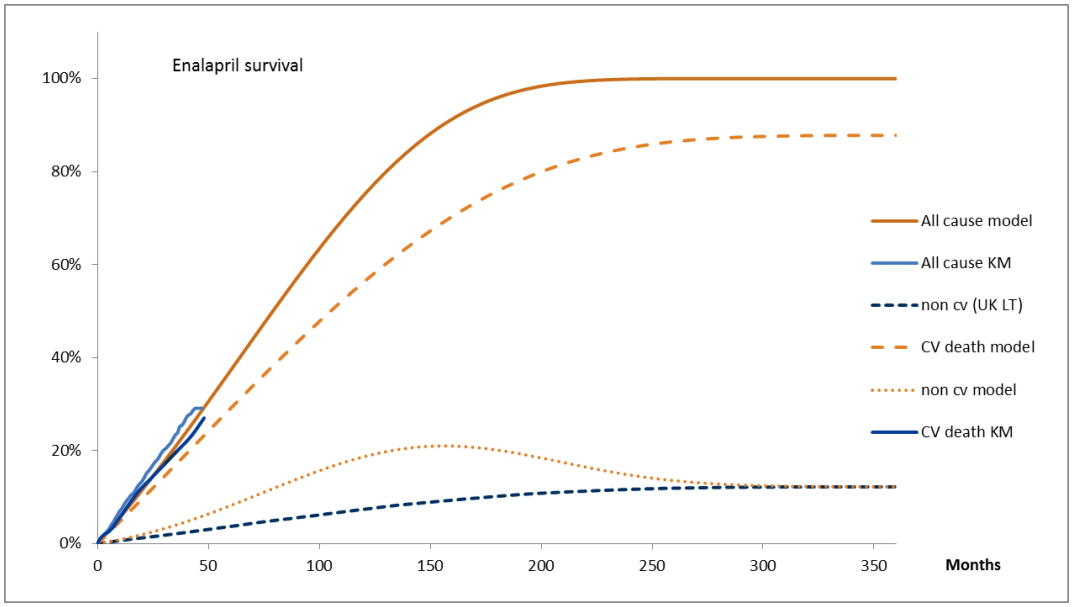


Figure 21. Enalapril survival (all-cause and CV mortality, observed and estimated)



5.5.7.2 Use of estimated data for the within trial period

As discussed in Section 5.5.5.2, the company decided to model the within trial period with predicted data from the mortality (and hospitalisation) models instead of using observed trial data. This approach is less robust as it uses estimated data instead of real data when the latter is available. Even though it would have been incompatible to use KM data with the patient-level approach, the company should have provided a scenario analysis using these data and a mean cohort approach. During the clarification stage, the ERG requested that the company run their base case model using KM mortality data from the PARADIGM-HF trial to model the within trial period, for a time period of 3 years (to reflect the trial period during which there are reliable data available) and for a lifetime horizon,

combining KM data with extrapolated data. Results are presented in Table 57 below. To note is that the results presented in Table 57 were obtained by using the observed rate of all-cause hospitalisation in the PARADIGM-HF trial instead of the estimated all-cause hospitalisation regression model. The ERG also requested that the company presented scenario analysis combining KM data for mortality and observed changes in QoL from the trial, which are presented in Section 5.5.8.

Due to time constraints, the ERG could not verify any of the outcomes reported in Table 57 as the company provided the Excel model used to run the aforementioned scenario analysis very late in the STA process.

Table 57. Scenario analysis using the PARADIGM-HF trial Kaplan-Meier data (reproduced from Table 5, company's response to clarification, B2)

Time horizon	Mortality	Quality of life	Total costs		Total QALYs		ICER
			Enalapril	Sacubitril valsartan	Enalapril	Sacubitril valsartan	
3 years	As base-case	As base case	£5,479	£8,130	1.97	2.03	£43,320
3 years	Kaplan-Meier	As base case	£5,524	£8,131	1.93	2.00	£39,222
Lifetime	Kaplan-Meier	As base case	£12,755	£20,030	4.34	4.78	£16,754
Abbreviations used in the table: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year							

5.5.7.3 Mortality modelling approach

The company conducted survival analysis in order to estimate the mortality benefits associated with sacubitril in the model. A Gompertz distribution was used to fit the PARADIGM-HF trial mortality data and predict all-cause mortality in the model, which was determined by the treatment received by the patient (sacubitril or enalapril) and patients' baseline characteristics from the PARADIGM-HF trial.

Other parametric distributions were assessed for their goodness of fit of all-cause mortality (and CV mortality as per the CS). The company looked at the exponential, Weibull, generalised gamma, log-logistic and lognormal distributions, additionally to the Gompertz. After inspection of the AIC and the BIC the company considered that these were insufficient to draw a conclusion on the best distribution to use as the values were quite similar, with the exception of the lognormal which was deemed to perform worse than other distributions. As can be observed from Table 58, the AIC and the BIC values are quite similar across the different distributions. Even though the difference in values is small, the AIC and BIC values for the Gompertz distribution seem to show that this distribution performs relatively worse than a Weibull, Gamma or loglogistic distribution. The company final decision to select the Gompertz distribution was based on this distribution presenting the most

plausible (i.e shortest) survival times (Figure 5, Section 5.4.4). The ERG believes that the company should have presented different modelling options, such spline models. No other approach outside parametric curves was tried, and this might have produced suboptimal results. Even though the Gompertz distribution produces the most plausible survival curves amongst the group of alternative distributions considered by the company, it could represent an overestimate of treatment effects compared to different (and potentially more appropriate) approaches.

Table 58: All-cause mortality, summary statistics for alternative parametric distributions

Model	Obs	ll(null)	ll(model)	df	AIC	BIC
Gompertz	8399	-5435	-5429	3	10864	10886
Weibull	8399	-5433	-5427	3	10860	10881
Exponential	8399	-5438	-5433	2	10869	10883
Gamma	8399	-5432	-5427	4	10862	10890
Loglogistic	8399	-5433	-5428	3	10861	10882
Lognormal	8399	-5459	-5453	3	10912	10933

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; df, degrees of freedom; ll, log-likelihood; obs, observations.

Figure 22 reports the effect of age at baseline on CV mortality in the in the company's model (using a mean cohort approach), all else being equal. It can be observed that from age 18 (minimum age in the trial) until age 40 at baseline, the higher the patients' age, the lower the mortality predicted by the model. Even though this seems counterintuitive, the model predictions are actually close to the trend observed in the trial. Figure 23 presents the observed CV mortality in the PARADIGM-HF trial according to age groups at baseline (data obtained from Jhund *et al.*(7)), which shows that the rate of events in both treatment arms was higher for the <55 year-old category than for the 55–64 year-old group (i.e. showing a decrease in the rate of CV mortality as age increases at baseline). Therefore, the model seems to appropriately capture the effect of age at baseline on CV mortality in the PARADIGM-HF trial.

Nonetheless the shape of the curves presented in Figure 23, require, once more, the discussion of the trial generalisability. As discussed in Section 5.5.3, the trial included a reasonable proportion of young patients (the youngest patient was 18 years-old and 32% of patients were below 55 years). Given that the expected average age of HFrEF patients in the UK is between 75 and 80 years-old, the trial not only portrays a younger HFrEF population but might also include slightly "different" HFrEF patients, who present with heart problems from a very young age. This could explain the higher CV mortality in younger patients, when compared to slightly older patients, who present with more "typical" HFrEF. The shapes of the curves become more plausible from age 60, where increasing age leads to higher CV mortality.

Even though the modelled effect of age at baseline in CV mortality seems to be appropriate to capture the PARADIGM-HF trial data, the unexpected shape of the curve presented in Figure 22 leads to other issues in the economic analysis, such as the lack of face validity of the predicted life expectancy in the model. In Figure 24 the predicted life expectancy by the mortality survival model indicates that 21-year-old patients have the same life expectancy as 87-year-old patients. Equally implausible, 72-year-old patients have a much higher life expectancy than 18 year olds. The ERG appreciated that this is a direct implication of the modelled effect of age at baseline on CV mortality (Figure 22), which in its turn is a direct consequence of the PARDIGM-HF trial data (Figure 23).

Also worth noting is the slope of the curves in Figure 24. Even though the shape of the curves after 60 years of age is more plausible from a clinical point of view, the slope of the curves is not very steep, as it would be expected with the increasing age of patients. For example, a 64-year-old patient on sacubitril has a life expectancy of approximately 9 years, while a 75-year-old patient has a life-expectancy of 7 years, therefore implying a difference of 2 years in life expectancy between 64 and 75 year-old patients. The UK Life Tables report that on average, 64 year-old patients have a life expectancy of 22 years while 75 year-old patients have a life expectancy of 13 years (a difference of 9 years). Even though it might be argued that HF patients do not exhibit the same life expectancy (thus the same differences in life expectancy) as the average UK population, it seems likely that a difference in life expectancy of 2 years is an underestimation for patients aged 64 or 75 years old. For example, when the ERG changed the starting age of the model from 64 to 75 years, the change in life expectancy and the final ICER is relatively small.

Figure 22. Effect of baseline age on CV mortality in the company's model

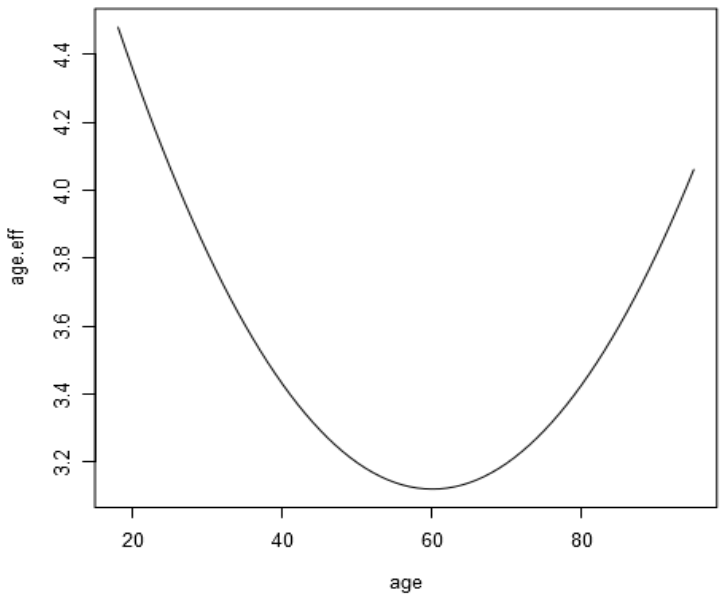


Figure 23. CV mortality by age group in the PARADIGM-HF trial

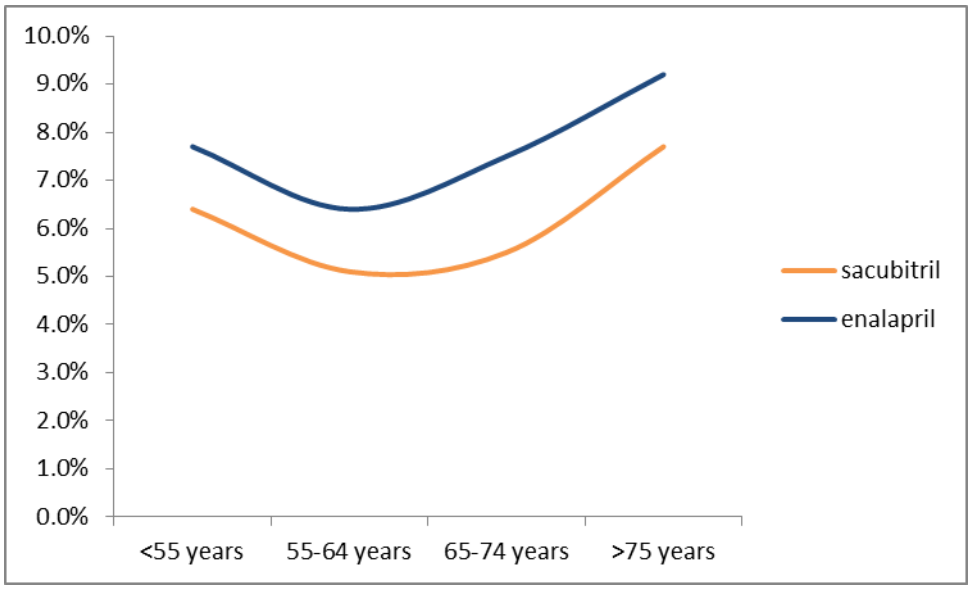
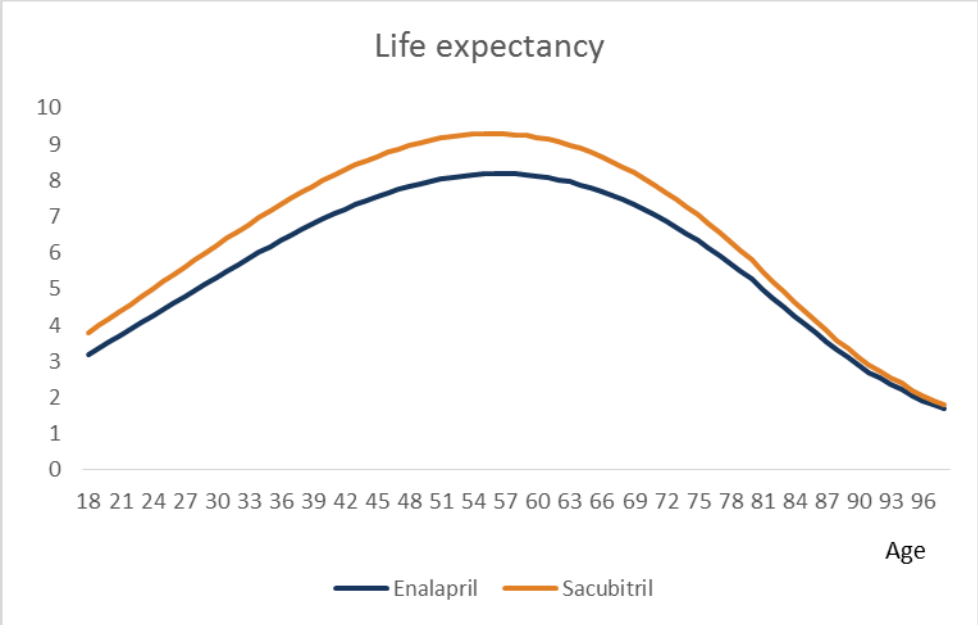


Figure 24. Predicted life expectancy according to age in the company's model



Therefore while the economic model appears reliable to make predictions around the mean PARADIGM-HF patient characteristics and outcomes, deviations from the mean values should be interpreted with caution.

In conclusion the modelling approach taken by the company, while necessary to capture the PARADIGM-HF trial data, resulted in an inflexible economic model. The model seems accurate in

replicating the trial data but cannot be changed to portray a population more representative of UK patients. This is particularly true with regards to the starting age of the model population. The trend observed in CV mortality by age group at baseline reinforces the ERG's point that the PARADIGM-HF trial population is not representative of the UK HF population, especially when deviations are made from the mean age trial population (64 years).

To note is that the ERG investigated all-cause mortality data in the PARADIGM-HF trial by age group at baseline and the same issues described here for CV mortality apply to all-cause mortality.

The effect of age at baseline on CV and all-cause mortality is discussed separately for the Western Europe region in Section 5.6.2 of the ERG report.

5.5.7.4 Starting age in the model and impact on mortality

In this section the ERG discusses the effectiveness of sacubitril in reducing mortality in older populations and the issue of running the economic analysis with a younger population, which (even if we assume that the effectiveness of sacubitril remains unchanged with age) lives longer and in theory would rip the benefits associated with the drug for longer.

Effectiveness of sacubitril in reducing mortality across different age groups

The Jhund *et al.* study results are reproduced again in Figure 25 for convenience and these show that for the <55 years' category and the ≥75 years' category the CV mortality HRs for sacubitril versus enalapril are non-statistically significant. However, as discussed in the hospitalisation section (Section 5.5.5.4) the results of the Jhund *et al.* study need to be carefully interpreted.(7) While sacubitril appears to maintain the same direction of effect across age groups, the size of the effect is not as easily established. The authors in Jhund *et al.* conclude that the effect of sacubitril compared with enalapril was consistent across age groups even though HRs were non-statistically-significant in older groups.(7) This is somewhat consistent with the expert opinion provided to the ERG that for patients around 80 years old presenting with HFrEF, clinicians expect treatment (with ACEi or other drugs) to improve patients' QoL and symptoms but improve mortality.

In light of this the ERG has conducted a scenario analysis using the HR obtained in Jhund *et al.* for mortality which was 0.79 (95% CI 0.64 to 0.98) in the 55-64 years' category.(7) As the confidence interval for the HR of CV deaths in the 55–64 years population is wide, the ERG also ran a scenario analysis using both limits of the 95% confidence interval. The ICERs resulting from the ERG analysis are presented in Section 6 of the report.

The ERG has also run a model for an older baseline population (75 year old group). The ERG used the respective HR reported for this category in the Jhund *et al.* study.(7) However and as previously

mentioned, this HR was not statistically significant in the analysis, therefore the ERG also ran a scenario analysis where the HR for sacubitril compared with enalapril for hospitalisation was 1 in the 75 year-old population. The ICERs resulting from the ERG analysis are presented in Section 6 of the report.

Figure 25. Clinical outcomes in Jhund *et al.* according to age category.

	<55 years (*n* = 1624)		55–64 years (*n* = 2655)		65–74 years (*n* = 2557)		≥75 years (*n* = 1563)	
Outcome	**Enalapril (*n* = 786)**	**LCZ696 (*n* = 838)**	**Enalapril (*n* = 1382)**	**LCZ696 (*n* = 1273)**	**Enalapril (*n* = 1265)**	**LCZ696 (*n* = 1292)**	**Enalapril (*n* = 779)**	**LCZ696 (*n* = 784)**
CV death or HF hosp.								
No. rate[a]	204 13.4 (11.7, 15.3)	178 10.4 (9.0, 12.0)	352 12.5 (11.3, 13.9)	253 9.6 (8.5, 10.8)	329 12.7 (11.4, 14.2)	275 10.1 (8.9, 11.3)	232 14.8 (13.0, 16.8)	208 12.7 (11.1, 14.6)
HR[b]	0.78 (0.64, 0.96)		0.76 (0.65, 0.90)		0.80 (0.68, 0.93)		0.86 (0.72, 1.04)	
CV death								
No. rate[a]	127 7.7 (6.5, 9.2)	117 6.4 (5.4, 7.7)	199 6.4 (5.6, 7.4)	144 5.1 (4.4, 6.0)	210 7.5 (6.6, 8.6)	163 5.5 (4.8, 6.5)	157 9.2 (7.9, 10.8)	134 7.7 (6.5, 9.1)
HR[b]	0.84 (0.65, 1.08)		0.79 (0.64, 0.98)		0.74 (0.60, 0.90)		0.84 (0.67, 1.06)	
HF Hosp.								
No. rate[a]	112 7.3 (6.1, 8.8)	93 5.4 (4.4, 6.6)	223 7.9 (7.0, 9.0)	156 5.9 (45.1, 6.9)	188 7.3 (6.3, 8.4)	169 6.2 (5.3, 7.2)	135 8.6 (7.3, 10.2)	119 7.3 (6.1, 8.7)
HR[a]	0.75 (0.57, 0.98)		0.74 (0.61, 0.91)		0.86 (0.70, 1.06)		0.85 (0.66, 1.09)	
All-cause death								
No. rate[a]	148 9.0 (7.6, 10.5)	131 7.2 (6.1, 8.6)	231 7.5 (6.6, 8.5)	183 6.5 (5.6, 7.5)	251 9.0 (7.9, 10.2)	215 7.3 (6.4, 8.4)	205 12.0 (10.5, 13.8)	182 10.5 (9.0, 12.1)
HR[b]	0.80 (0.64, 1.02)		0.87 (0.72, 1.06)		0.81 (0.68, 0.97)		0.87 (0.71, 1.07)	

CV, cardiovascular; HF, heart failure; HR, hazard ratio.
[a]Rate per 100 patient-years (95% CI). [b]Hazard ratio (95% CI).

Age with which patients receive sacubitril

As mentioned in Section 5.5.3.2, the starting age of a model population has, by itself, an impact on patients' survival thus impacting on the additional benefits and costs that patients incur while on different treatment regimens. To note is that according to the UK life tables, the average life expectancy for a 64 year-old male is 19 years and 22 years for a female the same age, while the average life expectancy for a 75 year-old male is 11 years and 13 years for a female the same age. At the clarification stage, the company explained that other factors override age when it comes to determining life-expectancy in HF patients, such as time since diagnosis and co-morbidities. The ERG agrees with the company in that the difference in life expectancy in the general population between 64 year-olds and 75 year-olds (8 years for males and 9 years for females) cannot be expected to be applicable in 64 year-olds and 75 year-olds HF patients. The main reason being that there is an overwhelming mortality observed during the first year after the diagnosis of HF (30% to 40% according to NICE CG108 (6)) and that 50% of patients are expected to have died 5 years after the diagnosis of HF. However, for those patients surviving at 5 years post-diagnosis, it does matter if

patients are 69 or 80 as there is still a difference of 8 years in the average life expectancy between these patients. The ERG considers that the starting age in the economic analysis is a critical factor for assessing the cost-effectiveness of sacubitril, but this could not be assessed properly in the company's model. This is due to the inflexibility of the model in reflecting different ages at baseline (compared to the mean age at baseline) explained in the previous subsection.

Therefore, the additional analysis ran by the ERG for older populations at baseline (i.e. for the 75 year-old population) need to be interpreted with caution. These are reported in Section 6 of the report.

5.5.7.5 Secondary base case analysis – ARBs

In the secondary base case analysis, the all-cause mortality and all-cause hospitalisation models used the NMA results to estimate the effectiveness of sacubitril compared with candesartan. The ERG has some issues with the validity of the NMA results, as previously discussed in Section 4. The evidence included in the NMA shows that it is likely that sacubitril reduces the risk of both all-cause and CV mortality when compared to ARBs (p(better)=[redacted] for all-cause mortality and p(better)=[redacted] or CV mortality, CS, Table 32, page 90). The ERG also notes that the credible intervals around the NMA HRs for mortality indicate that the differences between sacubitril vs ARBs to be non-statistically significant.

In conclusion, in addition to the technical issues discussed in this section, the mortality observed in the trial is not reflective of newly diagnosed HFrEF patients. The mortality in the model and in the trial portrays a scenario representative of the use of sacubitril for established HF patients. This reinforces the ERG's view that the evidence presented in this submission is primarily relevant to the use of sacubitril as a second-line treatment option, given to HFrEF patients who are still symptomatic despite being on an ACEi drug therapy. Furthermore because the PARADIGM-HF trial patients are symptomatic patients, despite having been treated with ARBs and ACEi, the impact of continuing these patients on ACEi is likely to be a misrepresentation compared to what would happen in treatment-naïve patients. This has an impact on the observed effectiveness of sacubitril, which might be overrepresented in the trial population when compared to treatment-naïve patients. Therefore, the trial and the economic analysis herein presented should be interpreted with caution when making extrapolations to the effectiveness of sacubitril as a first-line treatment option. When analysing the modelled mortality in the context of a second-line treatment population the following issues should be considered:

- The company's decision to select the Gompertz distribution was based on this distribution presenting the most plausible (i.e shortest) survival time. The ERG believes that the company should have presented different modelling options, such as spline models. No other approach outside parametric curves was tried, and this might have produced suboptimal results. Even

though the Gompertz distribution produces the most plausible survival curves amongst the group of alternative distributions considered by the company, represent an overestimate of treatment effects compared to different (and potentially more appropriate) approaches;

- The modelling approach taken by the company, while necessary to capture the PARADIGM-HF trial data, resulted in an inflexible economic model. The model seems accurate in replicating the trial data but cannot be changed to portray an older population at baseline and generalise the model results. The trend observed in CV mortality by age group at baseline reinforces the ERG's point that the PARADIGM-HF trial population is not representative of the UK HF population, especially when deviations are made from the mean age trial population (63 years);

- While patients' age at diagnosis might not be very relevant in determining patients' survival in the next year (and to a less extent in the 5 years after diagnosis) it is still relevant how old patients are if they survive 5 years after diagnosis even though this could not be fully assessed in the company's model.

5.5.8 Health-related quality of life

The ERG has several concerns regarding the estimation of the impact of sacubitril on patients' QoL in the model. The key issues identified and discussed in this section are detailed below:

- Comparability of trial results with literature data and generalisability to the UK population;

- Baseline health-related QoL: comparability between intervention and comparator groups and severity of the scores observed;

- Statistical modelling approach taken for EQ-5D data;

- Impact of sacubitril in patients' symptoms and disutility associated with AEs;

- Excel model issues in the utility and QALY calculations.

5.5.8.1 Comparability of trial results with literature data and generalisability to the UK population

The comparison between the PARADIGM-HF trial population and the average HF population in the UK has been already discussed in Section 5.5.3, where the ERG explained the reasons for concern with the generalisability of the trial (and modelled) population.

Regarding the results of the literature search, the company reported only that the utility values identified were broadly consistent with the baseline utility values in the PARADIGM-HF trial

(Section 5.4.6 of the CS), without producing quantitative and/or qualitative comparisons. Clinical expert opinion sought by the ERG confirmed that the population included in the trial is similar to a stable chronic HFrEF outpatient population. As such, the ERG considers that the studies by Austin *et al.*(9) Iqbal *et al.*(77) and Peters *et al.*(82) to be extremely relevant to the decision problem given that they focused on chronic HFrEF UK patients. Furthermore the studies by Eurich *et al.*(74) and Kraai *et al.*(80) are also relevant as, even though these were carried out in different countries, these based the EQ-5D scoring on UK tariffs, and can therefore be used as comparators. These studies obtained QoL measurements directly from the patients, according to the NICE reference case.(5) The summaries of the studies, together with the observed utility scores, are reported in Table 26.

The ERG notes that among the identified studies, utility scores collected in trial-based studies were consistently higher than in other types. This might be explained by the common tendency to have healthier trial patients than the ones observed in clinical practice. In the PARADIGM-HF trial for example, the EQ-5D scores were collected at randomisation, at which point the patients had gone through the inclusion and exclusion criteria selection process at screening and the two run-in periods as per trial design. Therefore the ERG believes that the QoL observed in the trial population at randomisation was higher than the QoL associated with chronic patients seen in the UK outpatient practice.

Given the relationship between the QoL at baseline and the trial outcomes (highlighted by the regression models, which for example show a correlation between EQ-5D scores and mortality), the ERG is concerned that the overestimation of patients' QoL at baseline might impact the benefits observed in the trial when compared with real clinical practice. The ERG conducted a scenario analysis and varied the baseline utility score to match the mean estimates by Berg *et al.*(8) and by Austin *et al.(9)* at baseline, who reported values equal to 0.712 and 0.660, respectively. The impact of this on the ICER is explored in Section 6.

5.5.8.2 Baseline health-related QoL in the intervention and comparator groups

Comparability of health-related QoL at baseline was reported only in a brief study report commissioned by the company (separate from the main submission).(91) These data have been previously described in Section 5.4.5.3.

The document reported that at baseline [redacted] ([redacted]%) and [redacted] ([redacted]%) patients had complete EQ-5D index data in the enalapril and sacubitril arms, respectively. The mean EQ-5D values at baseline were [redacted] (SD [redacted]) for both arms. A two-sample *t* test was performed to compare the two distribution means and [redacted] (p-value = [redacted]). Nonetheless this conclusion needs be considered with caution as the [redacted] shape of the distribution at baseline might indicate that the mean difference are not sufficient to prove that

the two populations were similar at baseline. EQ-5D data by treatment arm (except for the mean value) were not reported by the company. Additionally the company did not include any comment in the CS to explain why [redacted]% of the patients in the trial reported to have a QoL considered to be worse than death at baseline (i.e. negative utility scores).

The company supplied the values of the KCCQ clinical summary score as part of the supplementary EQ-5D analysis document, which reported [redacted] as well as other dimensions of the KCCQ scores (described in Section 5.4.5.3). The ERG is concerned that [redacted], could be considered clinically meaningful, and how this might relate to the EQ-5D scores by treatment arm. As the EQ-5D data were not available separately by arm, it is unclear if [redacted] impacted the EQ-5D scores.

In summary the ERG cannot be certain if there was a statistically significant difference or not at baseline for patients' EQ-5D scores. The immediate implication of this are problematic; if there were clinically significant differences in patients' disease severity at baseline ([redacted]) and QoL across treatment and comparator arms, there would be a population imbalance at baseline which could potentially have biased the trial and consequently the model outcomes. Assuming patients in a healthier state would have better outcomes, the potential imbalance in disease severity observed ([redacted]) might have [redacted] in the PARADIGM-HF trial.

5.5.8.3 Statistical modelling approach taken for EQ-5D data

As described in Section 5.4.5.3, the company used a linear mixed model to predict the utility scores in the model, which was based on patients' baseline characteristics, time since randomisation, hospitalisation and AEs. No adjustments were applied to account for the non-normality in distribution and multimodality of the EQ-5D scores in the statistical model. The ERG is concerned that the likelihood used might not be appropriate to model these data because of their asymmetry and the high concentration on the EQ-5D index ceiling value ([redacted]% of patients had a score equal to 1 at baseline). As different modelling approaches were not explored, the ERG believes that the chosen model might not be the most adequate one to extrapolate the QoL scores over time.

The CS reported a QoL study by Berg *et al.*(8) which analysed data from 5,334 patients with EQ-5D questionnaire information available, following inpatient or outpatient care between 2008 and 2010.

The data were from the Swedish Heart Failure Registry.(8) This study analysed the EQ-5D data using both the Swedish and UK tariffs and presented two different statistical models:

- An ordinary least squares (OLS) regression with robust standard errors;
- A two-part model, predicting the probability of obtaining the ceiling utility value (i.e. 1 using the UK tariff) with a logistic regression model and the index value for patients not reaching the ceiling value with an OLS model. Robust standard errors were used in both steps.

The ERG notes that the concentration around the ceiling EQ-5D utility value observed in the PARADIGM-HF trial (Figure 7) suggests that a two-part model specification (as used in Berg *et al*.(8)) would have been appropriate. The ERG asked the company why other regression models (for example the use of a logistic transformation) were not considered to model QoL data. The company's response is reported in Box 17.

Box 17. Company's response to regression analysis for utility data (Company's response to clarification, B14)

"In addition to the models estimated to examine the time trend in QoL, an ordinary least squares regression was considered in order to test the consistency of the mixed model outcomes. No transformations of the dependent variable were considered. Mixed regression models have been used previously to model health-related quality of life (QoL) in heart failure and other cardiovascular conditions, with no transformations reported. In addition, the ivabradine manufacturer submission to NICE used a mixed regression model, with no transformations reported, and the ERG considered this to be clinically plausible."

The ERG does not consider the previous use of a modelling approach to be sufficient justification for not testing alternative and potentially more appropriate model specifications, in particular because the company had knowledge of the study researching the same question (analysis of EQ-5D data in chronic HF) fitting a model appropriate to the data at hand, i.e. Berg *et al*.(8)

Furthermore the NICE DSU (Longworth *et al*.) evaluated mapping methodologies to obtain EQ-5D utility values by reviewing the literature and providing recommendations regarding modelling choices.(111) In the ERG's opinion these recommendations were not (or only partly) followed by the company, as the following results of the EQ-5D data analysis were not provided in the submission:

- Description and examination of the dataset prior to estimation to inform model selection and specification;
- Description and comparison between observed and predicted EQ-5D values;

- Provision of a justification explaining why the selected regression model was chosen;
- Model validation (i.e. cross-validation).

Given the distribution of the QoL data, the ERG believes that the modelling approach used by the company is not appropriate. Alternative approaches could have been followed, such as developing a two-part model.

5.5.8.4 Impact of sacubitril in patients' symptoms and disutility associated with AEs

During the clarification stage, the ERG asked the company to explain the clinical rationale behind the beneficial effect of sacubitril over enalapril on QoL, beside the impact of sacubitril on mortality, hospitalisation and AEs. The company's reply is presented in Box 18.

Box 18.Company's response to sacubitril effect on HF symptoms (Company's response to clarification, B11)

> "… in PARADIGM-HF patients experienced increased HF symptoms and physical limitation (based on a reduced KCCQ clinical summary score); however, with sacubitril valsartan the worsening in symptoms was significantly less than with enalapril […] Sacubitril valsartan improves the following symptoms associated with heart failure: shortness of breath, fatigue and swelling in feet, ankles and/or legs".

The ERG however notes that [redacted] (clinical summary score, sacubitril vs enalapril: [redacted] and [redacted]; p-value = [redacted]), and that [redacted]. Therefore the justification is not considered sufficient to explain the QoL benefit associated with the improvement in symptoms caused by sacubitril, as [redacted]. The ERG's clinical expert's opinion was that no impact was expected beyond the effect on mortality, hospitalisation and AEs, and potentially some improvement in symptoms such as swollen ankles. Nonetheless, there seems to be a lack of robust clinical evidence suggesting that sacubitril would lead to measurable improvements in patients' QoL outside its effect on hospitalisations and AEs.

The effect of hospitalisation on QoL accounted for in the linear mixed model was based on all-cause hospitalisation which included serious AEs requiring hospitalisation. The impact of less serious AEs (managed outside the hospital) on QoL was modelled separately. The AEs (managed in the outpatient

setting) considered in the trial were: angioedema, elevated serum creatinine, elevated serum potassium, hypotension and cough. Even though these events were assumed to impact on the resource use (see Section 5.4.6.7), only hypotension and cough were assumed to have an effect on the health-related QoL of patients.

The decrement in QoL associated with hospitalisation was considered reasonable by clinical expert opinion provided to the ERG. The assumption of patients needing a rehabilitation period of about 90 days to recover their pre-hospitalisation utility level is also appropriate.

The company decided to exclude elevated serum creatinine and elevated serum potassium from the QoL analysis as it was considered that these events do not have an impact on QoL and that this was a conservative approach since there were fewer events in the sacubitril than in the enalapril arm. The company also excluded angioedema from the QoL analysis as it was considered that there were too few events to infer on their impact on QoL (even though these were costed). Expert opinion provided to the ERG advised that angioedema should have been included even when it's less severe form. From a methodological point of view, including the costs of less severe angioedema but excluding the impact of these events in patients' QoL is not a robust approach. The ERG raised this issue with the company during the clarification stage and the company's reply is presented in Box 19.

Box 19. Company's response to sacubitril effect on heart failure symptoms (Company's response to clarification, B11)

"The total number of angioedema events that did not require hospitalisation during randomised treatment was 25. A hypothetical extreme scenario was explored in which a utility decrement of 1.0 was applied for the model cycle in which an angioedema event occurred…Even in this extreme scenario, differences in the number of QALYs as compared with the base-case model are not observable at the second decimal place. This scenario is associated with a change in the ICER of 0.1% vs. the base-case. It is considered that including the effect of angioedema on EQ-5D explicitly would therefore have a negligible impact on the ICER."

The ERG agrees that while the impact of including angioedema is close to 0, from a methodological point of view this should have been included (or the costs of less severe angioedema excluded).

Finally, clinical opinion sought by the ERG advised that there is uncertainty around the assumed duration of AEs. Hypotension and cough were assumed to last for 64.9 and 73.3 days, respectively in the model, however clinical experts explained that cough symptoms and hypotension will usually persist until drug discontinuation (which is not accounted for in the economic model).

5.5.8.5 Excel model issues in the utility and QALY calculations

The ERG identified three errors in the calculation of utility scores and QALYs in the economic model. The first one is related to the utility score at baseline, the second to the half-cycle correction implemented in the model and the third to the maximum and minimum utility values estimated. These are now explored in turn.

Baseline utility value

The company used the utility value of 0.81 as the baseline utility in the QoL regression model. Nonetheless the CS reported that the value used at baseline was 0.78. Upon clarification, the company confirmed that the 0.78 utility value should have been used instead and presented the corrected ICER. This is reported in Section 5.6.

Half-cycle correction

The half-cycle correction was not correctly implemented as the model attributed the utility score at the end of every two-cycle period to both the patients alive at the beginning of the first and at the beginning of the second cycle, as demonstrated in the following equation:

$$QALM_t^* = \left(\frac{u_t(p_t + p_{t-1})}{2} + d_t^*\right)\frac{1}{12}$$

Where $QALM_t^*$ is the half-cycle-corrected estimate of the Quality-Adjusted Life Months (QALM) at cycle t; u_t is the utility score associated with patients at the end of time t, not including the effect of hospitalisation and adverse events; p_t is the proportion of patients alive at the beginning of the cycle at time t and d_t^* is the total disutility associated with hospitalisation and adverse events at time t taking into account the half-cycle correction.

The ERG corrected the formula by calculating the half-cycle-corrected QALMs by averaging the utility scores weighted by the proportion of patients alive in each cycle, and then adding the half-cycle-corrected disutilities associated to hospitalisations and adverse events:

$$QALM_t^* = \left(\frac{u_{t-1} \cdot p_{t-1} + u_t \cdot p_t}{2} + d_t^*\right)\frac{1}{12}$$

This modification led to a very small change in the final estimated QALYs as the error identified was generating only a minor underestimation of the total QALYs.

Estimated utility range

Utility scores were not calculated correctly in the company's scenario analysis where treatment discontinuation was considered. The utility scores could exceed 1 or decrease below -0.594 (the

minimum value according to the UK tariffs), as only the weighted average was constrained to assume value in this interval. The original calculations did not account for these bounds separately by cohort (patients who discontinued or not), and was equal to $\bar{u}_t = \min(\max(u^1 p_t^1 + u^2(1 - p_t^1) + \beta t, -0.594), 1)$ while it should have been:

$$\bar{u}_t = \min(\max(u^1 + \beta t), -0.594), 1) \cdot p_t^1 + \min(\max(u^2 + \beta t), -0.594), 1) \cdot p_t^2.$$

Where $\bar{u}_t$ is the overall utility score at time t; u^1 is the utility score for patients who did not discontinue first-line treatment; u^2 is the utility score for patients who discontinued first-line treatment and moved to second line; p_t^1 and p_t^2 are the proportions of patients alive at time t who are receiving first- and second-line treatment, respectively; β is the effect of time (in model cycles) on the EQ-5D utility score.

The correction of this error alone (not considering the other two modifications above) had no impact on the results of the discontinuation scenario analysis.

In conclusion, the ERG is concerned with the validity of the QoL analysis undertaken by the company. Firstly the ERG cannot be certain if there was a baseline statistically significant difference, or not, in patients' EQ-5D scores. The immediate implication of this is problematic; if there were clinically significant differences in patients' disease severity at baseline ([redacted]) and QoL across treatment and comparator arms, there would be a population imbalance at baseline which could potentially have biased the trial and consequently the model outcomes. Assuming patients in a healthier state would have better outcomes, the potential imbalance in disease severity observed ([redacted]) might have favoured the sacubitril arm in the PARADIGM-HF trial. Given the relationship between the QoL at baseline and the trial outcomes the ERG is concerned that the overestimation of patients' QoL at baseline might impact the benefits observed in the trial when compared with real clinical practice. The ERG conducted a scenario analysis and varied the baseline utility score to match the mean estimates by Berg *et al.*(8) and by Austin *et al.*(9) at baseline, and base case ICER increased considerably.

Given the distribution of the QoL data, the ERG believes that the modelling approach used by the company is not appropriate. Alternative approaches could have been followed, such as developing a two-part model. The ERG developed a simpler, more transparent QoL model which is presented in Section 6 of this report.

5.5.9 Resources and costs

The ERG identified some issues in the company's approach to the estimation of resource use and costs in the economic model. The ERG believes that the overarching issue is the pooling of very different data sources without appropriate adjustment, leading to inconsistencies and lack of face validity in the model costs when analysed in an integrated fashion. As discussed in Section 5.4.6, the economic model relied on many different resource use data sources which were based on different populations. The key issues identified relate to:

- Pharmacological costs;
- Hospitalisation costs;
- HF management resource use and costs;
- AEs resource use and costs.

5.5.9.1 Pharmacological costs

Despite stating that the cost of sacubitril in the model was estimated based on the target dose of sacubitril in the PARADIGM-HF trial, the company used the observed dose of sacubitril to estimate its costs in the economic analysis. The company also estimated the daily cost of enalapril per patient based on the average observed drug dose in the PARADIGM-HF trial. Standard care and background therapy use were also based on the PARADIGM-HF trial data. The daily doses for other therapies were based on the BNF (94), with the exception of aspirin and warfarin. The choice of the sources used to model the doses of aspirin and warfarin the model were not clearly reported in the CS.

The ERG notes that the assumptions regarding the daily drug doses were not consistent across different treatments. For some treatments, the doses were estimated as the average between the minimum and maximum dose and for other drugs, the doses were based on maximum doses. The ERG believes that the company should have used drug's target doses or, when the target dose was not available, the maximum dose for the purpose of estimating the treatment cost consistently across all drugs regimens. The ERG undertook additional analysis to reflect consistent drug dose assumptions. The re-estimated drug costs are presented in Table 59, while the impact on the final ICER is presented in Section 6.

As mentioned in Section 5.5.4.2, the most commonly used ACEi in the UK is ramipril. The company undertook scenario analysis where the cost of enalapril was replaced by the cost of ramipril in the economic model. The ERG notes that even though the company took the daily dosage of ramipril from the BNF, this seems to be in conflict with UK general practice. The ERG's clinical experts explained that the key advantage of ramipril over enalapril is the fact that is can be given as a daily

dose regimen, which helps with medication adherence. Therefore, even though the BNF recommends administrating ramipril in two daily 5 mg doses (94), the ERG re-estimated the monthly cost of ramipril to better reflect UK clinical practice. The re-estimated cost of ramipril is presented in Table 59, while the impact on the final ICER is presented in Section 6.

Table 59.ERG estimates of the monthly drug costs

Intervention	CS daily dose assumption	ERG daily dose assumptions	CS monthly cost	ERG monthly cost	Notes
Enalapril	18.9 mg	Two 10 mg tabs	£2.10	£2,22	Maximum dose assumed
Ramipril	Two 5 mg tabs	One 10 mg tab	£2.70	£1.45	Clinical experts stated that ramipril is offered as a single daily dose
Digoxin	One 62.5 µg or 125 µg tab	One 125 µg tab	£1.38	£1.13	Maximum dose assumed
Atorvastatin	One 20 mg tab	One 80 mg tab	£1.53	£2.95	Maximum dose for secondary prevention assumed
Furosemide	One 20 mg or 40 mg tab	Two 40 mg tabs	£1.01	£1.91	Maximum dose for resistant hypertension assumed
Clopidogrel	One 75 mg tab	One 75 mg tab	£1.98	£1.86	Cost calculated using a 30-tab pack
Abbreviations in table: BNF, British National Formulary; CS, company submission; ERG, Evidence Review Group; mg, milligram; µg, microgram.					

The dose of aspirin was based on a study by Bermingham *et al.*(95). The authors reported data on 1476 patients enrolled in a disease management program in Ireland after HF hospitalisation. The proportion of patients with HFrEF in the study population was 64.8% (797 out of 1476). Among all HF patients included, 828 patients were receiving aspirin at a dose of 75 mg, 15 patients at 150 mg, 49 patients at 300 mg and 584 patients were not receiving aspirin, for an average dose of 54 mg. In their economic model the company assumed that 52% of patients (as observed in the PARADIGM-HF trial) would receive 75 mg of aspirin, based on the most frequent dose observed by Bermingham *et al.*(95) for a mean dose of 39 mg. Given the low cost of aspirin however the ERG deems this difference not to have any impact on the cost estimates.

The referenced data source for the daily dose of warfarin (drugs.com) reports that the usual adult dose for congestive heart failure ranges from 2 to 10 mg orally or intravenously once a day, while a dose of 5 mg was assumed in the model.(96) The ERG considers the 5 mg dose to be a reasonable assumption and notes that variations have no impact on the economic results.

The standard care and background therapy use in the economic model (based on the PARADIGM-HF trial data) might be misrepresenting clinical practice in the UK. The CPRD analysis highlighted

substantially lower proportions of prescribed medications than the ones observed in the trial (98). This is likely to result from the trial population being better managed than average HF UK patients. The distribution observed in the trial is similar to the data reported by the British Society for Heart Failure for the treatment prescriptions at discharge for patients with left systolic ventricular disease. The distributions are reported in Table 60. Even though the use of concomitant therapy in the trial seems to be overestimated when compared to CPRD data, this assumed equal across the two treatment arms and the impact on the final ICER is therefore likely to be very minor.

Table 60. Comparison of proportion of patients using key concomitant medications

Therapy	Baseline use in PARADIGM-HF(2)	Concomitant medication use (CPRD data)(98)	Treatment at discharge (BSHF data)(1)
Beta blockers	93%	[redacted]	82%
Aldosterone antagonists	56%	[redacted]	49%
Digoxin	30%	[redacted]	22%
Statins	56%	[redacted]	NR
Diuretics	80%	[redacted]*	91%*
Aspirin	52%	[redacted]	NR
ADP antagonists	15%	[redacted]	NR
Abbreviations in table: ADP, adenosine diphosphate; CPRD, Clinical Practice Research Datalink; BSHF, British Society for Heart Failure. * Loop diuretics			

In the economic model the proportions of patients taking concomitant therapies were assumed to be equal across treatment arms and constant over time. The ERG looked at the use of concomitant medications in the double-blind period based on the safety set. As the proportion of patients taking each drug class was very similar over time in the PARADIGM-HF trial, the assumption of the baseline concomitant therapies remaining constant over time is considered appropriate.

In addition, the ERG notes the following discrepancies between values reported in the economic model and the current prices listed on the BNF, as of September 2015:(94)

- Furosemide: the price of the 500 mg tab is £29.02 and not £27.52;
- Valsartan: the price of the 40 mg 7-tab pack is £2.82 and not £2.89; the price for the 320 mg 28-tab pack is £15.29 and not £15.69.

Nonetheless, these discrepancies have no impact on the economic analysis as they were not used in the base case analysis cost calculations.

5.5.9.2 Hospitalisation costs

As reported in Section 5.4.6.5, average hospitalisation costs were calculated by combining the admission causes observed in the PARADIGM-HF trial and the NHS HRG hospital admission and cost data. Hospitalisation costs were also assumed to be constant over time and independent of treatment received.

Clinical expert opinion sought by the ERG confirmed that the assumption of constant hospitalisation over time is not reflective of clinical practice. For example, a higher proportion of interventional procedures and shorter length of stay would be expected for younger patients than for elder patients. Therefore the hospitalisation cost would be expected to depend on starting age and time. The ERG is uncertain about the impact of this in the economic results. Potentially younger patients would be hospitalised for a shorter time and undergo more expensive procedures while older patients would have longer stays but with a lower associated daily cost (therefore it is likely that the resulting differences might cancel themselves out over time). However, clinical experts stated that the incidence of hospitalisation caused by renal failure appeared to be lower than expected, and that the cause could be due to the population being younger and healthier than in UK clinical practice. Thus the starting age in the model impacts the cost savings caused by the reduction in hospitalisations as the reduction in hospitalisation rate would decrease together with increasing average age. This effect would be caused by a lower hospitalisation cost differential between the treatments and therefore lead to a higher cost differential.

Causes for hospitalisation in the model

The company assumed that sacubitril reduces hospitalisation equally for any cause. Packer *et al*. reported that a higher rate reduction in HF than in non-HF hospitalisations was observed in the PARADIGM-HF trial, as detailed in Table 61, (70) which could impact the cost of hospitalisation. However, given the small incidence of hospitalisation and the relatively small variation in the differential across different reasons for hospitalisation the ERG does not believe this to be an issue.

Table 61. Incidence rate by hospitalisation type

Event rate	Sacubitril valsartan	Enalapril*	Relative rate reduction^
Hospitalisation, any reason	0.38 (3564/9308)*	0.44 (4053/9235)*	15%
Hospitalisation, HF	0.09 (851/9308)*	0.12 (1079/9235)*	28%
Hospitalisation, non-HF	0.29 (2713/9308)*	0.32 (2974/9235)*	10%
Hospitalisation, CV	0.24 (2216/9308)*	0.27 (2537/9235)*	15%
Hospitalisation, non-CV	0.14 (1348/9308)*	0.16 (1516/9235)*	13%

Abbreviations in table: CV, cardiovascular; HF, heart failure.
Source: Packer *et al*.(70).
* Crude event rates were calculated by the ERG by dividing the number of events by the total exposure time for the two treatments expressed in patient years.
^ The relative rate reductions are based on adjusted rates in Packer *et al*.(70).

Furthermore, because all-cause hospitalisation included the more serious AEs managed in the hospital, the consequence of assuming equal reasons for hospitalisation admission across treatment arms is that the incidence of AEs leading to hospitalisation was effectively reduced at the same rate as hospitalisations. Given that the incidence of AEs leading to hospitalisation is unknown by the ERG, it is unclear if this assumption has any impact (for example, it may be that hypotension leading to hospitalisation was higher in the sacubitril arm than in the enalapril arm).

The only AE leading to hospitalisation costed in the model was hypotension. This led to a double counting of hypotension events as the overall observed incidence rate is used to determine the number of events managed in the outpatient setting, but hypotension is also included in the all-cause hospitalisation model. This leads to an overestimation of the costs attributed to hypotension, while at the same time producing an incorrect estimate of the differential costs. Given that the proportion of hypotension cases requiring hospitalisation in the model was assumed to be lower than 2.25% the ERG is not concerned with this issue.

Angioedema was not included as a serious AE needing hospitalisations for the purposes of estimating hospitalisation costs. The company justified this by explaining that the number of admissions due to angioedema did not reach 30 cases. Clinical expert opinion provided to the ERG explained angioedema can be a serious condition requiring hospital management, thus it should have been included in the model.

The ERG notes that the hospitalisation causes were also assumed to be the same across different geographical regions, and thus all physician-reported admission reasons were used to estimate the average hospitalisation cost. Clinical expert opinion sought by the ERG explained that the determinants of hospitalisation are likely to differ across the regions included in the trial. As NHS data were used in the model to estimate the hospitalisation costs, the use of Western Europe-specific data would likely make the estimate more robust. In their scenario analysis, the company based the inpatient resource use on the Western European subgroup only which led to an average hospitalisation cost estimate of £3,161, compared to the base-case average cost of £2,866. This is further explored in Section 5.6.1.

Finally, the ERG notes that the average hospitalisation cost reported in the appendices to the submission (Appendix 13, Section 8.13 of the CS) does not match the value reported in the main submission (Section 5.5.4 of the CS). However the latter value was applied in the model and it is the correct value.

5.5.9.3 HF management costs

The resource use for HF management was estimated based on the data obtained from the company-commissioned analysis of the CPRD dataset (98). The ERG has already expressed some concerns regarding the applicability of the CPRD data to the trial population, as it was observed to be different in several aspects (see Section 5.4.6 and Section 5.6.2) The ERG sought clinical expert advice for the validation of the background resource use in the model, reported in Table 40, Section 5.4.6.6. The experts interviewed by the ERG stated that:

- Too few cardiologist visits are assumed ([redacted] per patient year).(98) Younger patients would be seen once a year by a cardiologist, while older patients would receive a visit every 5 years on average, with a high degree of variation depending on disease severity;

- The number of A&E referrals is too low, as the average observed in clinical practice is around 5 or 6 per year on average. [redacted] referrals per patient year are assumed in the model;(98).

- The two experts did not agree on the average number of GP visits per year. One expert stated that the [redacted] monthly visits assumed were reasonable, while the other stated that stable patients would be seen about twice a year on average.(98)

Background medical resource use was not associated with age, disease severity and time since diagnosis. However clinical expert opinion confirmed there is an association between these characteristics and the number of A&E referrals, GP and cardiologist visits. The resource use assumed was not compared against previous economic models or trial data for validation. The cost assumed for HF management in the economic model for TA267 (ivabradine for treating chronic heart failure) was £26.77, which compares to £69.31 in the CS.(57) However given that HF management costs are the same across treatment arms in the economic model (with the exception of the effect caused by differential mortality); this background cost has very little impact on the economic results.

5.5.9.4 Resource use and costs associated with AEs

Resource use associated with AEs not requiring hospitalisation is described in Section 5.4.6.7. The company included five different adverse events in this category: hypotension, cough, elevated serum creatinine, elevated serum potassium and angioedema. The incidence rates were based on trial data and assumed constant over time and independent on patient characteristics. Resource use and cost associated with each adverse event are reported in Table 41, Section 5.4.6.7.

The ERG sought clinical expert opinion to validate the resource use assumed. The experts considered the resource use associated with hypotension and elevated serum potassium to be reasonable, but noted that:

- Blood tests are unlikely to be performed for cough events;
- Often more than two GP visits are required for patients with elevated serum creatinine;
- Mild angioedema events are managed by GPs. An average of two visits is considered reasonable, without referrals to a cardiologist;
- Severe angioedema events might lead to hospitalisation or A&E referral. One or two GP visits would be performed anyways. Assuming glucocorticoid treatment is appropriate.

The ERG modified the resource use assumed in the CS in light of the experts' comments aforementioned. The amended resource use and cost associated with each AE id reported in Table 62. The requirement of a blood test associated with cough was removed from the costs, two GP visits were assumed for patients with angioedema and hospitalisation was considered for severe angioedema events. The 35% chance of hospitalisation was calculated based on the PARADIGM-HF trial data and the assumed probability of severe angioedema, as [redacted]% of the events led to hospitalisation in the double-blind period.(90) The cost of hospitalisation was assumed to be equal to the average hospitalisation cost already used in the model, i.e. £2866.35 per event. To avoid double counting, patients with serious angioedema were assumed to either have an A&E referral or be hospitalised, and thus it was assumed that 65% of patients with severe angioedema would be referred to A&E. The ERG notes that the model resulted were insensitive to changes in the AE cost, with a variation in the base case ICER equal to £5.

Table 62. Resource use associated with AEs modified according to clinical expert opinion

Event	Resource use	Resource cost	Source of cost	Total cost
Hypotension	2 GP visits	£35.00	PSSRU(99)	£70.00
Cough	2 GP visits	£35.00	PSSRU(99)	**£70.00**
	No blood test	**£0.00**	**NA**	
Elevated serum creatinine	2 GP visits	£35.00	PSSRU(99)	£73.00
	Blood test	£3.00	NHS National Schedule of Reference Costs 2013-2014(97)	
Elevated serum potassium	2 GP visits	£35.00	PSSRU(99)	£73.00
	Blood test	£3.00	NHS National Schedule of Reference Costs 2013-2014(97)	
Angioedema, mild (60% of cases)	**2 GP visits**	**£35.00**	**PSSRU(99)**	**£70.56**
	Antihistamine treatment (Cetirizine 10 mg for 14 days)	£0.04 per day	BNF(94)	
Angioedema, severe	**A&E visit (65%)**	£123.67	NHS National Schedule of Reference Costs	**£1155.46**

Event	Resource use	Resource cost	Source of cost	Total cost
(40% of cases)			2013-2014(97)	
	Hospitalisation (35%)	**£2,866.35**	**Novartis**	
	2 GP visits	£35.00	PSSRU(99)	
	Glucocorticoid treatment (Prednisolone 40 mg for 5 days)	£0.37 per day	BNF(94)	
Source: adapted from CS, Table 69. Resource use was based from clinical expert opinion. Abbreviations in table: A&E, accident and emergency (department); BNF, British National Formulary; GP, general practitioner; mg, milligram; NHS, National Health Service; PSSRU, Personal Social Services Research Unit.				

Finally the ERG notes that CS did not clearly state what preparations of cetirizine and prednisolone were assumed to be used for the management of mild and severe angioedema. The ERG checked the doses and costs against the current guidelines and found them appropriate.

5.6 Results included in company's submission

5.6.1 Base case results

The ERG presents the company's primary and the secondary base case results in Table 63 and Table 64, respectively. The ERG notes that the results presented are for the patient-level model, all-cause mortality approach and post-clarification stage, where the ICER comparing sacubitril with enalapril decreased from £18,187 to £17,939 per QALY gained.

The primary base case results show that sacubitril + standard of care presents a cost per QALY gained of £17,939 compared with enalapril + standard of care. Compared with enalapril, sacubitril results in more QALYs, and is more costly. The secondary base case results compare enalapril with ARB (candesartan). These are presented in Table 64. Sacubitril + standard of care presents a cost per QALY gained of £16,481 compared with candesartan + standard of care.

Table 63.Company's primary base case results

Results per patient	Enalapril+Standard Care (1)	Sacubitril+Standard Care (2)	Incremental value (2-1)
Total costs (£)	£13,287	£20,801	£7,514
QALYs	4.60	5.02	0.42
ICER			**£17,939**

Table 64.Company's secondary base case results

Results per patient	Candesartan+ Standard Care (1)	Sacubitril+ Standard Care (2)	Incremental value (2-1)

Total costs (£)	£12,288	£20,801	£8,513
QALYs	4.50	5.02	0.62
ICER			**£16,481**

The results obtained using the all-cause mortality approach and the mean cohort model are £17,383 per QALY gained for the company's primary results and £15,885 for the secondary analysis.

The company presented modelled survival from month 0 to month 36 (three years) in the economic analysis and compared this with the observed survival in PARADIGM-HF for the same period of time. Hospitalised rates predicted by the model and observed in the PARADIGM-HF trial were also provided. These results are provided in Section 5.7.2 of the CS.

Table 65 and Table 66 present the ICERs for the company's primary and secondary analysis, respectively, using the CV mortality (instead of all-cause mortality) approach for the patient-level model. The ICER in Table 65 is slightly higher than the one reported in Table 63, as expected however the ICER for the secondary analysis using the CV mortality approach is slightly lower than the ICER using the all-cause mortality approach, reported in Table 64.

Table 65. Company's primary base case results, CV approach

Results per patient	Enalapril+SoC (1)	Sacubitril+SoC (2)	Incremental value (2-1)
Total costs (£)	£14,814	£23,458	£8,644
QALYs	5.08	5.60	0.52
ICER			**£16,678**

Table 66.Company's secondary base case results, CV approach

Results per patient	Candesartan+SoC (1)	Sacubitril+SoC (2)	Incremental value (2-1)
Total costs (£)	£13,835	£23,458	£9,623
QALYs	5.02	5.60	0.58
ICER			**£16,569**

5.6.2 Sensitivity analysis

5.6.2.1 Deterministic sensitivity analysis

In this section the ERG presents the results for the deterministic sensitivity analysis reported in Sections 5.8.5 to 5.9.5 of the CS. The company performed three distinct types of deterministic

sensitivity analyses (DSA): one-way parameter variations, scenario analyses and subgroup analyses. These are reported in the subsections below together with the ERG's commentary.

5.6.2.2 One-way deterministic sensitivity analyses

Univariate one-way DSAs were presented in Sections 5.8.5 and 5.8.6 of the CS. A list of key parameters was identified in the economic model and varied one by one independently and systematically. The values were varied to the upper or lower bounds of the 95% confidence intervals surrounding the point estimate and, when a confidence interval was not available, by increasing or decreasing the parameter value by an arbitrary proportion equal to 25%. The confidence intervals were derived from either modelling (e.g. regression coefficients) or data analysis (e.g. proportion of patients treated with aspirin at baseline).

The variables included in the one-way DSAs are listed in Table 128, Appendix 15 of the CS. The ERG found numerous errors in the values reported in Table 128 in Appendix 15 however the parameter values included in the economic model and the results reported in the main submission appear to be correct. The parameter included in the DSA are summarised in Table 67 below.

Table 67. Variables included in the univariate DSAs (adapted from Table 128, Appendix 15 of the CS)

Variable or set of variables	Reference for uncertainty
CV mortality model coefficients	95% CI from regression model
All-cause mortality model coefficients	95% CI from regression model
Discontinuation model coefficients	95% CI from regression model
Hospitalisation model coefficients	95% CI from regression model
Utility model coefficients	95% CI from regression model
AE rates: hypotension, cough, angioedema, elevated serum potassium, elevated serum creatinine	95% CI from trial data
AEs mean duration (days): hypotension, cough	95% CI from trial data
Primary therapy costs: enalapril, ramipril, perindopril, lisinopril, valsartan, losartan, candesartan	Arbitrarily set to ±25%
Background therapy costs: carvedilol, bisoprolol, spironolactone, digoxin, atorvastatin, simvastatin, furosemide, aspirin, warfarin, clopidogrel	Arbitrarily set to ±25%
Proportion of patients at baseline on: BB, AA, digoxin, lipid lowering medications, diuretics, aspirin, anticoagulants, ADP antagonists	95% CI from trial data
AEs costs, hypotension: cost per GP visit, number of GP visits required	Arbitrarily set to ±25%
AEs costs, elevated serum creatinine: cost per GP visit, number of GP visits required, cost per lab test	Arbitrarily set to ±25%
AEs costs, elevated serum potassium: cost per GP visit, number of GP visits required, cost per lab test	Arbitrarily set to ±25%
AEs costs, cough: cost per GP visit, number of GP visits required, cost per lab test	Arbitrarily set to ±25%
AEs costs, angioedema: proportion with milder angioedema, cost per outpatient contact, number of outpatient visits required, daily costs of antihistamines, number of days on antihistamines, cost per A&E visit, cost per GP visit, A&E visits required, GP visits required, daily cost of glucocorticoids, number of days on glucocorticoids	Arbitrarily set to ±25%

Titration costs: cost per cardiologist visit, number of cardiologist visits required, NT-proBNP test, number of outpatient visits required (NT-proBNP test), cost per outpatient contact	Arbitrarily set to ±25%
Background medical resource use: GP emergency visits, A&E referrals, GP visits, cardiologist visits, other physician visits, GP home visits, GP hospital visits, GP nursing home visits, GP home visits, GP phone calls to patient, GP visits with third parties	Arbitrarily set to ±25%
Background medical resource cost: GP emergency visits, A&E referrals, GP visits, cardiologist visits, other physician visits, GP home visits, GP hospital visits, GP nursing home visits, GP home visits, GP phone calls to patient, GP visits with third parties	Arbitrarily set to ±25%
Source: adapted from Table 128, Appendix 15 of the CS. Abbreviations used in table: AA, aldosterone anagonist; ADP, adenosine diphosphate; AE, adverse event; A&E, accident and emergency (department); BB, beta blocker; CI, confidence interval; CV, cardiovascular; DSA, deterministic sensitivity analysis; GP, general practitioner; NT-proBNP, N-terminal of the prohormone brain natriuretic peptide.	

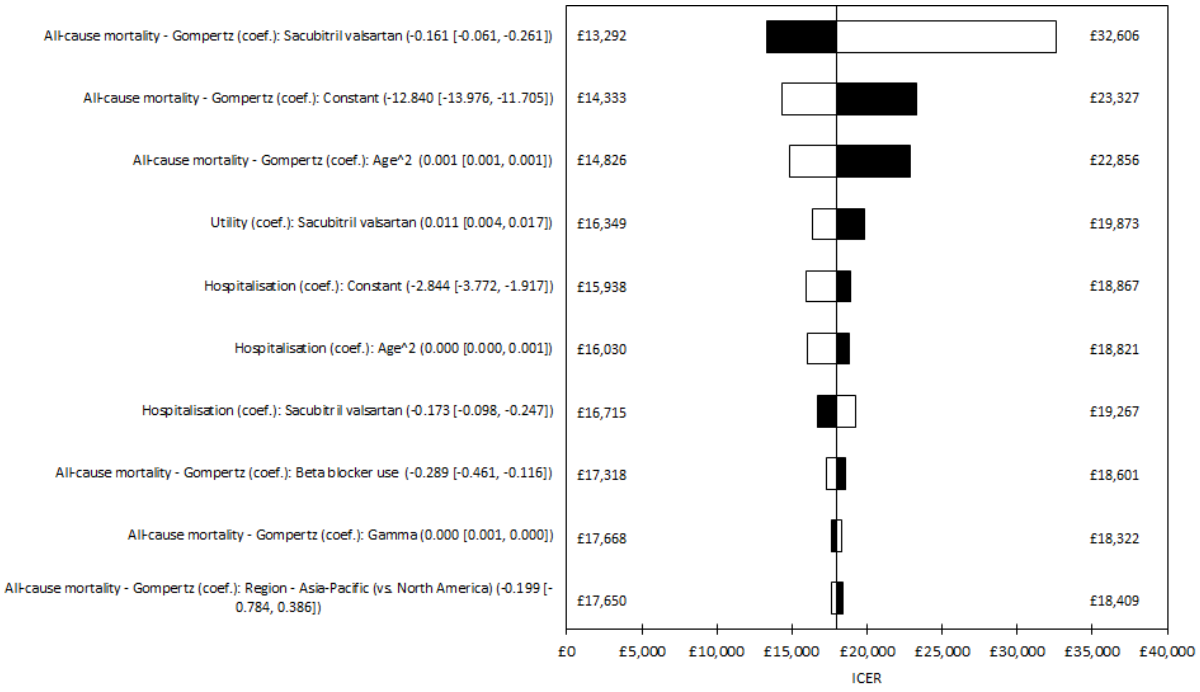
The company performed univariate variations for all included parameters in the mean patient model. The 10 most influential ones in terms of range of variation in the ICER were re-tested in the individual patient-based model, and the ICER recorded. The ICERs for these parameters are reported in Table 68 and represented graphically in the tornado plot shown in Figure 26.

Table 68. Most influential parameters in the one-way DSAs (reproduced from Table 16, Clarification Response Addendum; Novartis)

Parameter	**Mean (range varied between)**	**ICER with low value**	**ICER with high value**
All-cause mortality - Gompertz (coef.): sacubitril valsartan	-0.161 (-0.061, -0.261)	£13,292	£32,606
All-cause mortality - Gompertz (coef.): Constant	-12.840 (-13.976, -11.705)	£23,327	£14,333
All-cause mortality - Gompertz (coef.): Age^2*	0.0009 (0.0006, 0.0011)	£22,856	£14,826
Utility (coef.): Sacubitril valsartan	0.011 (0.004, 0.017)	£19,873	£16,349
Hospitalisation (coef.): Constant	-2.844 (-3.772, -1.917)	£18,867	£15,938
Hospitalisation (coef.): Age^2*	0.0005 (0.0002, 0.0007)	£18,821	£16,030
Hospitalisation (coef.): Sacubitril valsartan	-0.173 (-0.098, -0.247)	£16,715	£19,267
All-cause mortality - Gompertz (coef.): BB use	-0.289 (-0.461, -0.116)	£18,601	£17,318
All-cause mortality - Gompertz (coef.): Gamma	0.00037 (0.00021, 0.00053)	£17,668	£18,322
Abbreviations used in table: BB, beta blockers; DSA, deterministic sensitivity analysis; ICER, incremental cost-effectiveness ratio. *Note:* the company included only the 9 most influential parameters in this table, and not 10 as reported.			

As expected, the most influential parameter in the model is the magnitude of the mortality reduction attributed to sacubitril. The variation of the associated coefficient in the all-cause mortality parametric model determined a variation in the ICER equal to £19,314 per QALY gained between the lower and upper bound of the 95% confidence interval estimated in the regression model.

Figure 26. Tornado plot for most influential parameters in the DSA (Source: Figure 8, Clarification Response Addendum; Novartis)



Abbreviations used in figure: coef., coefficient; DSA, deterministic sensitivity analysis; ICER, incremental cost-effectiveness ratio.

The ERG notes that the one-way DSA did not include any parameter related to baseline patient characteristics, and therefore the influence of these parameters on the model outcomes was not analysed. As discussed throughout the report, the PARADIGM-HF trial population lack generalisability in many aspects when compared to the UK HF population. By not including patient characteristics as part of the sensitivity analyses, the company might have underestimated the impact of these variables on the cost-effectiveness results and the uncertainty related to both the variability of the parameters and the translation to general practice. This uncertainty was only partially explored as part of the company's scenario analyses.

5.6.2.3 Deterministic scenario analyses

The company produced several scenario analyses, presented in Section 5.8.8 of the CS. The results are shown in Table 69.

Table 69. Scenario analyses performed by the company. (reproduced from Table 22 in the clarification responses addendum, updating Table 99 in the CS)

Scenario name	Sacubitril valsartan		ACEi		ICER	% change from base case
	Costs	QALYs	Costs	QALYs		
Base case analysis	£20,801	5.02	£13,287	4.60	£17,939	–
Discount rates altered to reflect historic NICE discount rates of 6% for costs and 1.5% for outcomes	£18,581	5.54	£11,977	5.05	£13,390	-25%
Weibull distribution used in all-cause mortality model	£27,080	6.40	£17,009	5.81	£17,135	-4%
Exponential distribution used in model of all-cause mortality	£29,714	6.95	£18,709	6.33	£17,698	-1%
Annual rate of decline in EQ-5D halved	£20,801	5.15	£13,287	4.71	£17,236	-4%
Annual rate of decline in EQ-5D doubled	£20,801	4.75	£13,287	4.37	£19,535	9%
No decline in EQ-5D over time	£20,801	5.28	£13,287	4.83	£16,588	-8%
No decline in EQ-5D after 5 years	£20,801	5.11	£13,287	4.67	£17,238	-4%
No decline in EQ-5D after 10 years	£20,801	5.04	£13,287	4.61	£17,688	-1%
Effect of sacubitril valsartan on EQ-5D (beyond differences in hospitalisation / adverse event rates) assumed to be zero	£20,801	4.95	£13,287	4.60	£21,516	20%
Effect of sacubitril valsartan on hospitalisation rates assumed to apply to HF hospitalisation only	£21,556	5.01	£13,287	4.60	£19,895	11%
Effect of sacubitril valsartan on hospitalisation rates assumed to apply to CV hospitalisation only	£21,217	5.01	£13,287	4.60	£19,013	6%
Effect of hospitalisation on EQ-5D assumed to be zero	£20,801	5.05	£13,287	4.63	£18,032	1%
Sacubitril valsartan treatment effects assumed to cease at year 5	£20,521	4.82	£13,287	4.60	£31,808	77%
Sacubitril valsartan treatment effects assumed to cease at year 10	£20,677	4.95	£13,287	4.60	£20,941	17%
Treatment discontinuation considered over lifetime time horizon	£18,623	4.89	£13,293	4.60	£18,150	1%
Treatment discontinuation considered up to year 3	£19,548	4.95	£13,290	4.60	£17,932	0%
Treatment discontinuation assumed to result in reduced therapy costs; efficacy estimates as in trial	£18,660	5.02	£13,293	4.60	£12,814	-29%
Hospitalisation costs doubled	£27,620	5.02	£20,726	4.60	£16,458	-8%
Hospitalisation costs halved	£17,391	5.02	£9,567	4.60	£18,680	4%
Proportions of hospitalisation types derived using Western Europe population	£21,503	5.02	£14,053	4.60	£17,787	-1%
All adverse event rates set to zero	£20,703	5.02	£13,195	4.60	£17,909	0%
Primary therapies costed assuming target doses from PARADIGM-HF	£20,801	5.02	£13,296	4.60	£17,918	0%
Cost of ramipril applied to ACEi arm	£20,801	5.02	£13,330	4.60	£17,835	-1%
Cost of titration included	£21,062	5.02	£13,287	4.60	£18,564	3%
Increased risk of hospitalisation over time	£28,500	4.99	£21,193	4.57	£17,443	-3%

Abbreviations used in table: ACEi, angiotensin-converting enzyme inhibitor; CV, cardiovascular; EQ-5D, European Quality of Life 5-dimensions; HF, heart failure; ICER, incremental cost-effectiveness ratio; NICE, National Institute for Health and Care Excellence; QALY, quality-adjusted life year.

The ERG notes that a deterministic sensitivity analysis around the discount rates was performed only for discount rates of 6% for costs and 1.5% for health outcomes. However the NICE Guide to the Methods of the Technology Appraisal recommends performing scenario analyses with a discount rate of 1.5% for both costs and benefits.(5) A more comprehensive analysis has been performed by the ERG using the mean cohort model, reported in Table 70. As expected, higher discount rates lead to higher ICERs.

Table 70. Univariate DSA for discount rates

Discount rate		ICER (cost per QALY gained)	Difference from base case
Costs	**Effects**		
3.5%	3.5%	£17,314 (base case)	NA
0%	0%	£15,895	-£1,419
1.5%	1.5%	£16,498	-£816
6%	6%	£18,348	£1,034
6%	1.5%	£13,179	-£4,135

Abbreviations used in table: DSA, deterministic sensitivity analysis; ICER, incremental cost-effectiveness ratio; NA, not applicable; QALY, quality-adjusted life year.

Note: Analysis carried out by the ERG and performed on the company's base case after applying the utility corrections reported in Section 5.5.8.5.

The discontinuation scenario analysis assumed that patients would switch to an ACEi if originally on sacubitril and to an ARB if previously on ACEi therapy. Even though clinical expert opinion sought by the ERG confirmed this to be a reasonable assumption, the rates of discontinuation observed in the trial are likely to be an underestimation of clinical practice, not only in a first-line treatment scenario but also in a second-line treatment situation. This is due to the fact that drug tolerability in the trial is likely to be overestimated, as discussed in Section 5.5.3.2.

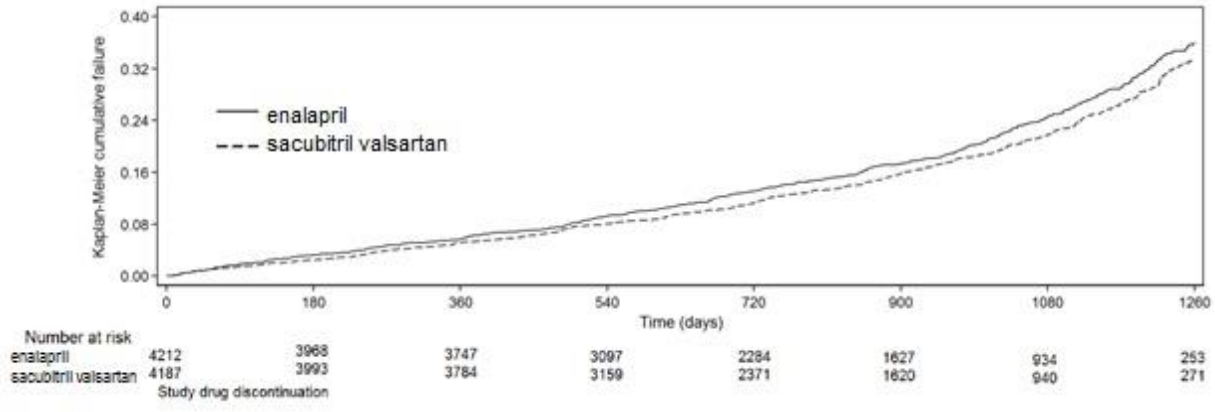
The company acknowledged there is substantial uncertainty on the long-term discontinuation of sacubitril, and made the following assumptions:

- Discontinuations occur over the entire time horizon;
- The reduction in discontinuations attributed to sacubitril persists over time;
- Patients discontinuing sacubitril switch to ACEi efficacy for mortality, hospitalisation, QoL and adverse events.

The scenario analysis used an exponential parametric survival model to estimate the rate of discontinuations, with death considered a censoring event in the analysis. The Kaplan Meier curve for the analysis is reported in Figure 27. An increase in the hazard discontinuation was noted towards the end of the trial, which was believed to represent an artefact of the study design and/or reporting. The

constant hazard assumption implied by the exponential model specification was considered to be reasonable by the company as it avoids the risk of extrapolating what was considered to be an implausible trend observed at the end of the trial.

Figure 27. Kaplan Meier discontinuation (not caused by death) in PARADIGM-HF (FAS). (reproduced from CS, Figure 41)



Abbreviations used in figure: FAS, full analysis set.

The parametric model used for discontinuation events is reported in Table 98 of the CS. The HR for the reduction in the risk of discontinuation events attributed to sacubitril was 0.89 and significantly different from zero at a confidence level of $1 - \alpha = 0.95$. A substantial variation across geographical areas was observed, with patients in Western Europe and North America being more likely to discontinue treatment than in the other areas of the world. The ERG notes that goodness of fit statistics, visual analyses and alternative model specifications were not reported in the CS.

The scenario analysis does not result in a change in the estimated QALYs for the ACEi arm as no difference is assumed between ACEi and ARBs with the exception of costs and those differ only slightly. The ICER increases from the base case estimate as the cost savings caused by patients switching to the cheaper ARB therapy in the sacubitril arm are overweighed by a loss in the incremental efficacy compared to ACEi. To also note is that the exponential model is likely to be underestimating the discontinuation rates, [redacted] (Section 5.5.3.2).

Variation in hospitalisation was assessed in several deterministic scenario analyses, looking at changes in event rates, costs and treatment effects. Expert opinion sought by the ERG confirmed that the assumption of a constant rate of hospitalisation was not a reasonable assumption, and that hospitalisation rates, cause and length of stay varies with age (Section 5.5.9). The scenario analysis included in the CS which increased the hospitalisation rate by 10% yearly, proved the model relatively insensitive to this variation (the ICER increased by about £500 per QALY gained).

The company also produced a scenario analysis where the reasons for hospitalisation were derived only from the Western European patient subgroup (about 2000 patients). These are reported in Table 71. Clinical expert opinion sought by the ERG explained that the determinants of hospitalisation are likely to differ across the different regions included in the trial. As NHS data were used to estimate the hospitalisation costs in the model, the use of Western Europe-specific data is likely to be more robust for the estimation of an average hospitalisation event costs. [redacted] The different distribution in the admission reasons led to an average hospitalisation cost estimate equal to £3,162, compared to the base-case average cost of £2,866.

Table 71. Western Europe subgroup hospitalisation resource use. (adapted from Table 125, Appendix 13 of the CS)

Hospitalisation Type	% in FAS	% in Western Europe subgroup
Surgical procedure	[redacted]	[redacted]
Coronary artery bypass grafting	[redacted]	[redacted]
Mitral valve repair/ mitral valve replacement/ other valve surgery	[redacted]	[redacted]
Other cardiac surgery	[redacted]	[redacted]
Left ventricular aneurysmectomy	[redacted]	[redacted]
Ventricular assist device	[redacted]	[redacted]
Heart transplantation	[redacted]	[redacted]
Interventional procedure	[redacted]	[redacted]
Implantable cardioverter defibrillator	[redacted]	[redacted]
Cardiac pacemaker - biventricular, defibrillating	[redacted]	[redacted]
Cardiac pacemaker - biventricular, non-defibrillating	[redacted]	[redacted]
Cardiac pacemaker - conventional	[redacted]	[redacted]
Coronary angioplasty	[redacted]	[redacted]
Percutaneous coronary intervention - multiple	[redacted]	[redacted]
Percutaneous coronary intervention - single	[redacted]	[redacted]
Medical management	[redacted]	[redacted]
Cardiac failure/ cardiac failure congestive/ cardiac failure chronic/ cardiac failure acute/ dyspnoea	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]
Atrial fibrillation/ ventricular tachycardia	[redacted]	[redacted]
Cerebrovascular accident	[redacted]	[redacted]
Non-cardiac chest pain	[redacted]	[redacted]
Syncope	[redacted]	[redacted]
Chronic obstructive pulmonary disease	[redacted]	[redacted]
Angina pectoris/ angina unstable	[redacted]	[redacted]
Ischaemic stroke	[redacted]	[redacted]
Myocardial infarction/ acute myocardial infarction	[redacted]	[redacted]
Renal failure acute	[redacted]	[redacted]
Congestive cardiomyopathy/ hypotension	[redacted]	[redacted]

Hospitalisation Type	% in FAS	% in Western Europe subgroup
Transient ischaemic attack	[redacted]	[redacted]
Urinary tract infection	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]
Coronary artery disease	[redacted]	[redacted]
Abbreviations used in table: FAS, full analysis set.		

The resulting ICER decreased from the base case by 1% as the reduction in hospitalisations associated with sacubitril produced greater cost savings compared to the base case.

CPRD-based re-weighting scenario analysis

The company undertook scenario analysis to adjust the trial population characteristics to those of the UK HF population by using the results from the CPRD analysis. In Section 5.8.8.1 of the CS, it is reported that, "subjects in PARADIGM-HF were generally younger, more likely to be male, and more likely to be current smokers than those in CPRD. These differences have consequences for estimating, amongst other things, the baseline mortality rate". The company built the scenario analysis using a raking (or sample balancing) method, which broadly consists on attributing weights to each patient in order to adjust for differences between the observed and the target population. However the company did not describe the raking procedure undertaken and no further details were provided, other than that the main assumption of the procedure was that no unobserved confounding factors remain unbalanced after re-weighting. In light of this, the ERG's critique on this scenario analysis is largely based on the ERG's interpretation of the submitted evidence.

Two raking-based analyses were performed using the estimates from the CPRD analysis as the target population values. The first analysis took into account only age and gender, while the second one included all the variables contained in the CPRD dataset which could be used for raking, i.e. the proportion of patients with prior stroke, eGFR levels lesser than 60 ml/min and current smokers, in addition to age at baseline and gender.

Table 72. Comparison of PARADIGM-HF and CPRD characteristics and model characteristics after reweighting of subjects. (CS, Table 90)

Variable	PARADIGM-HF	CPRD	Re-weighted PARADIGM-HF from model	
			Age and gender only	All available variables
18-49 years	[redacted]	[redacted]	[redacted]	[redacted]
50-54 years	[redacted]	[redacted]	[redacted]	[redacted]
55-64 years	[redacted]	[redacted]	[redacted]	[redacted]
65-69 years	[redacted]	[redacted]	[redacted]	[redacted]
70-74 years	[redacted]	[redacted]	[redacted]	[redacted]
75-84 years	[redacted]	[redacted]	[redacted]	[redacted]

Variable	PARADIGM-HF	CPRD	Re-weighted PARADIGM-HF from model	
			Age and gender only	All available variables
85+ years	[redacted]	[redacted]	[redacted]	[redacted]
Mean age (SD)	63.8 (11)	[redacted]	[redacted]	[redacted]
Gender (% female)	22	[redacted]	[redacted]	[redacted]
Prior stroke (%)	8.6	[redacted]	[redacted]	[redacted]
eGFR <60 mL/min (%)	36.4	[redacted]	[redacted]	[redacted]
Current smoker (%)	14.4	[redacted]	[redacted]	[redacted]

Abbreviations used in table: CPRD, Clinical Practice Research Datalink; eGFR, estimated glomerular filtration rate; min, minute; mL, millilitre; SD, standard deviation.

† New HF patients and LVSD within 6 months of HF diagnosis in CPRD, 2005-2013 (n=18,028)

‡ Characteristics of patients with HFrEF, based on CPRD-HES linked data set, 2005-2013, at index date (n=10,646)

Age was partitioned into 7 arbitrary categories: 18–49, 50–54, 55–64, 65–69, 70–74, 75–84 and over 85 years.

[redacted] The implications of this are not explored in the CS. It is the ERG opinion that the age categories should have been built with fewer categories (no more than 6 categories) [redacted].(112) Moreover, the age distribution in the CPRD was derived from patients who had their HF diagnoses in the previous 6 months. In contrast, 70% of patients in PARADIGM-HF were diagnosed more than one year prior to randomisation and 31% more than 5 years before. The ERG believes that this causes a problem in the re-weighting process as time since diagnoses is correlated with age and is assumed to predict mortality, hospitalisation, utility scores and discontinuation in the model. It might have been more appropriate to re-weight only newly diagnosed patients in the trial or adjust the distribution obtained from the CPRD for the time lag since diagnosis.

As shown in Table 72, the raking procedure was effective in fitting the CPRD distribution and led to a convergence of the trial data to the target values. Given that the re-weighting method using all available variables seem to produce better (i.e. more comparable) results than re-weighting using only age and gender, the ERG focuses on the latter. A comparison of the mean baseline characteristics between the trial population, the re-weighted one (using all available variables) and the Western European subgroup is reported in Table 73.

Even though this scenario analysis was designed based on the need to provide estimates representative of the UK HF population, the final weights attributed to the profiles of patients from outside Western Europe was substantial (a total of 71% according to Table 73). This is an issue given that not all of the

other baseline characteristics could be adjusted to reflect CPRD data (note that only variables in bold in Table 73 have been adjusted and re-weighted according to CPRD data). Re-weighting the population characteristics using the entire trial population seems to be inappropriate for the purpose of trying to replicate the UK population. This is due to the fact that a considerable weight (71%) is still being given to patient profiles not related to the Western European populations.

Table 73. Comparison of baseline patient characteristics for the FAS, CPRD re-weighted FAS and West European subgroup

Baseline characteristic	**PARADIGM-HF trial FAS**	**CPRD re-weighted trial population**	**West European subgroup**
Age	63.80	[redacted]	[redacted]
Female	21.81%	[redacted]	[redacted]
Region - North America	7.17%	[redacted]	[redacted]
Region - Latin America	17.06%	[redacted]	[redacted]
Region - Western Europe	24.42%	[redacted]	[redacted]
Region - Central Europe	33.65%	[redacted]	[redacted]
Region - Asia-Pacific	17.70%	[redacted]	[redacted]
Race - white	66.01%	[redacted]	[redacted]
Race - black	5.10%	[redacted]	[redacted]
Race - Asian	17.97%	[redacted]	[redacted]
Race - other	10.93%	[redacted]	[redacted]
NYHA class I	4.63%	[redacted]	[redacted]
NYHA class II	70.63%	[redacted]	[redacted]
NYHA class III	24.03%	[redacted]	[redacted]
NYHA class IV	0.71%	[redacted]	[redacted]
NYHA class III/IV	24.74%	[redacted]	[redacted]
LVEF (%)	29.49	[redacted]	[redacted]
SBP (mmHg)	121.38	[redacted]	[redacted]
Heart rate (bpm)	72.35	[redacted]	[redacted]
eGFR (mL/min/1.73m^2)	67.70	[redacted]	[redacted]
NT-proBNP (pg/mL)	2891.04	[redacted]	[redacted]
Sodium (mmol/L)	141.46	[redacted]	[redacted]
Potassium (mmol/L)	4.51	[redacted]	[redacted]
QRS duration (ms)	117.36	[redacted]	[redacted]
BMI (kg/m^2)	28.16	[redacted]	[redacted]
Diabetes	34.61%	[redacted]	[redacted]
Hypertension	70.72%	[redacted]	[redacted]
Prior ACEi use	77.77%	[redacted]	[redacted]
Prior ARB use	22.53%	[redacted]	[redacted]
BB use	93.00%	[redacted]	[redacted]
AA use	55.61%	[redacted]	[redacted]
Digoxin use	30.23%	[redacted]	[redacted]
Lipid lowering medication use	56.30%	[redacted]	[redacted]
Allopurinol use	4.83%	[redacted]	[redacted]

Baseline characteristic	PARADIGM-HF trial FAS	CPRD re-weighted trial population	West European subgroup
≤ 1 year since HF diagnosis	30.04%	[redacted]	[redacted]
1-5 years since HF diagnosis	38.48%	[redacted]	[redacted]
> 5 years since HF diagnosis	31.48%	[redacted]	[redacted]
Ischaemic aetiology	59.96%	[redacted]	[redacted]
Prior stroke	8.63%	[redacted]	[redacted]
Prior atrial fibrillation/ flutter	36.80%	[redacted]	[redacted]
Prior angina	0.40%	[redacted]	[redacted]
Prior cancer	4.31%	[redacted]	[redacted]
Current smoker	14.38%	[redacted]	[redacted]
Prior HF hospitalisation	62.79%	[redacted]	[redacted]
EQ-5D	0.78	[redacted]	[redacted]

Abbreviations used in table: AA, aldosterone antagonist; ACEi, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin receptor blocker; BB, beta blocker; BMI, body mass index; bpm, beats per minute; CPRD, Clinical Practice Research Datalink; eGFR, estimated glomerular filtration rate; EQ-5D, European Quality of Life 5-Dimensions; FAS, full analysis set; HF, heart failure; ICER, incremental cost-effectiveness ratio; kg, kilogram; L, litre; LVEF, left ventricular ejection fraction; min, minute; mL, millilitre; mmHg, millimetre of mercury; mmol, millimole; ms, millisecond; m^2, squared metre; NT-proBNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association; QALY, quality-adjusted life year; SBP, systolic blood pressure.

Source: Novartis, data elaborated by the ERG.

* Variable used in the raking procedure.

The ICER resulting from the CPRD re-weighted population resulted in a slight increase compared to the base case ICER (£17,939 to £18,167).

5.6.2.4 Deterministic subgroup analysis

The company presented a high number of deterministic subgroup analyses. The subgroup analyses were based on the patient-level modelling approach, and were performed by selecting only the results of the patient profile-based cohorts corresponding to certain baseline characteristics out of the 8,399 cohorts. It is therefore unclear whether the differences in the results were driven only by the selected trait (e.g. baseline age ≥75) or there were other baseline characteristics influencing the outcomes (e.g. eGFR levels). The results of the subgroup analyses are presented in Table 74.

Table 74. Subgroup analyses. (Table 23 in the clarification responses addendum, updating Table 100 in the CS)

#	Subgroup	Δ Costs	Δ QALYs	ICER	% change from base case
1	Full analysis set	£7,514	0.42	£17,939	0%
2	Baseline age < 65 years	£7,932	0.44	£18,189	1%
3	Baseline age ≥ 65 years	£7,079	0.40	£17,657	-2%
4	Baseline age < 75 years	£7,789	0.43	£18,137	1%
5	Baseline age ≥ 75 years	£6,312	0.37	£16,944	-6%
6	Region - North America	£7,453	0.41	£18,119	1%
7	Region - Latin America	£7,020	0.42	£16,619	-7%

#	Subgroup	Δ Costs	Δ QALYs	ICER	% change from base case
8	Region - Western Europe	£7,930	0.44	£18,173	1%
9	Region - Central Europe	£7,511	0.39	£19,208	7%
10	Region - Asia-Pacific	£7,447	0.45	£16,651	-7%
11	Baseline NYHA class I/ II	£7,842	0.44	£17,709	-1%
12	Baseline NYHA III/ IV	£6,516	0.35	£18,836	5%
13	Baseline LVEF ≤ median	£7,140	0.41	£17,235	-4%
14	Baseline LVEF > median	£7,948	0.42	£18,738	4%
15	Baseline SBP ≤ median	£7,427	0.42	£17,563	-2%
16	Baseline SBP > median	£7,619	0.41	£18,404	3%
17	Baseline eGFR < 60	£6,746	0.39	£17,175	-4%
18	Baseline eGFR ≥ 60	£7,954	0.43	£18,336	2%
19	Baseline NT-proBNP ≤ median	£8,748	0.46	£19,203	7%
20	Baseline NT-proBNP > median	£6,184	0.38	£16,304	-9%
21	Diabetes at baseline	£6,835	0.39	£17,344	-3%
22	No diabetes at baseline	£7,874	0.43	£18,227	2%
23	Hypertension at baseline	£7,432	0.41	£18,114	1%
24	No hypertension at baseline	£7,713	0.44	£17,546	-2%
25	Prior use of ACEi	£7,555	0.42	£18,030	1%
26	Prior use of ARB	£7,369	0.42	£17,620	-2%
27	Use of BB at baseline	£7,603	0.42	£18,051	1%
28	No use of BB at baseline	£6,328	0.39	£16,321	-9%
29	Use of AA at baseline	£7,415	0.42	£17,852	0%
30	No use of AA at baseline	£7,638	0.42	£18,047	1%
31	≤ 1 year since diagnosis of HF	£8,486	0.46	£18,606	4%
32	1-5 years since diagnosis of HF	£7,253	0.41	£17,764	-1%
33	> 5 years since diagnosis of HF	£6,905	0.40	£17,427	-3%
34	Ischaemic aetiology	£7,282	0.41	£17,885	0%
35	Non-ischaemic aetiology	£7,862	0.44	£18,014	0%
36	Prior AF at baseline	£7,141	0.40	£17,911	0%
37	No prior AF at baseline	£7,731	0.43	£17,954	0%
38	Prior HF hospitalisation	£7,220	0.41	£17,609	-2%
39	No prior HF hospitalisation	£8,011	0.43	£18,466	3%

Abbreviations used in table: AA, aldosterone antagonist; ACEi, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin receptor blocker; BB, beta blocker; eGFR, estimated glomerular filtration rate; HF, heart failure; ICER, incremental cost-effectiveness ratio; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association; QALY, quality-adjusted life year; SBP, systolic blood pressure.

Note: the percentage variations were corrected by the ERG

Western European subgroup

As part of the clarification process the ERG asked the company to run the economic model based on the subgroup analysis of the Western European population in the trial. The ERG considers this to be crucial analysis given the ERG's clinical experts' advice that geographical differences could potentially be driving trial outcomes. This is mainly related to:

- Access to and use of care across different regions, in particular for hospitalisation, mechanical implants and devices;
- Management of HF patients, including non-pharmacological standards of care;
- HF aetiology and diagnosis;
- Non-CV causes of death (such as infection);
- Previous care and management of patients before commencement of the trial;
- Patient profiles at baseline.

Subgroup analysis by region of the PARADIGM-HF trial outcomes showed variation in the results across regions both in the primary composite outcome and in CV mortality between sacubitril and enalapril.

[redacted] While the trial was not designed and powered to detect differences in geographical subgroups, the ERG notes that the two treatment groups were randomly stratified by geographical region. Most importantly, statistically significant differences between treatments groups were shown for subgroups considerably smaller in size than Western Europe (2051 patients). For example, North America (602 patients) and Latin America (1433 patients) were associated with statistically significant results even though the number of patients were more than three times smaller in the case of North America or half in case of Latin America. The ERG believes this might indicative of a different relative effect of sacubitril compared to enalapril across geographical areas. However no causal association can be established as the trial was not designed to answer this question.

A comparison of the baseline characteristics between the entire trial population and the Western European subgroup is include in Table 75. Western European patients were, on average, [redacted] older than the entire trial population and [redacted]. Some of the prognostic parameters differed but only slightly. The NYHA class distribution at baseline indicates,

[redacted], compared the entire trial population. The average time since diagnosis [redacted] for the Western European group, with [redacted] diagnosed with HF more than 5 years prior to randomisation. Previous drug use is also slightly different, with a [redacted], lipid lowering medications

[redacted] and allopurinol [redacted]. [redacted] No comparisons could be made with regards to use of device use at baseline as NICE impeded the ERG to request these data from the company during the clarification stage.

Table 75. Comparison of baseline characteristics between all-trial population and Western European subgroup

Baseline characteristics	All trial population (N=8399)	Western European subgroup (N=2051)
Age	63.80	[redacted]
Female	21.81%	[redacted]
Region - North America	7.17%	[redacted]
Region - Latin America	17.06%	[redacted]
Region - Western Europe	24.42%	[redacted]
Region - Central Europe	33.65%	[redacted]
Region - Asia-Pacific	17.70%	[redacted]
Race - white	66.01%	[redacted]
Race - black	5.10%	[redacted]
Race - Asian	17.97%	[redacted]
Race - other	10.93%	[redacted]
NYHA class I	4.63%	[redacted]
NYHA class II	70.63%	[redacted]
NYHA class III	24.03%	[redacted]
NYHA class IV	0.71%	[redacted]
NYHA class III/IV	24.74%	[redacted]
LVEF (%)	29.49	[redacted]
SBP (mmHg)	121.38	[redacted]
Heart rate (bpm)	72.35	[redacted]
eGFR (mL/min/1.73m^2)	67.70	[redacted]
NT-proBNP (pg/mL)	2891.04	[redacted]
Sodium (mmol/L)	141.46	[redacted]
Potassium (mmol/L)	4.51	[redacted]
QRS duration (ms)	117.36	[redacted]
BMI (kg/m2)	28.16	[redacted]
Diabetes	34.61%	[redacted]
Hypertension	70.72%	[redacted]
Prior ACEi use	77.77%	[redacted]
Prior ARB use	22.53%	[redacted]
BB use	93.00%	[redacted]
AA use	55.61%	[redacted]
Digoxin use	30.23%	[redacted]
Lipid lowering medication use	56.30%	[redacted]
Allopurinol use	4.83%	[redacted]
≤ 1 year since HF diagnosis	30.04%	[redacted]
1-5 years since HF diagnosis	38.48%	[redacted]
> 5 years since HF diagnosis	31.48%	[redacted]
Ischaemic aetiology	59.96%	[redacted]
Prior stroke	8.63%	[redacted]
Prior atrial fibrillation/ flutter	36.80%	[redacted]
Prior angina	0.40%	[redacted]
Prior cancer	4.31%	[redacted]
Current smoker	14.38%	[redacted]
Prior HF hospitalisation	62.79%	[redacted]
EQ-5D	0.78	[redacted]
Abbreviations used in table: AA, aldosterone antagonist; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BB, beta blocker; BMI, body mass index; eGFR, estimated glomerular filtration rate; EQ-5D, European Quality of Life 5-Dimensions; HF, heart failure; L, litre; LVEF, left		

ventricular ejection fraction; min, minute; mL, millilitre; mmHg, millimitre of mercury; mmol, millimole; ms, millisecond; m^2, squared metre; NYHA, New York Heart Association; pg, picogram; SBP, systolic blood pressure.
Source: ERG elaboration of the trial data included in the submitted economic model.

At the clarification stage, the company provided the ERG with a new additional economic model in which the baseline characteristics of the Western European subgroup were used and all the regression models (i.e. all-cause mortality, CV-related mortality, hospitalisation and QoL) were fitted solely on the data the Western European trial subgroup. The company also submitted a version of the model where the effect of sacubitril was estimated based on the entire trial population rather than on the Western European population, with only baseline characteristics from the Western European group used. The ERG considers the latter approach to be the most robust one thus results of this analysis are now presented.

The company's regression analysis used the same model specifications as the ones used in the base case analysis for the entire trial. Other modelling approaches were not tested, parameters with non-statistically significant effects on the dependent variable were not excluded from regression models and parameters not included in the original model were not tested for inclusion. The subgroup-specific regression models for CV mortality, all-cause mortality, hospitalisation and utility scores are reported below in Table 76, Table 77, Table 78 and Table 79 respectively.

Table 76. Cardiovascular mortality Gompertz regression model: comparison with Western European subgroup model

Parameter	All trial population				Western Europe subgroup			
	Coef.	HR	SE	P > z	Coef.	HR	SE	P > z
Sacubitril valsartan	-0.216	0.806	0.057	0.000	[redacted]	[redacted]	[redacted]	[redacted]
Age*	-0.092	0.912	0.018	0.000	[redacted]	[redacted]	[redacted]	[redacted]
Age^2	0.001	1.001	0.000	0.000	[redacted]	[redacted]	[redacted]	[redacted]
Female	-0.357	0.699	0.077	0.000	[redacted]	[redacted]	[redacted]	[redacted]
Region - Latin America (vs. North America)	0.625	1.869	0.145	0.000	n/a	n/a	n/a	n/a
Region - Western Europe (vs. North America)	0.168	1.182	0.131	0.200	n/a	n/a	n/a	n/a
Region - Central Europe (vs. North America)	0.529	1.697	0.132	0.000	n/a	n/a	n/a	n/a
Region - Asia-Pacific (vs. North America)	-0.187	0.830	0.317	0.556	n/a	n/a	n/a	n/a
Race - Black (vs. Caucasian)	0.409	1.505	0.144	0.005	[redacted]	[redacted]	[redacted]	[redacted]
Race - Asian (vs. Caucasian)	0.962	2.618	0.299	0.001	[redacted]	[redacted]	[redacted]	[redacted]
Race - Other (vs. Caucasian)	0.168	1.184	0.123	0.169	[redacted]	[redacted]	[redacted]	[redacted]
NYHA class III/IV (vs. I/II)	0.296	1.344	0.067	0.000	[redacted]	[redacted]	[redacted]	[redacted]
LVEF*	-0.017	0.983	0.005	0.000	[redacted]	[redacted]	[redacted]	[redacted]
log(eGFR)*	-0.238	0.788	0.105	0.024	[redacted]	[redacted]	[redacted]	[redacted]
log(NT-proBNP)*	0.443	1.558	0.030	0.000	[redacted]	[redacted]	[redacted]	[redacted]

Parameter	All trial population				Western Europe subgroup			
	Coef.	HR	SE	P > z	Coef.	HR	SE	P > z
Sodium*	-0.027	0.974	0.010	0.007	[redacted]	[redacted]	[redacted]	[redacted]
QRS duration*	0.002	1.002	0.001	0.002	[redacted]	[redacted]	[redacted]	[redacted]
Diabetes	0.229	1.257	0.060	0.000	[redacted]	[redacted]	[redacted]	[redacted]
Beta blocker use	-0.320	0.726	0.096	0.001	[redacted]	[redacted]	[redacted]	[redacted]
1-5 years since HF diagnosis (vs. ≤1 year)	0.210	1.233	0.075	0.005	[redacted]	[redacted]	[redacted]	[redacted]
>5 years since HF diagnosis (vs. ≤1 year)	0.344	1.411	0.080	0.000	[redacted]	[redacted]	[redacted]	[redacted]
Ischaemic aetiology	0.156	1.168	0.063	0.013	[redacted]	[redacted]	[redacted]	[redacted]
Previously hospitalised for HF	0.159	1.172	0.062	0.010	[redacted]	[redacted]	[redacted]	[redacted]
EQ-5D*	-0.563	0.569	0.127	0.000	[redacted]	[redacted]	[redacted]	[redacted]
Constant	-12.665	-	0.648	0.000	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	0.000	-	0.000	0.010	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations used in table: coef., coefficient; eGFR, estimated glomerular filtration rate; EQ-5D, European Quality of Life 5-Dimenions; HF, heart failure; HR, hazard ratio; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association; P, probability; SE, standard error.
*Centred on the mean.

The model fitted for the Western European patient-level data found a non-statistically significant effect for sacubitril compared with enalapril. The estimated HR was [redacted] This compares to the CV HR for the entire population of 0.81 (95% CI: 0.72 to 0.90). Gender, ethnicity, LVEF, sodium levels, QRS duration, diabetes, beta blocker use, aetiology, previous hospitalisation for HF and EQ-5D score at baseline were found to have a non-significant effect on CV mortality.

Table 77. All-cause mortality Gompertz regression model: comparison with Western European subgroup model

Parameter	All trial population				Western Europe subgroup			
	Coef.	HR	SE	P > z	Coef.	HR	SE	P > z
Sacubitril valsartan	-0.161	0.851	0.051	0.002	[redacted]	[redacted]	[redacted]	[redacted]
Age*	-0.102	0.903	0.016	0.000	[redacted]	[redacted]	[redacted]	[redacted]
Age^2	0.001	1.001	0.000	0.000	[redacted]	[redacted]	[redacted]	[redacted]
Female	-0.384	0.681	0.069	0.000	[redacted]	[redacted]	[redacted]	[redacted]
Region - Latin America (vs. North America)	0.542	1.719	0.127	0.000	n/a	n/a	n/a	n/a
Region - Western Europe (vs. North America)	0.130	1.139	0.112	0.243	n/a	n/a	n/a	n/a
Region - Central Europe (vs. North America)	0.364	1.439	0.114	0.001	n/a	n/a	n/a	n/a
Region - Asia-Pacific (vs. North America)	-0.199	0.820	0.298	0.505	n/a	n/a	n/a	n/a
Race - Black (vs. Caucasian)	0.295	1.343	0.130	0.023	[redacted]	[redacted]	[redacted]	[redacted]
Race - Asian (vs. Caucasian)	0.715	2.045	0.283	0.012	[redacted]	[redacted]	[redacted]	[redacted]
Race - Other (vs. Caucasian)	0.087	1.091	0.110	0.430	[redacted]	[redacted]	[redacted]	[redacted]
NYHA class III/IV (vs. I/II)	0.214	1.239	0.061	0.000	[redacted]	[redacted]	[redacted]	[redacted]

Parameter	All trial population				Western Europe subgroup			
	Coef.	HR	SE	P > z	Coef.	HR	SE	P > z
LVEF*	-0.014	0.987	0.004	0.001	[redacted]	[redacted]	[redacted]	[redacted]
Heart rate*	0.006	1.006	0.002	0.009	[redacted]	[redacted]	[redacted]	[redacted]
log(eGFR)*	-0.228	0.796	0.095	0.017	[redacted]	[redacted]	[redacted]	[redacted]
log(NT-proBNP)*	0.391	1.478	0.027	0.000	[redacted]	[redacted]	[redacted]	[redacted]
Sodium*	-0.031	0.969	0.009	0.000	[redacted]	[redacted]	[redacted]	[redacted]
QRS duration*	0.002	1.002	0.001	0.002	[redacted]	[redacted]	[redacted]	[redacted]
Diabetes	0.207	1.230	0.054	0.000	[redacted]	[redacted]	[redacted]	[redacted]
Beta blocker use	-0.289	0.749	0.088	0.001	[redacted]	[redacted]	[redacted]	[redacted]
1-5 years since HF diagnosis (vs. ≤1 year)	0.204	1.227	0.067	0.002	[redacted]	[redacted]	[redacted]	[redacted]
>5 years since HF diagnosis (vs. ≤1 year)	0.291	1.338	0.072	0.000	[redacted]	[redacted]	[redacted]	[redacted]
Ischaemic aetiology	0.158	1.171	0.057	0.005	[redacted]	[redacted]	[redacted]	[redacted]
Prior stroke	0.168	1.182	0.083	0.043	[redacted]	[redacted]	[redacted]	[redacted]
Previously hospitalised for HF	0.153	1.165	0.055	0.006	[redacted]	[redacted]	[redacted]	[redacted]
EQ-5D*	-0.532	0.587	0.115	0.000	[redacted]	[redacted]	[redacted]	[redacted]
Constant	-12.840	-	0.579	0.000	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	0.000	-	0.000	0.000	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations used in table: coef., coefficient; eGFR, estimated glomerular filtration rate; EQ-5D, European Quality of Life 5-Dimenions; HF, heart failure; HR, hazard ratio; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association; P, probability; SE, standard error.
*Centred on the mean.

Similarly to the CV mortality model, a non-statistically significant effect for sacubitril compared with enalapril was observed for all-cause mortality. The subgroup-specific HR was [redacted] which compares to 0.85 (95% CI 0.77 to 0.94) in the base case model. It can be noted that while the HRs for CV mortality and for all-cause mortality in the main trial are similar (0.81 and 0.85 respectively), the HRs for CV mortality and all-cause mortality in the Western European group are substantially different [redacted] Several parameters (i.e. LVEF, sodium, QRS duration, diabetes, beta blocker use, years since diagnosis, prior stroke, EQ-5D score at baseline) were found to have a non-significant effect on all-cause mortality at the 1-α=0.95 level, nonetheless these were not excluded from the model.

Table 78. Hospitalisation negative binomial model: comparison with Western European subgroup model

Parameter	All trial population				Western Europe subgroup			
	Coef.	RR	SE	P > |z|	Coef.	RR	SE	P > |z|
Sacubitril valsartan	-0.173	0.841	0.038	0.000	[redacted]	[redacted]	[redacted]	[redacted]
Age*	-0.054	0.947	0.013	0.000	[redacted]	[redacted]	[redacted]	[redacted]
Age^2	0.000	1.000	0.000	0.000	[redacted]	[redacted]	[redacted]	[redacted]
Female	-0.297	0.743	0.049	0.000	[redacted]	[redacted]	[redacted]	[redacted]
Region - Latin America (vs. North America)	-0.362	0.696	0.084	0.000	n/a	n/a	n/a	n/a
Region - Western Europe (vs. North	0.017	1.017	0.074	0.820	n/a	n/a	n/a	n/a

Parameter	All trial population				Western Europe subgroup			
	Coef.	RR	SE	P > |z|	Coef.	RR	SE	P > |z|
America)								
Region - Central Europe (vs. North America)	-0.322	0.725	0.075	0.000	n/a	n/a	n/a	n/a
Region - Asia-Pacific (vs. North America)	-0.350	0.705	0.085	0.000	n/a	n/a	n/a	n/a
Heart rate*	0.007	1.007	0.002	0.000	[redacted]			
log(eGFR)*	-0.477	0.621	0.072	0.000				
log(NT-proBNP)*	0.228	1.256	0.020	0.000				
Sodium*	-0.021	0.979	0.007	0.001				
QRS duration*	0.003	1.003	0.001	0.000				
Diabetes	0.333	1.395	0.040	0.000				
Prior use of ACEi	-0.104	0.901	0.047	0.026				
Beta blocker use	-0.328	0.721	0.073	0.000				
Lipid lowering medication use	0.073	1.075	0.043	0.091				
1-5 years since HF diagnosis (vs. ≤1 year)	0.265	1.303	0.049	0.000				
>5 years since HF diagnosis (vs. ≤1 year)	0.402	1.494	0.052	0.000				
Ischaemic aetiology	0.085	1.089	0.044	0.054				
Prior stroke	0.147	1.159	0.065	0.023				
Prior atrial fibrillation/ flutter	0.095	1.099	0.042	0.023				
Prior cancer	0.164	1.178	0.088	0.061				
Current smoker	0.209	1.232	0.054	0.000				
Previously hospitalised for HF	0.334	1.396	0.041	0.000				
EQ-5D*	-0.487	0.615	0.089	0.000				
Constant	-2.844	-	0.473	0.000				

Abbreviations used in table: ACEI, angiotensin-converting enzyme inhibitor; coef., coefficient; eGFR, estimated glomerular filtration rate; EQ-5D, European Quality of Life 5-Dimenions; HF, heart failure; NT-proBNP, N-terminal pro-brain natriuretic peptide; P, probability; RR, rate ratio; SE, standard error.
*Centred on the mean.

The comparison between the two models for hospitalisation is shown in Table 78. It can be observed that sacubitril was effective in reducing hospitalisation, and on average more effective in the Western European subgroup than in the overall trial population [redacted] vs. 0.84 [95% CI: 0.78 to 0.91]). Notably, age at baseline was not a good predictor of the rate of hospitalisation in the subgroup model.

Table 79. Utility score linear mixed model: comparison with Western European subgroup model

Parameter	All trial population			Western Europe subgroup		
	Coef.	SE	P > |z|	Coef.	SE	P > |z|
Sacubitril valsartan	0.011	0.003	0.001	[redacted]		
Age*	-0.001	0.000	0.000			
Female	-0.031	0.004	0.000			
Region - Latin America (vs. North America)	0.041	0.007	0.000	n/a	n/a	n/a
Region - Western Europe (vs. North America)	0.013	0.007	0.063	n/a	n/a	n/a

Parameter	All trial population			Western Europe subgroup		
	Coef.	SE	P > |z|	Coef.	SE	P > |z|
Region - Central Europe (vs. North America)	0.000	0.007	0.969	n/a	n/a	n/a
Region - Asia-Pacific (vs. North America)	0.041	0.008	0.000	n/a	n/a	n/a
NYHA class II (vs. I)	-0.009	0.008	0.224	[redacted]	[redacted]	[redacted]
NYHA class III (vs. I)	-0.051	0.008	0.000	[redacted]	[redacted]	[redacted]
NYHA class IV (vs. I)	-0.092	0.021	0.000	[redacted]	[redacted]	[redacted]
Heart rate*	0.000	0.000	0.049	[redacted]	[redacted]	[redacted]
log(NT-proBNP)*	-0.009	0.002	0.000	[redacted]	[redacted]	[redacted]
Sodium*	0.001	0.001	0.071	[redacted]	[redacted]	[redacted]
BMI	-0.002	0.000	0.000	[redacted]	[redacted]	[redacted]
Diabetes	-0.014	0.003	0.000	[redacted]	[redacted]	[redacted]
1-5 years since HF diagnosis (vs. ≤1 year)	-0.017	0.004	0.000	[redacted]	[redacted]	[redacted]
>5 years since HF diagnosis (vs. ≤1 year)	-0.023	0.004	0.000	[redacted]	[redacted]	[redacted]
Ischaemic aetiology	-0.007	0.003	0.033	[redacted]	[redacted]	[redacted]
Prior stroke	-0.012	0.006	0.039	[redacted]	[redacted]	[redacted]
Current smoker	-0.013	0.005	0.005	[redacted]	[redacted]	[redacted]
EQ-5D*	0.488	0.008	0.000	[redacted]	[redacted]	[redacted]
Hospitalised within previous 30 days	-0.105	0.006	0.000	[redacted]	[redacted]	[redacted]
Hospitalised 30-90 days previously	-0.054	0.004	0.000	[redacted]	[redacted]	[redacted]
Adverse event - cough	-0.028	0.007	0.000	[redacted]	[redacted]	[redacted]
Adverse event - hypotension	-0.029	0.006	0.000	[redacted]	[redacted]	[redacted]
Time (years)	-0.008	0.001	0.000	[redacted]	[redacted]	[redacted]
Constant	0.822	0.010	0.000	[redacted]	[redacted]	[redacted]

Abbreviations used in table: ACEI, angiotensin-converting enzyme inhibitor; coef., coefficient; eGFR, estimated glomerular filtration rate; EQ-5D, European Quality of Life 5-Dimenions; HF, heart failure; NT-proBNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association; P, probability; RR, rate ratio; SE, standard error.
*Centred on the mean.

There were no substantial differences in the estimated effects of baseline characteristics on QoL. The Western European subgroup regression model presents a higher constant term, reflective of the greater score at baseline [redacted] and a faster deterioration of QoL over time: the utility scores were estimated to decrease twice as quickly than in the base case model.

The ERG found an error in the electronic version of the model submitted by the company for the subgroup analysis, as the baseline characteristics from the subgroup population were not properly accounted for in the regression analyses. The ERG notes that the correction resulted in a reduction in the ICER of about £1,000 per QALY gained.

The ICER for the Western European subgroup using CV mortality is presented in Table 80. Estimating the ICER in the subgroup population led to an increase in the ICER from £16,678 to £21,548 per QALY gained. This is mainly due to the increase in the HR for sacubitril vs enalapril for CV mortality.

Table 80. Western Europe subgroup results: CV mortality model and UK life tables

Results per patient	Enalapril+SoC (1)	Sacubitril+SoC (2)	Incremental value (2-1)
Total costs (£)	£16,400	£23,642	£7,242
QALYs	4.71	5.04	0.34
ICER			**£21,560**
Abbreviations used in table: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; SoC, standard of care.			

The ICER for the Western European subgroup using all-cause mortality is presented in Table 81. The all-cause mortality ICER increased from £17,939 to £31,594. This difference is mostly driven by the higher HR for all-cause mortality, which translates into a reduction in the mortality benefits of sacubitril over enalapril compared to the entire trial population.

Table 81. Western Europe subgroup results: all-cause mortality model

Results per patient	Enalapril+SC (1)	Sacubitril+SC (2)	Incremental value (2 – 1)
Total costs (£)	£12,974	£18,147	£5,174
QALYs	3.82	3.98	0.16
ICER			**£31,594**
Abbreviations used in table: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; SC, standard care.			

5.6.2.5 Probabilistic sensitivity analysis

Parameter uncertainty was explored through PSA, reported in Section 5.8 of the CS. The company designed the PSA into the patient-level modelling approach. The model results for each of the 8,399 patient-based cohorts were ran 1,000 times with Monte Carlo simulations where selected model parameters were varied. The outcomes were averaged over the 8,399 cohorts, producing a set of 1,000 observations of the costs and effects.

The ERG is concerned that too many potentially important parameters were not varied in the PSA, such as baseline age and EQ-5D score. The methodology applied in the PSA anchors the values of patients' baseline characteristics to the set of values observed in the trial, limiting the propagation of uncertainty to the trial results and making the PSA very inflexible to variations in the parameters. Additionally the extremely high number of simulations (1,000) combined with running the model as a patient-level model using 8,399 patient-level cohorts resulted in a PSA running of approximately seven days. As such it was impractical for the ERG to re-run the PSA for the individual-level data and therefore the company's PSA results have not been validated. However the PSA could be re-run in substantially reduced time when using the mean cohort model.

The company reported that where the covariance structure between parameters was known, correlated random draws were sampled from a multivariate normal distribution. Sampling from multivariate normal distributions was reported to have been performed using code developed by the Centre for Bayesian Statistics in Health Economics.(113) The company stated that unit costs were not varied where there was lack of information regarding uncertainty around these quantities. Model parameters and respective probability distributions were reported in Table 128, Section 8.15 of the CS Appendix. The ERG notes that Table 128 includes several inconsistencies and errors when compared to the values reported in the economic model. Many of the parameters reported did not match the values used in the economic model (e.g. GP visit cost), or were not included in the PSA. The ERG amended the reported list of parameters varied stochastically in the PSA, and reports these in Table 82.

Table 82. Summary of the parameters varied stochastically in the PSA

Parameter	Probability distribution	Uncertainty source
CV mortality model coefficients	Multivariate normal	Regression model
All-cause mortality model coefficients	Multivariate normal	Regression model
Pct. of deaths with CV cause, sacubitril valsartan	Beta	95% CI from trial
Pct. of deaths with CV cause, ACEi	Beta	95% CI from trial
Discontinuation model coefficients	Multivariate normal	Regression model
Hospitalisation model	Multivariate normal	Regression model
Utility regression model coefficients	Multivariate normal	Regression model
AE annual rate: hypotension, sacubitril valsartan	Lognormal	95% CI from trial
AE annual rate: hypotension, ACEi	Lognormal	95% CI from trial
AE mean duration: hypotension, sacubitril valsartan	Lognormal	95% CI from trial
AE mean duration: hypotension, ACEi	Lognormal	95% CI from trial
AE annual rate: cough, sacubitril valsartan	Lognormal	95% CI from trial
AE annual rate: cough, ACEi	Lognormal	95% CI from trial
AE mean duration: cough, sacubitril valsartan	Lognormal	95% CI from trial
AE mean duration: cough, ACEi	Lognormal	95% CI from trial
AE annual rate: elevated serum creatinine, sacubitril valsartan	Lognormal	95% CI from trial
AE annual rate: elevated serum creatinine, ACEi	Lognormal	95% CI from trial
AE annual rate: elevated serum potassium, sacubitril valsartan	Lognormal	95% CI from trial
AE annual rate: elevated serum potassium, ACEi	Lognormal	95% CI from trial
Pct. of patients on BB	Beta	95% CI from trial
Pct. of patients on AA	Beta	95% CI from trial
Pct. of patients on digoxin	Beta	95% CI from trial
Pct. of patients on lipid lowering medications	Beta	95% CI from trial
Pct. of patients on diuretics	Beta	95% CI from trial
Pct. of patients on aspirin	Beta	95% CI from trial
Pct. of patients on anticoagulants	Beta	95% CI from trial
Pct. of patients on ADP antagonists	Beta	95% CI from trial

Parameter	Probability distribution	Uncertainty source
Pct. of mild angioedema	Beta	95% CI from trial
GP emergency visits: mean annual use	Lognormal	95% CI from CPRD
A&E referrals: mean annual use	Lognormal	95% CI from CPRD
GP visits: mean annual use	Lognormal	95% CI from CPRD
Cardiologist visits: mean annual use	Lognormal	95% CI from CPRD
Other physician visits: mean annual use	Lognormal	95% CI from CPRD
GP home visits: mean annual use	Lognormal	95% CI from CPRD
GP hospital visits: mean annual use	Lognormal	95% CI from CPRD
GP nursing home visits: mean annual use	Lognormal	95% CI from CPRD
GP residential home visits: mean annual use	Lognormal	95% CI from CPRD
GP phone calls to patient: mean annual use	Lognormal	95% CI from CPRD
GP visits with third parties: mean annual use	Lognormal	95% CI from CPRD
ARB comparison: CV mortality HR ARB vs. ACEi	Lognormal	NMA
ARB comparison: all-cause mortality HR ARB vs. ACEi	Lognormal	NMA
ARB comparison: hospitalisation rate ratio ARB vs. ACEi	Lognormal	NMA
ARB comparison: hypotension annual rate	Lognormal	Assumed equal to sacubitril valsartan
ARB comparison: cough annual rate	Lognormal	Assumed equal to sacubitril valsartan
ARB comparison: elevated serum creatinine annual rate	Lognormal	Assumed equal to sacubitril valsartan
ARB comparison: elevated serum potassium annual rate	Lognormal	Assumed equal to sacubitril valsartan
Abbreviations used in table: AA, aldosterone antagonist; ACEi, angiotensin-converting enzyme inhibitor; AE, adverse event; A&E, accident and emergency (department); ARB, angiotensin-receptor blocker; BB, beta blocker; CI, confidence interval; CPRD, Clinical Practice Research Datalink; CV, cardiovascular; GP, general practitioner; HR, hazard ratio; Pct., percentage.		

The ERG believes that patients' baseline characteristics should have been included in the PSA and varied stochastically. No reasonable justification was provided by the company for why baseline characteristics could not be considered uncorrelated and thus sampled independently from probability distributions. In the absence of such information the ERG's opinion is that an assumption of no correlation rather than no variation outside the specified set of observed values would have been more appropriate. Furthermore, baseline characteristics are key parameters in the economic model given that these have been included as determinant of mortality, hospitalisation, QoL and costs in the analysis. Therefore the ERG is concerned that parameter uncertainty in the economic analysis was not appropriately accounted for.

Upon clarification, the company resubmitted the PSA results for the corrected ICER (described in Section 5.6.1). The corrected probabilistic ICER in the base case is £18,818, therefore higher than the deterministic one (£17,939) by about £1,000 per QALY gained. The difference seems to be caused by

a reduction in the average QALY differential compared to the deterministic base case. Cost-effectiveness acceptability curves (CEACs) were also provided for each relevant comparison. These are reported in Figure 28 and Figure 29. Figure 28 shows that the probability of sacubitril (compared with enalapril) being cost-effective is 64% and 93%, respectively for the £20,000 and £30,000 per QALY gained thresholds. Figure 29 shows that the probability of sacubitril being cost-effective compared with candesartan does not exceed 90%, with a probability of 60% for cost-effectiveness at the £20,000 per QALY gained and about 77% probability of cost-effectiveness at a £30,000 per QALY gained threshold.

The cloud of points representing the 1,000 PSA simulations is represented in Figure 30 for sacubitril versus enalapril and in Figure 31 for sacubitril versus candesartan. In Figure 30 all the simulations seem to fall in the north-eastern quadrant of the cost-effectiveness plane thus indicating an almost certain gain in health-related benefits but an increase in health expenditure when comparing sacubitril to enalapril. In Figure 31, the majority of the simulations fall in the north-eastern quadrant of the cost-effectiveness plane while some fall in the north-western quadrant, indicating that while sacubitril is expected to be more expensive than candesartan, there is some uncertainty as to whether it produces higher QALYs.

Figure 28.Cost-effectiveness acceptability curve – ACEi comparison (Figure 5 in CS addendum)

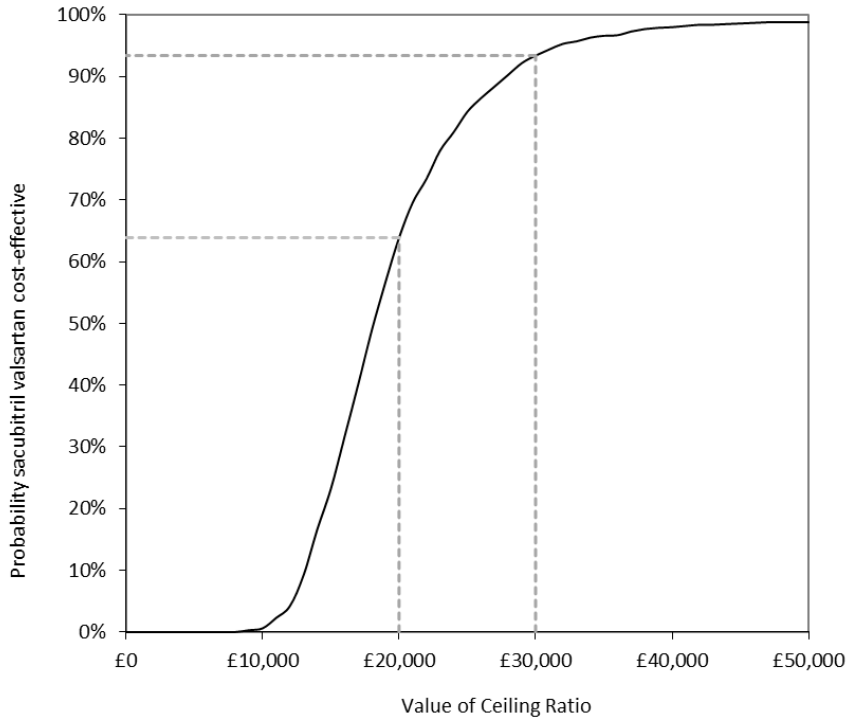


Figure 29.Cost-effectiveness acceptability curve – ARB comparison (Figure 7 in CS addendum)

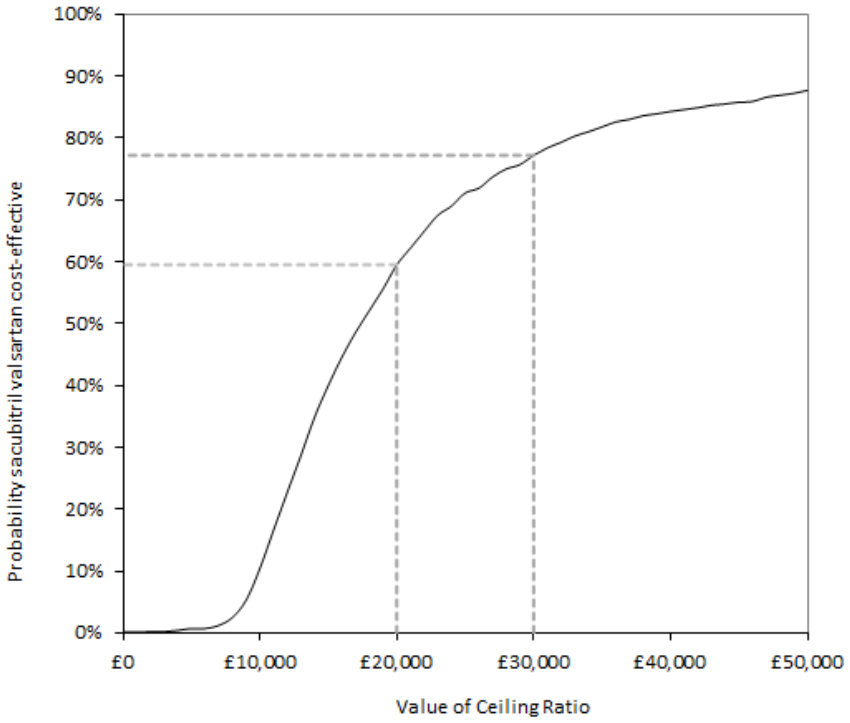


Figure 30.Cost-effectiveness plane and 95% confidence ellipse – ACEi comparison (Figure 4 in CS addendum)

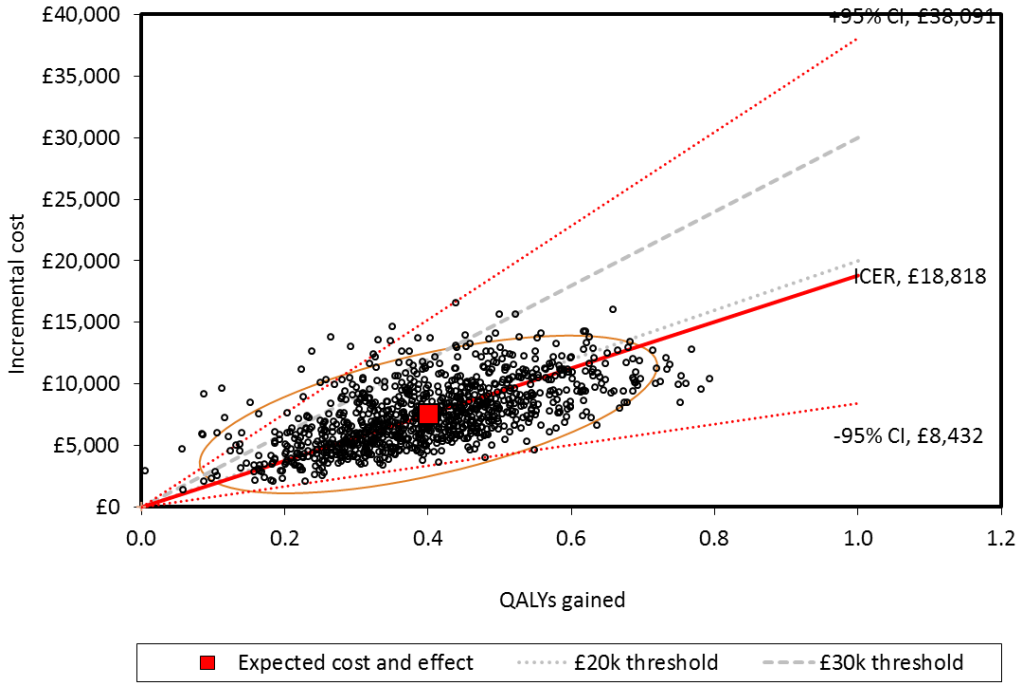
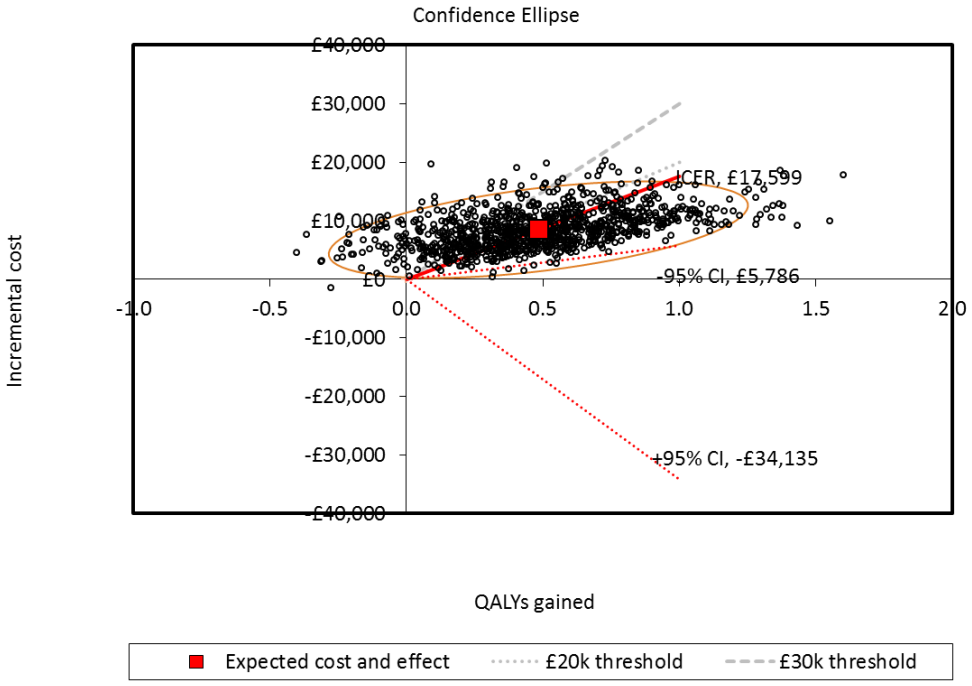


Figure 31. Cost-effectiveness plane and 95% confidence ellipse – ARB comparison (Figure 6 in CS addendum)



The ERG notes that the electronic model provided by the company also included the estimation of the expected value of perfect information (EVPI). However this was not presented as part of the PSA in the CS.

6 ADDITIONAL WORK UNDERTAKEN BY THE ERG

The ERG carried out minor model corrections (Section 6.1), and several scenario analyses (Section 6.2) on the company's model. In addition, the ERG presents a second-line ICER estimate, which aims to approximate the company's ICER to the second-line HFrEF population in the UK (Section 6.3). The ERG used the mean cohort model and the CV mortality approach for all the additional work undertaken.

6.1 Model corrections

The ERG has corrected the mistake in the half-cycle adjustment found in the estimation of the utility values as explained in Section 5.5.8. The ERG also corrected a mistake found in the company's discontinuation scenario analysis.

After these corrections were applied in the model, the base case ICERs changed from £15,529 per QALY gained for the company's primary results and £15,343 for the secondary analysis to £15,026 and £14,931 for the primary and secondary analysis, respectively, using the mean cohort and the CV mortality approaches. These ICERs are presented in Table 83.

Table 83. ERG corrected ICERs

Results per patient	**Enalapril+SC (1)**	**Sacubitril+SC (2)**	**Candesartan+SC (3)**	**Incremental value (2 – 1)**	**Incremental value (3 – 1)**
Total costs (£)	£22,961	£14,308	£13,335	£8,653	£9,626
QALYs	5.40	4.82	4.76	0.58	0.64
ICER				**£15,026**	**£14,931**

6.2 ERG scenario analysis

The scenario analyses undertaken by the ERG are explained throughout Section 5 of the report and were ran for a population with a mean starting age of 64 years (as per the company's base case) and for a mean starting age of 75 years to reflect the UK HF population. The ERG used the CV mortality approach and the mean cohort model. Results are presented in Table 84.

The additional scenario analysis ran for the 64-year-old population are the following:

1. The ERG changed the CV mortality HR in the model to reflect the Jhund *et al.* HR estimate for the 55**–**64 year category.(7) The HR used was 0.79 (CI 0.64 to 0.98);

    1.1. As the confidence interval for the HR of CV mortality in the 55–64 years population is wide, the ERG also used both limits of the 95% confidence interval;

2. The ERG used the baseline utility score of 0.712 reported by Berg *et al.(8);*

3. The ERG used the baseline utility score of 0.660 reported by Austin *et al.*(9);

4. Given the issues found in the modelling approach of QoL in the model, the ERG adopted a simplified approach, where the impact of sacubitril on patients' QoL was linked to the incidence of AE and hospitalisation events and disease progression (i.e. time) in both treatment arms. Therefore, the QoL regression model was not used, even though some of its estimates were used as these were validated by clinical experts. The impact of sacubitril alone on QoL was also removed to reflect the lack of robust evidence to support a measurable improvement in patients' QoL caused by sacubitril other than through hospitalisation, mortality and AEs. The impact of treatment regimens on QoL was assessed by the ERG through :

    - AEs and hospitalisation events: the ERG applied the same utility decrements used by the company to estimate the loss in QoL due to the incidence of AEs and hospitalisation;

    - Disease progression: the ERG applied the same utility decrement used by the company to reflect the loss of QoL as time progresses for HF patients.

5. The ERG changed the drug doses used in the model to reflect a consistent approach to the estimation of drug costs. The re-estimated drug costs are presented in Table 59, Section 5.5.9.1;

6. The ERG included the cost of ramipril (using the ERG drug dose assumption) as to reflect clinical practice in the UK;

7. The ERG used the option included in the company's economic model to run the ERG corrected model considering treatment discontinuation;

8. The ERG used the company's subgroup analysis results to run the ERG corrected model considering the Western European population. To note is that the mean baseline age for the Western European population is [redacted] years.

Table 84. Results of the ERG's scenario analysis for patients entering the model at 64 years

	Results per patient	**Sacubitril+SoC (1)**	**Enalapril+SoC (2)**	**Incremental value (1-2)**
0	**Base case (CV approach, mean cohort model) with ERG corrections**			
	Total costs (£)	£22,961	£14,308	£8,653

	QALYs	5.40	4.82	0.58
	ICER			**£15,026**
1	**HR for CV mortality changed to reflect *Jhund et al* point estimate (0.79)**			
	Total costs (£)	£23,167	£14,308	£8,859
	QALYs	5.45	4.82	0.62
	ICER (compared with base case)			**£14,246**
1.1	**HR for CV mortality changed to reflect *Jhund et al* upper CI limit (0.64)**			
	Total costs (£)	£25,360	£14,308	£11,052
	QALYs	5.93	4.82	1.11
	ICER (compared with base case)			**£9,977**
1.1	**HR for CV mortality changed to reflect *Jhund et al* lower CI limit (0.98)**			
	Total costs (£)	£20,939	£14,308	£6,631
	QALYs	4.95	4.82	0.12
	ICER (compared with base case)			**£53,803**
2	**Change in baseline utility to reflect *Berg et al* utility (0.72)**			
	Total costs (£)	£22,824	£14,299	£8,525
	QALYs	5.11	4.55	0.55
	ICER (compared with base case)			**£15,407**
3	**Change in baseline utility to reflect *Austin et al* utility (0.66)**			
	Total costs (£)	£22,688	£14,289	£8,398
	QALYs	4.82	4.29	0.53
	ICER (compared with base case)			**£15,821**
4	**Change in QoL modelling approach**			
	Total costs (£)	£22,961	£14,308	£8,653
	QALYs	5.30	4.80	0.50
	ICER (compared with base case)			**£17,413**
5	**Change in pharmaceutical costs to reflect drug target doses**			
	Total costs (£)	£23,085	£14,430	£8,655
	QALYs	5.40	4.82	0.58
	ICER (compared with base case)			**£15,030**
6	**Including the cost of ramipril**			
	Total costs (£)	£22,961	£14,257	£8,704
	QALYs	5.40	4.82	0.58
	ICER (compared with base case)			**£15,115**
7	**Including discontinuation (with ERG correction)**			
	Total costs (£)	£19,989	£14,316	£5,673
	QALYs	5.20	4.82	0.38
	ICER (compared with base case)			**£14,954**
8	**Western Europe subgroup (corrected, mean age at baseline=[redacted] years)**			
	Total costs (£)	£24,182	£17,341	£6,841
	QALYs	4.86	4.52	0.33
	ICER (compared with base case)			**£20,550**

Abbreviations used in the table: CI, confidence interval; SoC, standard of care; ICER, incremental cost-effectiveness ratio; HR, hazard ratio; QALYs, quality-adjusted life years; QoL, quality of life.

The additional analysis presented for the 64 year-old population is consistent with the company's sensitivity analysis in showing that the model results are most sensitive to changes in the mortality HR. In fact, the HR for CV mortality appears to be the key model driver (for the CV mortality approach), and when varied to the upper bound of the 95% CI reported in Jhund *et al.* (0.98) produces an ICER of £53,803 per QALY gained.(7) To note is that the base case HR assumed for CV mortality by the company is 0.81 (95% CI: 0.72 to 0.90), which produces an ICER of £15,026 per QALY gained.

Using the Western Europe subgroup characteristics also has a considerable impact on the final ICER, increasing it from £15,026 in the entire trial population to £20,550 in the Western European population. This difference is mostly driven by the higher HR for CV mortality in the Western European group compared with the entire trial population, which translates into a reduction in the mortality benefits of sacubitril over enalapril. The ERG notes that the HRs for CV mortality in the Western European group was non-statistically significant and presented wide 95% CIs [redacted].

Changes in the QoL modelling approach led to an increase in the final ICER to £17,413 per QALY gained.

The additional scenario analysis ran for the 75-year-old population are the following:

1. The ERG changed the CV mortality HR in the model to reflect the Jhund *et al.* HR estimates for the ≥75 year category.(7) The HR used was 0.84 (95% CI: 0.67 to 1.06);

    1.1. As the confidence interval for the HR of CV mortality in the 55–64 years population is wide, the ERG also used both limits of the confidence interval;

    1.2. As the HR of CV mortality in the ≥75years is non-statistically significant the ERG ran the model with an HR of 1.

The additional analyses undertaken by the ERG for the 75-year-old population are the same as the ones reported for the 64-year-old group (from point 2 onwards). Results are presented in Table 85.

Table 85. Results of the ERG's scenario analysis for patients entering the model at 75 years

	Results per patient	**Sacubitril+SoC (1)**	**Enalapril+SoC (2)**	**Incremental value (1-2)**

0	**Base case (CV approach, mean cohort model) with ERG corrections**			
	Total costs (£)	£19,498	£12,562	£6,936
	QALYs	4.43	3.99	0.44
	ICER			**£15,843**
1	**HR for CV mortality changed to reflect *Jhund et al* point estimate (0.84)**			
	Total costs (£)	£19,172	£12,562	£6,610
	QALYs	4.35	3.99	0.37
	ICER (compared with base case)			**£18,021**
1.1	**HR for CV mortality changed to reflect *Jhund et al* upper CI limit (1.06)**			
	Total costs (£)	£17,321	£12,562	£4,759
	QALYs	3.95	3.99	-0.04
	ICER (compared with base case)			**Dominated**
1.1	**HR for CV mortality changed to reflect *Jhund et al* lower CI limit (0.67)**			
	Total costs (£)	£20,924	£12,562	£8,362
	QALYs	4.73	3.99	0.75
	ICER (compared with base case)			**£11,192**
1.2	**HR for CV mortality changed to 1**			
	Total costs (£)	£17,787	£12,562	£5,225
	QALYs	4.05	3.99	0.06
	ICER (compared with base case)			**£81,329**
2	**Change in baseline utility to reflect *Berg et al* utility (0.72)**			
	Total costs (£)	£19,427	£12,581	£6,846
	QALYs	4.19	3.77	0.42
	ICER (compared with base case)			**£16,190**
3	**Change in baseline utility to reflect *Austin et al* utility (0.66)**			
	Total costs (£)	£19,355	£12,599	£6,757
	QALYs	3.96	3.56	0.41
	ICER (compared with base case)			**£16,571**
4	**Change in QoL modelling approach**			
	Total costs (£)	£19,498	£12,562	£6,936
	QALYs	4.40	4.02	0.38
	ICER (compared with base case)			**£18,357**
5	**Change in pharmaceutical costs to reflect drug target doses**			
	Total costs (£)	£19,600	£12,663	£6,937
	QALYs	4.43	3.99	0.44
	ICER (compared with base case)			**£15,845**
6	**Including the cost of ramipril**			
	Total costs (£)	£19,498	£12,520	£6,979
	QALYs	4.43	3.99	0.44
	ICER (compared with base case)			**£15,940**
7	**Including discontinuation (with ERG correction)**			
	Total costs (£)	£17,444	£12,568	£4,876
	QALYs	4.30	3.99	0.31
	ICER (compared with base case)			**£15,628**

8	**Western Europe subgroup (corrected)**			
	Total costs (£)	£20,961	£15,216	£5,744
	QALYs	4.16	3.87	0.28
	ICER (compared with base case)			**£20,321**
Abbreviations used in the table: CI, confidence interval ; SoC, standard of care; ICER, incremental cost-effectiveness ratio; HR, hazard ratio; QALYs, quality-adjusted life years; QoL, quality of life.				

As discussed in Section 5.5.7, caution should be taken when interpreting the model results for older populations given the inflexibility of the model in reflecting different starting ages (compared to the mean age at baseline in the PARADIGM-HF trial). It is likely that the additional analyses ran by the ERG for 75 year-old patients is not fully reflective of the true impact on the cost-effectiveness of sacubitril in older populations (even if we assume the same drug effectiveness across age groups). Overall there was a slight increase in the different presented ICERs for the older population.

Similarly to the 64 year-old population additional analyses, the model results have shown to be most sensitive to changes in the mortality HR for 75 year-old patients. When the ERG used the point estimate in Jhund *et al.* for CV mortality HR (0.84) the ICER increased to £18,021 per QALY gained.(7) To note is that the base case HR assumed for CV mortality by the company is 0.81 (95% CI: 0.72 to 0.90), thus an increase of 0.03 in the HR, led to an increase of nearly £2,200 in the final ICER. Given that the Jhund *et al.*(7) CV mortality HR was non-statistically significant in the over 75 year-old population, the ERG undertook a scenario analysis using a HR of 1 for CV mortality, which produced an ICER of £81,011 per QALY gained. When using the upper bound of the 95% CI around the company's base case HR for CV mortality (i.e. 0.90), the final ICER increased to £24,524 per QALY gained.

Using the Western Europe subgroup characteristics also had a considerable impact on the final ICER, increasing it from £15,843 in the entire trial population to £20,321 in the Western European population. Again, this difference is mostly driven by the higher HR for CV mortality in the Western European group compared with the entire trial population.

Changes in the QoL modelling approach led to an increase in the final ICER to £18,357 per QALY gained.

6.3 ERG second-line ICER

In this section the ERG presents a second-line ICER for sacubitril compared to enalapril in patients with HFrEF. The ICER estimated by the ERG is based on the trial effectiveness measures and population and as such is considered by the ERG to be a second-line ICER as discussed throughout

this report. Furthermore, the ERG aimed to approximate the second-line ICER to what would be observed in UK's clinical practice. In order to do so, the ERG assumed the following:

- Mean starting age of the model population is 75 years old;

9. Baseline utility value taken from Berg *et al.*(8)*;*

- The cost of ramipril instead of enalapril to reflect clinical practice in the UK;

- The effectiveness outcomes, costs, QALYs and population characteristics of the Western European subgroup analysis.

Additionally the ERG used its alternative QoL modelling approach and adjusted drug costs to reflect target doses consistently across the economic analysis. The second-line ICER estimated by the ERG is presented in Table 86.

Table 86. ERG's second-line ICER

Results per patient	**Sacubitril+SoC (1)**	**Enalapril+SoC (2)**	**Incremental value (1 – 2)**
Company's base case with ERG corrections			
Total costs (£)	£22,961	£14,308	£8,653
QALYs	5.40	4.82	0.58
ICER			**£15,026**
Mean age at baseline of 75 years			
Total costs (£)	£19,498	£12,562	£6,936
QALYs	4.43	3.99	0.44
ICER (compared with base case)			**£15,843**
ICER with all changes incorporated			**£15,843**
Change in baseline utility to reflect *Berg et al* utility (0.72)			
Total costs (£)	£22,824	£14,299	£8,525
QALYs	5.11	4.55	0.55
ICER (compared with base case)			**£15,407**
ICER with all changes incorporated			**£16,190**
Change in QoL modelling approach			
Total costs (£)	£22,961	£14,308	£8,653
QALYs	5.30	4.80	0.50
ICER (compared with base case)			**£17,413**
ICER with all changes incorporated			**£19,697**
Change in pharmaceutical costs to reflect drug target doses			
Total costs (£)	£23,085	£14,430	£8,655
QALYs	5.40	4.82	0.58
ICER (compared with base case)			**£15,030**
ICER with all changes incorporated			**£19,701**
Change in pharmaceutical costs to reflect the cost of ramipril			

Total costs (£)	£22,961	£14,257	£8,704
QALYs	5.40	4.82	0.58
ICER (compared with base case)			**£15,115**
ICER with all changes incorporated			**£19,843**
Western Europe subgroup			
Total costs (£)	£24,182	£17,341	£6,841
QALYs	4.86	4.52	0.33
ICER (compared with base case)			**£20,550**
ICER with all changes incorporated			**£29,478**
Abbreviation used in the table: Abbreviations used in the table; SoC, standard of care; ICER, incremental cost-effectiveness ratio; HR, hazard ratio; QALYs, quality-adjusted life years; QoL, quality of life.			

The second-line ICER estimated by the ERG amounts to £29,478 per QALY gained for sacubitril compared with enalapril, using a CV mortality approach and a mean cohort model. The results for sacubitril compared with candesartan (ARB) were consistently similar, with the final second-line ICER resulting in £30,140 per QALY gained.

However the ERG considers that the second-line ICERs reported must be interpreted with caution. The ERG believes there is too much uncertainty around the effectiveness of sacubitril compared with enalapril when analysed in the context of UK clinical practice. This uncertainty is mainly related to:

- The lack of representativeness of the trial treatment regimens compared to the UK clinical practice, more specifically with regards to the dose of valsartan (in combination with sacubitril) given to patients. The ERG has reasons to believe that the tolerability to the observed dose of valsartan (in combination with sacubitril) in the PARADIGM-HF trial is overestimated and that patients in real-life clinical practice are unlikely to be able to tolerate, on average, the dose of valsartan received in the trial. Caution should be taken when interpreting the effectiveness outcomes in the PARADIGM-HF trial as it is difficult to understand how the trial could inform the effectiveness of sacubitril if given at a lower mean dose of valsartan (for example, such as 106mg). Even though there is a small discrepancy between the average enalapril dose observed in the trial and the 4-year CPRD data analysis, this is substantially smaller than the discrepancy in values observed for valsartan;

- The lack of generalisability of the PARADIGM-HF trial population for second-line HFrEF UK patients. Firstly not only does the PARADIGM-HF trial include a younger HFrEF population compared to the UK HFrEF average, but might also include slightly "different" HFrEF patients, who present with heart problems from a very young age. This could explain the higher CV mortality in younger patients, when compared to slightly older patients, who present with more "typical" HFrEF. Secondly, opinion provided by the ERG's clinical experts

advised that the device use at baseline in PARADIGM-HF was lower than what would be expected in UK clinical practice and that this is an important prognostic factor in HFrEF;

- The fact that the Western European subgroup analysis reports a non-statistically significant mortality HR. While the PARADIGM-HF trial was not designed to estimate the effectiveness of sacubitril across different regions, and the sample size of the subgroup is smaller than that of the entire trial population, statistically significant differences between treatments groups were shown for regions considerably smaller in size than Western Europe (2,051 patients). For example, North America (602 patients) and Latin America (1,433 patients) were associated with statistically significant results even though the number of patients were more than three times smaller in the case of North America or half in case of Latin America. The ERG believes this might be indicative of a different relative effect of sacubitril compared to enalapril across geographical areas. However no causal association can be established. An example of the quantification of this uncertainty is that if the HR for CV mortality in the Western European subgroup is assumed to be 1 (to reflect the non-statistical significance of the HR), the final ICER increases to **£491,879** per QALY gained. Furthermore, using the 95% CIs of the HR for CV mortality in this population [redacted], leads to a variation in the final ICER which ranges from **£15,584** to a **dominated** ICER, with sacubitril being more expensive and producing less QALYs than enalapril;

- It is uncertain if the effectiveness of sacubitril differs across different age groups. While sacubitril appears to maintain the same direction of effect across different age groups, the size of the effect is not as easily established. The authors in Jhund *et al.* conclude that the effect of sacubitril compared with enalapril was consistent across age groups even though HRs were non-statistically-significant in older groups.(7) This is consistent with the expert opinion provided to the ERG that for patients around 80 years old presenting with HFrEF, clinicians expect treatment (with ACEi or other drugs) to improve patients' QoL and symptoms but not mortality. This is particularly relevant to the UK given that the average age of HFrEF patients is between 75 and 80 years-old. This adds to the uncertainty of having a non-statistically significant mortality HR in the Western European subgroup analysis;

- The inflexibility of the economic model to reflect an older population at baseline. The modelling approach taken by the company, while necessary to capture the PARADIGM-HF trial data, resulted in an inflexible economic model. The model cannot be changed to portray an older population at baseline and generalise the model results. The trend observed in CV (and all-cause) mortality by age group at baseline, where younger patients have higher mortality rates than 60-year old patients, reinforces the ERG's point that the PARADIGM-HF trial population is not representative of the typical UK HFrEF population, especially when

deviations are made from the mean age trial population (64 years). It is likely that the additional analysis ran by the ERG for 75 year-old patients is not fully reflective of the true cost-effectiveness of sacubitril in older populations (even if we assume that sacubitril's effectiveness is the same across age groups).

- The different modelling approaches used. While the ERG considers that, form a methodological point of view, the CV mortality approach is more robust than the all-cause mortality approach the results using all-cause mortality are provided for comparison with the company's base case analysis. The second-line ICER estimated by the ERG for all-cause mortality is **£49,009** per QALY gained. This compares to the £29,219 ICER obtained with the CV mortality approach. This conveys another example of the uncertainty surrounding the second-line ICER estimate.

- There is also uncertainty from a technical perspective. The company's decision to use a Gompertz distribution was based on this distribution presenting the most plausible (i.e shortest) survival time. The ERG believes that the company should have presented different modelling options, such as a Cox model or for example, spline models. No other approach outside parametric curves was tried, and this might have produced suboptimal results. Even though the Gompertz distribution produces the most plausible survival curves amongst the group of alternative distributions considered, it could represent an overestimate of treatment effects if compared to different (and potentially more appropriate) approaches. The company's regression analysis undertaken for the Western Europe subgroup used the same model specifications as the ones used in the base case analysis for the entire trial. Other modelling approaches were not tested and parameters with non-statistically significant effects on the dependent variable were not excluded from regression models.

7 OVERALL CONCLUSIONS

7.1 Summary of clinical-effectiveness issues

- The evidence provided by the company is collected from a stable, chronic population of patients with HF;
- The evidence to support the use of sacubitril as first-line management in a newly diagnosed population of CHF patients is limited;
- The results from the Western Europe region suggest that the benefits of sacubitril over enalapril may not be as large as the overall results from the PARADIGM-HF trial suggest.

7.2 Summary of cost-effectiveness issues

The company's cost-effectiveness analysis was based on the PARADIG-HF trial, a high quality randomised controlled trial. The formulae within the economic model are generally sound and the economic model is a good predictor of the trial outcomes. The company conducted scenario and subgroup analyses which were not requested in the NICE final scope but added value to the submission.

The company's anticipated positioning of sacubitril in the HFrEF pathway is first-line treatment in newly diagnosed patients. However, the ERG considers that a first-line ICER for sacubitril compared with enalapril cannot be estimated based on the PARADIGM-HF trial data. The extrapolation of sacubitril's effectiveness in the PARADIGM-HF trial to a first-line treatment scenario is deemed inappropriate given that:

- The PARADIGM-HF trial population does not reflect a treatment-naïve HFrEF population. About 78% and 23% of patients had received ACEi or ARB treatment, respectively, before randomisation. Additionally 70% of patients had been diagnosed for over 1 year at baseline and 31% had been diagnosed more than 5 years ago. Clinical opinion sought by the ERG indicates that based on the trial design, population and outcomes, the evidence supports the use of sacubitril in clinical practice is as a second-line treatment option, given to HFrEF patients who are still symptomatic despite being on an ACEi drug therapy. The trial (and therefore the model) population reflects a chronic, stable and symptomatic (95% of patients in the NYHA class II-IV) HFrEF population who has been on ACEi (or ARB) treatment for at least 1 month;

- The mortality in the trial (and in the model) portrays a scenario representative of the use of sacubitril for non-newly diagnosed patients. Less than 10% of patients in the trial had died by the end of year 1 and 20% were dead in both treatment arms by the end of the second year. When compared to the NICE CG108 prognosis that 30% to 40% of patients diagnosed with

HF die within a year, the observed mortality in the trial is substantially different (less than half)(6);

- Given that PARADIGM-HF patients are symptomatic, despite having been treated with ARBs and ACEi, the impact of continuing these patients on ACEi is likely to be a misrepresentation compared to what would happen in naïve patients. Given that, in principle, the ACEi treatment regimen is not effective in improving these patients' HFrEF symptoms, keeping them on the same treatment regime is unlikely to show any improvements. This has an impact on the observed effectiveness of sacubitril, which might be overrepresented in the trial population when compared to naïve patients.

The second-line ICER estimated by the ERG amounts to £29,478 per QALY gained for sacubitril compared with enalapril, using a CV mortality approach and a mean cohort model. The results for sacubitril compared with candesartan (ARB) were consistently similar, with the final second-line ICER resulting in £30,140 per QALY gained. However the ERG advises that the second-line ICERs here obtained must be interpreted with extreme caution. The ERG believes there is too much uncertainty around the effectiveness of sacubitril compared with enalapril in order to ascertain what the true second-line cost-effectiveness ICER is for sacubitril compared with enalapril. This uncertainty is related mainly to:

- The lack of representativeness of the trial treatment regimens compared to the UK clinical practice, more specifically with regards to the dose of valsartan (in combination with sacubitril) given to patients. The ERG has reasons to believe that the tolerability to the observed dose of valsartan (in combination with sacubitril) in the PARADIGM-HF trial is overestimated and that patients in real-life clinical practice are unlikely to be able to tolerate, on average, the dose of valsartan received in the trial. Caution should be taken when interpreting the effectiveness outcomes in the PARADIGM-HF trial as it is difficult to understand how the trial could inform the effectiveness of sacubitril if given at a lower mean dose of valsartan (for example, such as 106mg). [redacted] observed in the trial and the 4-year CPRD data analysis, this is [redacted] than the discrepancy in values observed for valsartan;

- The lack of generalisability of the PARADIGM-HF trial population for second-line HFrEF UK patients. Firstly not only the PARADIGM-HF trial portrays a younger HFrEF population compared to the UK HFrEF average, but might also include slightly "different" HFrEF patients, who present with heart problems from a very young age. This could explain the higher CV mortality in younger patients, when compared to slightly older patients, who

present with more "typical" HFrEF. Secondly, opinion provided by the ERG's clinical experts advised that the device use at baseline in PARADIGM-HF was lower than what would be expected in UK clinical practice and that this is an important prognostic factor in HFrEF;

- The fact that the Western European subgroup analysis reports a non-statistically significant mortality HR. While the PARADIGM-HF trial was not designed to estimate the effectiveness of sacubitril across different regions, and the sample size of the subgroup is smaller than that of the entire trial population, statistically significant differences between treatments groups were shown for regions considerably smaller in size than Western Europe (2051 patients). For example, North America (602 patients) and Latin America (1433 patients) were associated with statistically significant results even though the number of patients were more than three times smaller in the case of North America or half in case of Latin America. The ERG believes this might indicative of a different relative effect of sacubitril compared to enalapril across geographical areas. However no causal association can be demonstrated. An example of the quantification of this uncertainty is that if the HR for CV mortality in the Western European subgroup is assumed to be 1 (to reflect the non-statistical significance of the HR), the final ICER increases to **£491,879** per QALY gained. Furthermore, using the CIs of the HR for CV mortality in this population [redacted], leads to a variation in the final ICER which ranges from **£15,584** to a **dominated** ICER, with sacubitril being more expensive and producing less QALYs than enalapril;

- It is uncertain if the effectiveness of sacubitril differs across different age groups. While sacubitril appears to maintain the same direction of effect across different age groups, the size of the effect is not as easily established. The authors in Jhund *et al.* conclude that the effect of sacubitril compared with enalapril was consistent across age groups even though HRs were non-statistically-significant in older groups.(7) This is somewhat consistent with expert opinion provided to the ERG which advised that for patients around 80 years old presenting with HFrEF, clinicians expect treatment (with ACEi or other drugs) to improve patients' QoL and symptoms but not mortality. This is particularly relevant to the UK given that the average age of HFrEF patients is between 75 and 80 years-old. This adds to the uncertainty of having a non-statistically significant mortality HR in the Western European subgroup analysis;

- The inflexibility of the economic model to reflect an older population at baseline. The modelling approach taken by the company, while necessary to capture the PARADIGM-HF trial data, resulted in an inflexible economic model. The model cannot be changed to portray an older population at baseline and generalise the model results. The trend observed in CV (and all-cause) mortality by age group at baseline, where younger patients have higher mortality rates than 60-year old patients, reinforces the ERG's point that the PARADIGM-HF

trial population is not representative of the typical UK HFrEF population, especially when deviations are made from the mean age trial population (63 years). It is likely that the additional analysis ran by the ERG for 75 year-old patients is not fully reflective of the true cost-effectiveness of sacubitril in older populations (even if we assume that sacubitril's effectiveness is the same across age groups);

- The different modelling approaches used While the ERG considers that, form a methodological point of view, the CV mortality approach is more robust than the all-cause mortality approach the results using all-cause mortality are provided for comparison with the company's base case analysis. The second-line ICER estimated by the ERG for all-cause mortality is **£49,009** per QALY gained. This compares to the £29,690 ICER obtained with the CV mortality approach. This conveys another example of the uncertainty surrounding the second-line ICER estimate;

- There is also uncertainty from a technical perspective. The company's decision to use a Gompertz distribution was based on this distribution presenting the most plausible (i.e shortest) survival time. The ERG believes that the company should have presented different modelling options, such as spline models. No other approach outside parametric curves was tried, and this might have produced suboptimal results. Even though the Gompertz distribution produces the most plausible survival curves amongst the group of alternative distributions considered, it could represent an overestimate of treatment effects when compared to different (and potentially more appropriate) approaches. The company's regression analysis undertaken for the Western Europe subgroup used the same model specifications as the ones used in the base case analysis for the entire trial. Other modelling approaches were not tested and parameters with non-statistically significant effects on the dependent variable were not excluded from regression models.

- The ERG is concerned that parameter uncertainty in the economic analysis was not appropriately accounted for. The ERG believes that patients' baseline characteristics should have been included in the PSA and varied stochastically. No reasonable justification was reported by the company as for why baseline characteristics could not be considered uncorrelated and thus sampled independently from probability distributions. Furthermore, baseline characteristics are key parameters in the economic model given that these have been included as prognostic factors of mortality, hospitalisation, QoL and costs in the regression analyses.

In summary, even though the PARADIGM-HF trial results indicate that sacubitril (compared to enalapril) is effective in preventing hospitalisations and reducing mortality in the trial population.

However the ERG considers that there is too much uncertainty to make definitive predictions around the effectiveness of sacubitril for:

- Western European patients;
- Patients older (or younger) than 63 years old;
- A first-line treatment scenario;
- Different doses of sacubitril valsartan (in both first and second-line treatment scenarios).

7.3 Implications for research

The ERG considers there is a need for further research into:

- The use of sacubitril in newly diagnosed patients with chronic heart failure, compared to ACEi and ARB treatment, ideally in a population representative of a newly diagnosed HF UK population;
- Confirmation of the efficacy and safety of sacubitril in a population representative of the average chronic HF UK population who remain symptomatic on first-line treatment.

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9 APPENDICES

The ERG presented the evidence for the TITRATION trial along with its critique of this trial. This section of the report based on data designated as academic-in-confidence by the company as it is unpublished data.

[redacted]

Table A1. Summary of company's quality assessment for TITRATION (reproduced from Table 108 of the CS, pg 25 of the appendices)

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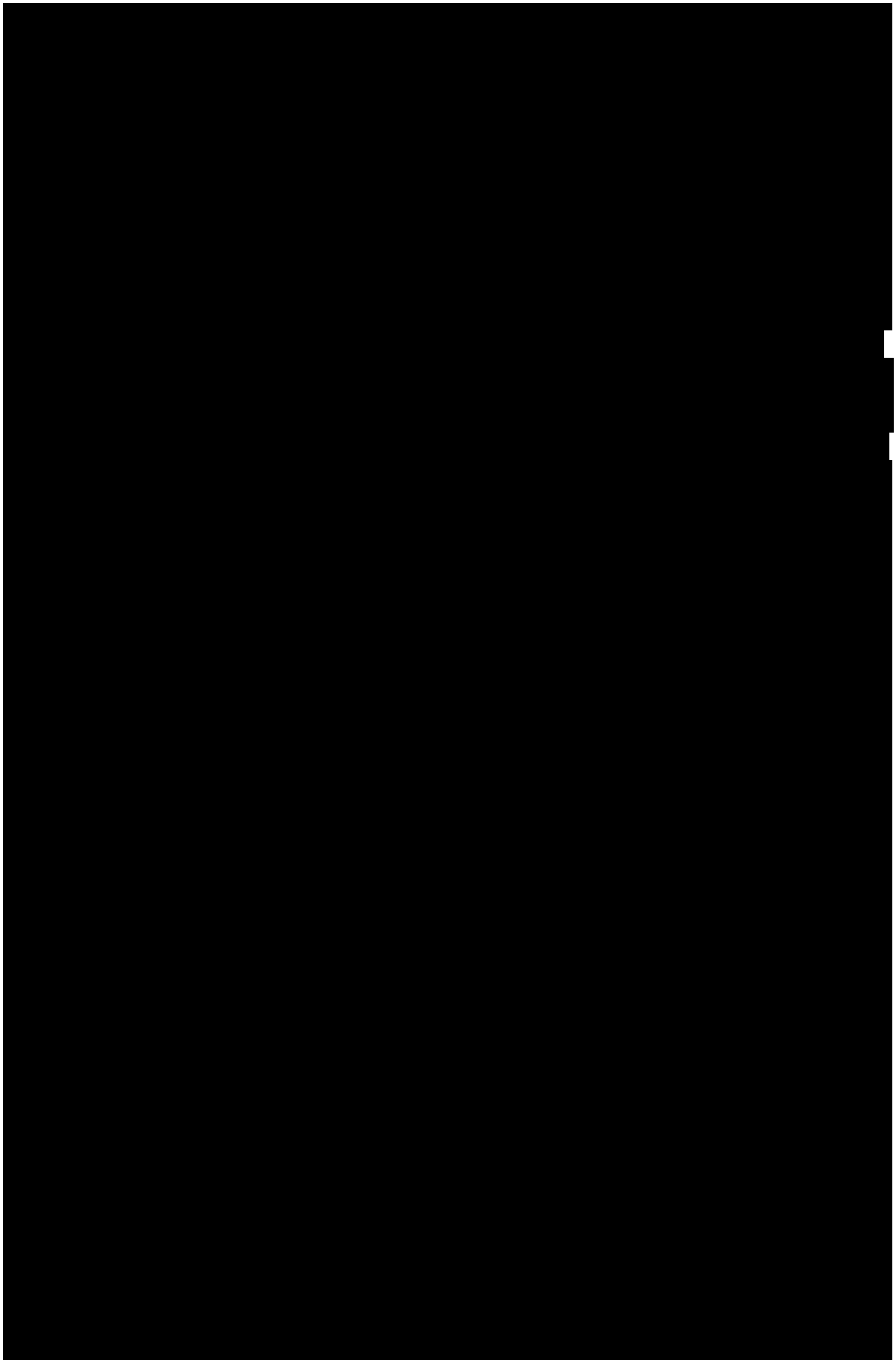

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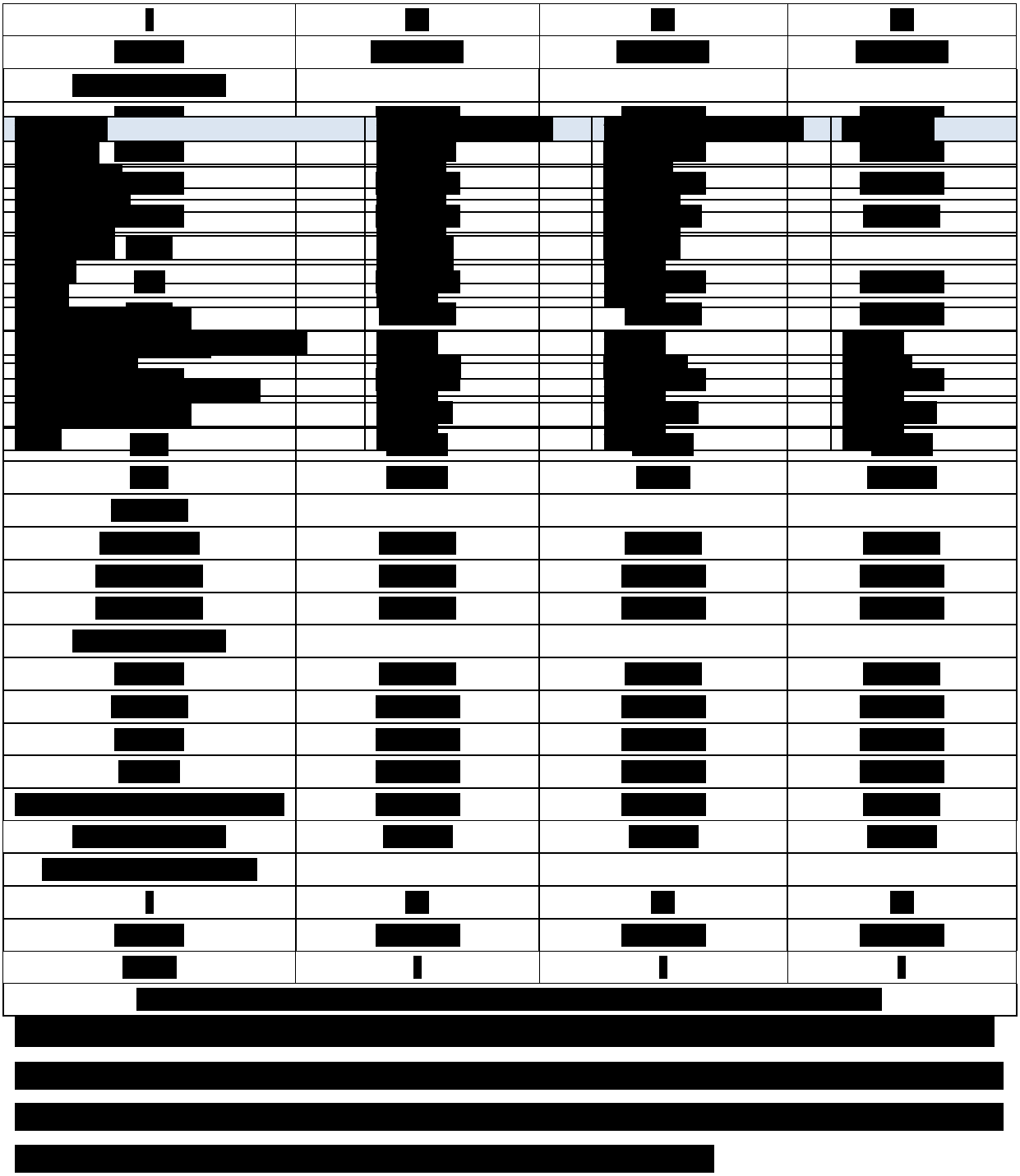
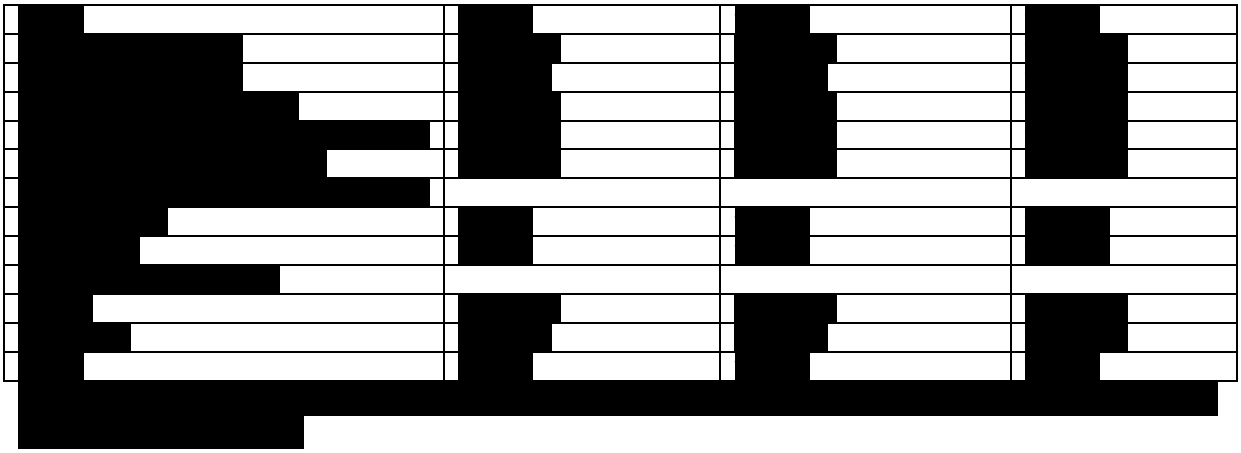




National Institute for Health and Care Excellence
Centre for Health Technology Evaluation

Pro-forma Response

ERG report

Sacubitril valsartan for treating heart failure with systolic dysfunction [ID822]

You are asked to check the ERG report from BMJ Technology Assessment Group to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies you must inform NICE by **5pm, 30 October 2015** using the below proforma 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 Evaluation report.

The proforma document should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Issue 1 Sacubitril valsartan being referred to as sacubitril

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Throughout the report sacubitril valsartan is referred to as sacubitril which is an inaccurate and misleading short-form of the drug name.	Sacubitril should be replaced with sacubitril valsartan throughout the entire document.	The correct drug name is sacubitril valsartan and this should be reflected in the report.	The ERG carefully acknowledges the full name of sacubitril valsartan at the beginning of the report before using the name sacubitril for reasons of efficiency. This is not factually incorrect.

Issue 2 Consistent use of terminology around CHF and HFrEF

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Throughout the report - The population is inconsistently referred to as either HFrEF or CHF.	When referring to the population in the CS, the ERG should update all instances of CHF to HFrEF throughout the document.	The ERG report should align with the population in the NICE scope which is referred to in the company submission as HFrEF (not CHF). This is to avoid confusion that a population broader than the license is being reviewed in this appraisal (i.e. CHF including both heart failure with reduced and preserved ejection fraction).	The ERG notes the title of the final scope by NICE, "Sacubitril valsartan for treating chronic heart failure". The ERG does not consider the use of the term chronic heart failure (CHF) to be a factual error.
Page 25 - The ERG state that they 'have adopted the wording definitions of CHF terms' using the ESC definition in Table 2 which states HFrEF to be LVEF ≤35%. Table 2 is referenced as the AHA guidelines, however the text	The ERG should clarify which ejection fraction limit they accept for HFrEF, ≤40% or ≤35% and use this consistently throughout the report. The ERG should report HFrEF consistently throughout and not use mild, moderate or severe as an additional differentiator of reduced	The ESC does not provide an accepted definition of HFrEF (the guidelines state 'The major trials in patients with HF and a reduced EF (HF-REF), or 'systolic HF', mainly enrolled patients with an EF ≤35%, and it is only in these patients that	The ERG thanks the company for identifying this error. The reference has been changed to the AHA guideline (reference 18).

states that the ESC guidelines are used.	ejection fraction. The ERG should either update the reference or update the data in the table to be aligned with reference.	effective therapies have been demonstrated to date.')	
Page 24 – The ERG state that men have higher prevalence of moderate to severe ejection fraction (defined as ejection fraction ≤40%).	Wording should be updated to: 'Men have a higher prevalence of HFrEF fraction (defined as LVEF <40%).'	Consistency of use of terminology for HFrEF. In this case HF is not mentioned, only moderate to severe ejection fraction.	The ERG thanks the company for highlighting the error. The wording has been amended to: Men have a higher prevalence of HFrEF (defined as left ventricular ejection fraction <40%).'
Page 43 – The ERG make reference to 'severe HF', and 'mild/moderate CHF'.	The ERG should amend wording to 'HFrEF' to ensure consistency of terms throughout the report. Wording should be updated to: '…were patients with HFrEF (based on LVEF ≤35%), and the observed benefits of treatment would be greater than in patients without reduced ejection fraction.'	Consistency of use of terminology for HFrEF, as different definitions are used in the report.	The ERG thanks the company for highlighting the error. The wording has been amended to; '…were patients with HFrEF (based on LVEF ≤35%), and the observed benefits of treatment with sacubitril would be greater than in patients without reduced ejection fraction.'
Page 47 – The ERG consider that 'the change from 45% to ≤35% LVEF means the population recruited from then would have had more severe disease.' Firstly, the change in LVEF inclusion criteria was from **≤40%** to <35% not 45% to 35%. In addition, as discussed above, CHF should be referred to as	Wording should be updated to: 'The ERG considers the change from LVEF **≤40%** to ≤35% means the population recruited from then would have had more severe HFrEF'	Incorrect reporting of change in LVEF inclusion criteria for the PARADIGM-HF study and inconsistent disease terminology.	The ERG thanks the company for highlighting the error. The wording has been amended to; The ERG considers the change from LVEF **≤40%** to ≤35% means that the population recruited from then would have had more severe HFrEF'.

HFrEF throughout.			
Page 60 – The ERG state '…patients had to have CHF (defined as LVEF ≤35% or reported as reduced and NYHA class II-IV.' The disease should be referred to as HFrEF not CHF. 'Reported as reduced' should be removed as an ECHO was required for an LVEF of <35% to be demonstrated.	Wording should be updated to: '…patients had to have HFrEF (defined as LVEF ≤35%) and NYHA class II-IV.'.	Incorrect disease terminology and inclusion criteria definition	As before, the scope from NICE is entitled, "Sacubitril valsartan for Chronic Heart Failure (CHF)" and the ERG therefore considers CHF to be a legitimate term. The use of the word "reported" refers to the reporting of the eligibility requirements in the CS and the manuscript by McMurray 2014b and is not therefore a factual error.

Issue 3 Prevalence

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 24 – The prevalence figures identified by the ERG (3% in UK men, 1.7% in UK women) are based on a source from 2001 and are a relatively high prevalence compared to more recent sources.	The ERG should remove the following sentence: 'The ERG identified published statistics on the epidemiology of CHF that suggest the overall prevalence of CHF is 3% in UK men and 1.7% in women in the UK (15).'	In the CS, a UK prevalence of 550,000 is used based on a 2014 source which the ERG agreed is appropriate on page 30 when reviewing the evidence on the estimated eligible patient population.	The ERG thanks the company for highlighting the error. The following sentence has been removed: "The ERG identified published statistics on the epidemiology of CHF that suggest the overall prevalence of CHF is 3% in UK men and 1.7% in women in the UK (15)."

Issue 4 Missing or incorrect reference

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 25 – Section 2.2 The reference used in this paragraph are the NICE clinical guidelines however the sentence beginning 'For those people with symptoms of CHF but no history of MI…' refers to 'the quality standard'.	The ERG should add the NICE Quality Standards as a reference for this statement.	Incorrect referencing - it is unclear if this statement relates to the NICE guideline or NICE Quality Standards.	NICE Clinical Guideline (CG108) section 1.1.3 , page 12 of 47 states: "Measure serum natriuretic peptides (B-type natriuretic peptide [BNP] or N-terminal pro-B-type natriuretic peptide [NTproBNP]) in patients with suspected heart failure without previous MI." The ERG does not consider the referencing to be factually incorrect.

Issue 5 Description of recommendation of NICE clinical guidelines

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 27 – The ERG state that 'An angiotensin receptor blocker (ARB) can also be used as an alternative to ACEi in patients who cannot tolerate an ACEi (Box 8). In cases where the patient then remains symptomatic, or has moderate to severe heart failure (NYHA class III–IV) or has experienced an MI in	Wording should be updated to: 'In cases where the patient remains symptomatic on ACEI *and* has moderate to severe heart failure (NYHA class III–IV) or has experienced an MI in the last month, an AA for HF is indicated.'	This sentence does not reflect the NICE treatment algorithm recommendations. The second sentence should state that patients first receive ACEi, if they cannot tolerate ACEi they will receive ARB and following this if still symptomatic they will then receive AA in certain populations. In	The statements in the ERG report are informed directly from NICE CG 108, page 18 and this does not constitute a factual error.

the last month, an AA for HF is indicated.' This does not reflect the guideline recommendations.		addition, the use of 'or' is used incorrectly as per the guidelines recommendations.	

Issue 6 Description of Novartis justification of change in the first-line management

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 28 – the ERG description of the justification used by Novartis for sacubitril valsartan to replace first-line therapy is incomplete.	The statement should include that the demonstrated significant improvement in mortality and hospitalisations by sacubitril valsartan are compared to an evidence-based dose of ACEi which is current first-line treatment. Wording should be updated to: 'The company justifies this proposed change in the first-line management of people with HFrEF because sacubitril valsartan has demonstrated significant improvement in mortality and hospitalisations compared to an evidence-based dose of ACEi, which is current first-line treatment.'	The justification for positioning sacubitril valsartan to replace first-line treatment is based on the comparison against current first-line therapy which was provided by head-to-head clinical trial data against ACEi. This should be reflected as the improvements could be against any other comparator, including placebo, based on the statement the ERG provided.	In the context of the paragraph the statement appears the ERG's statement clearly indicates the company's positioning of sacubitril valsartan as a replacement for ACEi in first-line treatment of HFrEF. The ERG does not consider this to be a factual error.

Issue 7 Description of Novartis justification of change in the first-line management

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 29 – The ERG' sentence 'Eligible patients will previously have had a diagnosis for HF … guideline CG108 (6)'	The ERG should remove this sentence as it does not reflect the description of resource implications in the CS.	This paragraph is describing what was included in the CS regarding additional resources. The CS did not include this statement regarding	The ERG considers that patients need to have been diagnosed with HF before sacubitril valsartan can be

This sentence is unrelated to resource implications of sacubitril valsartan and inaccurately reflects the description of resource implication used in the CS.		eligible patients and therefore it should be removed. In addition this statement seems unrelated to additional resource use which is what is described in this paragraph.	prescribed and so the sentence is not factually incorrect.

Issue 8 LVEF subgroup

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 33 – The ERG state that '89% of participants (n=7,438) in PARADIGM-HF had a CHF classification ≤35%. The results from the trial are therefore likely to be representative of this more severe CHF patient population.' Also as per Issue 2, CHF should instead be referred to as HFrEF throughout the report.	The ERG should remove this passage as it is not justified why the trial is not also representative of the remaining 11% of patients.	The subgroup analysis of patients with patients with an LVEF >35% and ≤40% versus patients with LVEF ≤35% shows no significance with regards to the p-value for interaction therefore no difference between treatment effect can be assumed.	The NICE scope relates to patients with a LVEF≤35%. The 11% of patients with LVEF 35% to 40% are out of scope.
Page 43 – The ERG assumes that the observed benefits of sacubitril valsartan would be greater in patients with LVEF ≤35%. However, in sections 4.8 and 8.4 of the CS the subgroup analysis presented shows no statistically significant p-value for interaction for treatment effect in patients with LVEF ≤35% versus >35% and ≤40%.	The ERG should delete this statement or add a reference to support this view.	Clinical trial data from PARADIGM-HF contradicts the ERG statement and no rationale is provided on why this would be the case.	On page 43 "The ERG's clinical experts advised that patients in the PARADIGM-HF trial were patients with severe HF (based on LVEF≤35%) and that the observed benefits of sacubitril would be greater than in patients with mild moderate CHF". The subgroup analysis (CS pg 69) indicates a greater benefit

			for sacubitril for those with a NYHA class I/II than for NYHA class III/IV. The ERG's statement reflects this. The ERG does not state that this is a *statistically significant* benefit. As such the ERG does not consider the statement to be a factual error.

Issue 9 Treatment naïve versus newly diagnosed patients

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 33 - The ERG state that '…the small amount of data provided for patients who have never taken an ACEi means there is little evidence to support the use of sacubitril as a first line treatment in newly diagnosed patients.' From this sentence it appears that the ERG are claiming that treatment naïve patients and newly diagnosed patients are the same. The difference between treatment naïve and newly diagnosed patients should be made clear. ACEi are used to treat several other diseases including hypertension (70% of PARADIGM-HF population) and post MI. A substantial proportion of patients are treated with ACEi prior to their HF diagnosis and are therefore not treatment naive. [redacted]	The ERG should correctly differentiate between treatment-naïve and newly diagnosed patients.	Newly diagnosed patients are not the same as treatment naïve patients. Limited evidence on treatment naïve	The ERG thanks the company for highlighting the error. The text has been changed to: "…little evidence to

	Wording should be updated to: '… little evidence to support the use of sacubitril valsartan as a first line treatment in treatment-naïve HFrEF patients.'	patients can therefore not support the conclusion that there is limited evidence on newly diagnosed patients. Additionally, the CHMP concluded that although evidence was limited on treatment naïve patients, a similar benefit can be expected in patients not	support the use of sacubitril as a first line treatment in treatment-naïve HFrEF patients."
Page 60 – The ERG state that TITRATION 'provides limited evidence …' There is a conclusion between treatment naïve and newly diagnosed patients			The ERG thanks the company for highlighting the error. The text has been changed to: "The company's inclusion of TITRATION provides limited

		previously treated with these medicines. There is no explanation of ERG why they disagree with the CHMP.	evidence for the effectiveness of sacubitril in treatment naive patients as only a fraction (6.6%) of patients included in the trial were treatment naïve".
Page 55/116/121 – In these sections the ERG suggests that the model population is not reflective of a newly diagnosed HFrEF population because most patients had received treatment with ACEi or ARB before the study.	The ERG should correct any wording that suggests the model population does not reflect a newly		Not a factual error. On page 116 and page 121 of the ERG report it is stated that "…the model population is not reflective

	diagnosed HFrEF population due to most patients being previously treated – as being treatment-naïve is not the same as being newly diagnosed.		of newly diagnosed HFrEF as 78% and 23% of patients had received ACEi or ARB treatment, respectively, for at least 4 weeks before the randomisation period and also 70% of patients had been diagnosed for over 1 year." This statement is a valid justification for

			showing that the PARADIGM-HF patients were not only not treatment-naïve but also not newly diagnosed, as 70% of patients had been diagnosed for over 1 year.
Page 56 – ERG states ‘As highlighted…the comparative effectiveness of sacubitril [valsartan] vs enalapril in newly diagnosed HF patients is unclear.’’ The subgroup identified, ‘ACEi naïve’ (also referred to on Page 13) is not a surrogate for newly diagnosed patients or treatment naïve patients. Additionally, the conclusion ERG makes is statistically incorrect as there is no p-value of interaction between the two subgroups (treated with ACEi and not treated with ACEi).	The conclusion on the ERG makes is statistically incorrect	Newly diagnosed patients are not the same as treatment naïve patients. Limited evidence on	The ERG makes no statements regarding the p-value for interaction. The ERG report consiste

		treatment naïve patients can therefore not support the conclusion that there is limited evidence on newly diagnosed patients. The subgroup of patients who were not treated with ACEi upon enrolment does not mean they are ACEi naïve. Additionally most	ntly highlights the lack of patients in PARADIGM-HF that were previously untreated and were newly diagnosed with HFrEF and the uncertainty associated with the estimates in this subgroup. In this context, the ERG does not consider this a factual error.

		of these were exposed to ARBs (potentially after intolerance to ACEi) which is also RAAS inhibition. Hence why this subgroup is not a surrogate for treatment naïve patients. Please see below for excerpt from Lancet publication regarding interpretation of subgroup analyses:	

		‘Reports of the significance of the effect of treatment in individual subgroups should be ignored, especially reports of lack of benefit in a particular subgroup in a trial in which there is overall benefit, unless there is a significant subgroup treatment effect interaction’. [1]	

[1]Rothwell (2005) Subgroup analysis in randomised controlled trials: importance, indications and interpretation. Lancet; 365: 176–86.

Issue 10 Definition of stable patients

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 34 – It is unclear what the ERGs description of stable patients is (‘…patients who are a chronic, but stable, HF population). Additionally this is not a clear reflection of the patients recruited in the trial which were HFrEF patients.	The ERG should not use the term ‘stable’ to describe a chronic, progressive, symptomatic disease like HFrEF and therefore this term should be removed throughout.	HFrEF is a chronic progressive symptomatic disease. In the population studied: • All patients were symptomatic at enrolment, and included patients with reduced ejection fraction. • 14% of patients had at least one HF hospitalisation • 15% of patients died of CV cause during the trial follow-up • Recruitment into the trial did not specify time since event or acute episode for example Additionally, mortality outcomes of the trial are comparable to CPRD as shown in Figure 40 Page 179.	The ERG has incorporated the clinical expert’s view of the population that it is both chronic and stable. However the ERG acknowledges that the word "stable" has not been defined. The ERG has removed this word throughout.

Issue 11 Dosing in PARADIGM-HF

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 34 – The ERG have not accurately captured the dosing of both treatment arms in the PARADIGM-HF trial which is	Wording should be updated to: ‘…the efficacy of sacubitril [valsartan] 200 mg **BID** compared with the ACEi enalapril 10mg **BID**.	Trial dosing was not accurately described.	The ERG thanks the company for highlighting the error. The text has been changed to: “the efficacy of sacubitril

twice daily.			200mg BID compared with the ACEi enalapril 10mg BID"

Issue 12 TITRATION

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 35 – The TITRATION study compares different dosing *regimens*. The target dose of sacubitril valsartan is the same between arms.	Wording should be updated to: 'A second trial TITRATION (n=498) compares different dosing regimens of sacubitril.'	Trial design was not accurately described.	On page 35 the ERG report states: "A second trial TITRATION (n = 498) compares different doses of sacubitril". This is not factually incorrect and the ERG has retained its original statement.

Page 122 – The ERG state that 'the company only provided the evolution of NYHA for sacubitril [valsartan] patients (total patients and treatment-naïve patients) and did not provide the results for the enalapril arm." The TITRATION study did not have an enalapril arm as it compared two sacubitril valsartan treatment arms, with 6-week and 3-week up-titration regimens, respectively	The ERG should remove this whole statement as it does not accurately reflect the data available from the TITRATION study.	Treatment arms in TITRATION study were not accurately described.	The ERG thanks the company for highlighting the error. The sentence referred to by the company has been amended to, "The company provided the evolution of NYHA for sacubitril patients only (total patients and treatment-naïve patients) as the TITRATION trial did not include treatment with enalapril. Therefore the additional data from TITRATION are of limited value given that they do not allow a comparison between treatment arms with respect to this outcome."

Issue 13 Incorrect definition of primary endpoint

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 12 – The ERG describe the primary outcome of the PARADIGM-HF trial as 'a composite of CV mortality and CV hospitalisation' which is incorrect.	Wording should be updated to: 'The primary outcome of the PARADIGM-HF trial was a composite of time to first occurrence of either CV death or first hospitalisation for HF.'	Incorrect definition of primary endpoint.	The ERG thanks the company for highlighting the error. on the text on page 12 has been changed to: "The primary outcome of the PARADIGM-HF trial was a composite of time to first occurrence of either CV death or first hospitalisation for HF".

Page 35 – The ERG state 'that the primary efficacy variable was time to first occurrence of either CV death or **HF hospitalisation from CV causes** and these were combined and presented as a composite variable.'	Wording should be updated to: 'The ERG notes that the primary efficacy variable was time to first occurrence of either CV death or **first hospitalisation for HF** and these were combined and presented as a composite variable'.	Incorrect definition of primary endpoint.	The ERG thanks the company for highlighting the error. The text has been amended to include the word ***first*** i.e.; 'The ERG notes that the primary efficacy variable was time to first occurrence of either CV death or **first hospitalisation for HF** and these were combined and presented as a composite variable'.

Issue 14 Duration of follow-up versus study duration

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 36 – the ERG states that the median duration of follow-up was 51 months (based on CSR page 23). However the CSR states 'the actual study duration was 51 months (Section 12.1.2).'	Wording should be updated to: 'The PARADIGM-HF trial had a median duration of follow-up of 27 months.' See page 183 of the CS.	Incorrect referencing of study duration (which includes run-in phase) versus duration of follow-up	The ERG thanks the company for highlighting the error. The text has been changed to: "the PARADIGM trial had an actual study duration of 51 months...."
Page 59 – The ERG refer to the trial duration of 51 months but this is not the same as follow-up of patients in the randomised phase (e.g., includes run-in phase and follow-up stops at death or end of study whichever comes first) so should not be related to statistical significance of the primary	Wording should be updated to: '…demonstrated statistical significance after a median follow-up of 27 months'.	Incorrect use of trial duration to describe time period over which statistical significance observed for primary composite outcome.	The ERG thanks the company for highlighting the error. The text has been changed to: "... significance after a median double-blind follow-up of 27 months..."

endpoint.			

Issue 15 Run-in phase description

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 41 – The ERG description of the run-in phase states 'followed by single-blind treatment with sacubitril [valsartan] for an additional 4-6 weeks…in the absence of unacceptable side effects'. This is not reflected in the description of the run-in phase in the CSR for PARADIGM-HF.	The ERG should remove 'in the absence of unacceptable side effects' from this sentence.	PARADIGM-HF CSR states that patients unable to tolerate enalapril 10 mg bid or LCZ696 200 mg bid during the run-in phase were not eligible for randomisation, and were discontinued from the study. Unacceptable side effects are not mentioned.	On page 40 the CS describes the enalapril run-in phase as: "If no unacceptable side effects occurred, this was followed by a sacubitril valsartan run-in phase: single-blind (patients were blinded) treatment with sacubitril valsartan for 4 to 6 weeks at a dose of 100 mg bid, which was increased to 200 mg bid." The ERG does not consider the statement on page 41 of the ERG report to be factually incorrect.
Page 44 – The ERG description in the first paragraph is not clear whether patients who received 5 mg to start with were only treated with ACEi for 2 weeks. In addition the wording 'in the absence of unacceptable side effects' is used again.	Wording should be updated to: 'As stated in Section 4.2, patients first entered a run-in phase where they were switched from the ACEi or ARB that they had been receiving to single-blind treatment with enalapril at a dose of 10 mg twice for *two weeks (daily*, although could be initiated at 5 mg bid for one or two weeks before up-titration in patients who were on ARBs or lower doses of ACEis) followed by single-blind treatment with sacubitril valsartan for an additional 4-6 weeks (initially at a dose of	There is a need to clarify in this section that if a patient received 5 mg enalapril at the start of the run-in phase, their enalapril run-in would be 4 weeks in total and these patients would have an additional visit (visit 2A - Page 41-44 of the CSR).	The wording of unacceptable side effects is taken from the CS (pg 40). The statement is not factually incorrect.

	100 mg twice daily, which was increased to 200 mg twice daily).		
Page 123/124 – There was an error in reporting of the proportion of patients in PARADIGM-HF discontinuing enalapril in the run-in phase. The correct proportion of patients is 10% (1,102/10,513 = 10.482%)	Wording should be updated to: "During the run-in phase, **10%** of patients in PARADIGM-HF discontinued enalapril…"	Correction in reporting of discontinuation in run-in phase.	The ERG has rounded the 10.48% to the unit (i.e 10%) in the paragraph in page 123 and 124 as per the company's suggestion.

Issue 16 Generalisability of age and gender distribution

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 43/55– The ERG note that the average age of female patients presenting with HF is ≥ 85 years which seems to be an overestimation based on the National Heart Failure Audit (average age of female patients at first admission was 80 years). This National HF audit is the source the ERG uses on page 55 (second paragraph) to describe the difference in outcomes between males and females and an average of 80 years for females is used here. Additionally, evidence shows that the average age of HFrEF is lower than HFpEF and the NHFA includes	Consistent use of one source should be applied throughout the report to describe the patient population (National Heart Failure Audit). Where clinical expert opinion differs this should be highlighted and the reason for the difference provided.	Base on published sources we believe the average age for women should be >80 years	The National HF audit states; "The patient's median age was 80 years.... The median age at admission was almost 5 years greater in women than men." The ERG doesn't to consider the statement in the report to be factually incorrect and this is supported by the opinion of our clinical experts.

both HFrEF as well as HFpEF patients so the actual age is estimated to be lower.			
Page 47 – The ERG has incorrectly quoted a sentence from the CS: '…there were no significant differences between groups regarding any of the baseline characteristics apart from some differences between English population with heart failure and the study population"	The text from the CS should be accurately reflected and updated to: '…there were no significant differences between groups regarding any of the demographic or baseline characteristics. However, some differences were observed between the English population with HF and the study population.'	This sentence is an inaccurate reflection of text the CS. The rephrasing of the sentence by ERG combines two separate statements from Novartis.	The ERG thanks the company for highlighting the error. The precise quote from the CS has been used: '…there were no significant differences between groups regarding any of the demographic or baseline characteristics. However, some differences were observed between the English population with HF and the study population.'
Page 55 – The ERG has been advised by clinical experts that men generally have better outcomes when treated for HF. When adjusted for age and other prognostic factors men and women have similar outcomes.	Published evidence does not support the statement that when adjusting for age and other prognostic factors, men and women had similar outcomes[2]	Published evidence disproves the ERG's view[2]. In addition the ERG does not reflect that HFrEF is a disease predominantly affecting men.	The ERG thanks the company for highlighting the error. The statement has been removed.

[2]Conde-Martel (2015) Gender related differences in clinical profile and outcome of patients with heart failure. Results of the RICA Registry. Rev Clin Esp. Oct;215(7):363-70

Issue 17 Device use

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 43 – The ERG states that data on patients with cardiac devices was not available in the CS. However, this data is available in the CSR which was provided as part of the CS. [redacted] Additionally, on page 43 or the ERG report, the ERG states the data from the CSR regarding the number of patients with fitted with a cardiac device.	The statement regarding data on patients with cardiac devices not being available in the CS should be removed and updated to: [redacted]	The NICE scope did not request subgroup analysis. Hence this could not be expected in the CS, although not presented it has been provided as part of the CS package, in the	The ERG acknowledges the data are available in the CSR but these were not submitted within the CS. This is therefore not a factual error.

		CSR: Page 1033 (Table 14.2-1.4.1.post.19 (Page 1 of 2).	
Page 126 – The ERG mention that subgroup analysis by device use should have been carried out by the company.	The ERG should remove the statement that subgroup analysis with device use at baseline has not been carried out by Novartis as this is not accurate and not presenting subgroup analyses is aligned with the NICE scope.	The data on cardiac devices as the NICE scope did not request this subgroup analysis, although not presented in the CS itself has been provided as part of	Not a factual error. The ERG acknowledges that the company has provided these data as part of the PARADIGM-HF CSR, which is an accompanying document to the CS.

		the CS package, in the CSR: Page 1033 (Table 14.2-1.4.1.post.19 (Page 1 of 2) .	However this analysis was not mentioned in the CS.

Issue 18 Treatment class effect and use of enalapril versus ramipril

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 44 – The ERG concludes that they are not aware of any evidence that there is a class effect for ACEi and that the conclusion in the CS on page 72 (that all ACEi are the same in terms of effectiveness) may not be valid. However, on Page 77 of the CS a reference to a recent meta-analysis[3] that has investigated the ACEi class effect (and includes trials on both ramipril and enalapril) was discussed.	The ERG should rephrase this sentence to state that an ACEi class effect is well-established both by NICE and published literature. This is further supported by the fact that the NICE scope referred to classes of drugs (ACEi, ARBs) as opposed to individual medicines.	The CS includes a study supporting a class effect which the ERG has been provided with From the CS: 'This assumption has been tested for ACEis in a SR and NMA by Chatterjee *et. al*., 2013 (185). The findings show that "benefits of ACEi in patients with heart failure appear to be due to a class effect" and note that "there is currently no statistical evidence in support of the superiority of any single agent over the others" (185).' In addition NICE guidelines have not	The class effect for ACEis is an assumed effect by the Cochrane authors but is not proven and the ERG therefore considers the text to be factually correct.

[3]Chatterjee et. al. (2013) A Network Meta-Analysis and Diversity-Adjusted Trial Sequential Analysis of Angiotensin Converting Enzyme Inhibitors in Patients With Heart Failure: Evidence of Class Effect. Circulation.128(A16320).

		identified any preference in their recommendations.	

Issue 19 PARADIGM-HF study schematic (Figure 2)

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 45 – The study schematic in Figure 2 does not represent the sacubitril valsartan PARADIGM-HF trial but for a NOAC trial.	Replace Figure 2 using Figure 3 page 41 from the CS.	Incorrect study schematic incorporated in ERG report.	The ERG thanks the company for highlighting the error. The figure on page 45 has been updated.

Issue 20 Western Europe subgroup

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 48 – The ERG states 'a post-hoc analysis to assess the treatment effect of subgroup of patients in Western Europe.' However, this post-hoc analysis was not a subgroup of patients in Western Europe, it was the entire Western Europe population i.e., without Israel and South Africa which were included for operational reasons in the primary subgroup analysis.	The ERG should use the wording that explains this in the CS on page 66: 'For operational reasons, patients from Israel and South Africa were pooled with Western European patients in the primary subgroup analyses. The post-hoc analysis is specific to Western Europe and excludes Israel and South Africa.'	The post-hoc analysis in Western Europe excluded Israel and South Africa, however, the primary subgroup analysis was a subgroup of Western Europe plus Israel plus South Africa.	The ERG has updated the text as follows; This was pre-planned with the exception of a post-hoc analysis to assess the treatment effect of ***the*** subgroup of patients in Western Europe.
Page 18/56/57/60–The ERG conclusion that the Western Europe subgroup analysis showed a non-significant	The ERG should remove this statement where mentioned throughout the report.	Interpretation of treatment effect in subgroups should be undertaken with caution and a non-significant treatment effect can only be	Not a factual error. As explained throughout the ERG report, there are several issues pointing to the lack of

treatment effect is statistically incorrect.		assumed if the p-value of interaction is significant between the subgroups. Please see below for excerpt from Lancet publication regarding this: 'Reports of the significance of the effect of treatment in individual subgroups should be ignored, especially reports of lack of benefit in a particular subgroup in a trial in which there is overall benefit, unless there is a significant subgroup treatment effect interaction'.[4]	generalisability of the entire trial population when compared to the UK HFrEF population. Therefore the ERG has chosen the Western European subgroup as the most representative population of UK patients (still with caveats to the subgroup generalisability). The ERG makes no statement concerning statistically significant differences between regions but does report the results from the most relevant subgroup.
Page 56 –The differences that the ERG highlights between the Western Europe population and the conclusion made on this are inconsistent and not factual i.e., a difference of 3 years in age is seen as similar however a 4% difference in patients on ACEi is concluded as different.	Differences that could be relevant should only be highlighted by the ERG if statistically and clinically relevant.	The ERG should make factual conclusions on difference between the Western Europe subgroup and the overall population based on correct statistical tests.	The ERG thanks the company for highlighting the error. The text has been updated accordingly.
Page 56 – NYHA classification for Western Europe is concluded to be II even though this is [redacted] of the population.	The ERG should rephrase this sentence stating '…with most patients having an NYHA classification of II.'	[redacted] of the Western Europe subgroup have a different NYHA class.	The ERG thanks the company for highlighting the error. The text has been updated accordingly.
Page 56 – The ERG state '…the	ERG should remove the statement that this	Conclusion being made by the ERG	The ERG makes no definitive

[4]Rothwell (2005) Subgroup analysis in randomised controlled trials: importance, indications and interpretation. Lancet; 365: 176–86.

differences in the numbers of the Western Europe population who are hypertensive (63% vs [redacted] of the overall trial population) which may suggest that the Western Europe HF population are in receipt of more intensive "standard care" compared to other regions in the trial.' Causes for hypertension can be multiple, this conclusion only considers one possible scenario not based on any facts. Page 57 - the more intensive standard care therapy is based on [redacted] more patients receiving ACEi, however, the intensity cannot be concluded based solely on proportion treated, as it could be dose-dependent. Additionally, the trial population received more ARB and less ACEi compared to the Western Europe subgroup with both groups receiving the same amount of ACEi and/or ARB.	implies these patients are more intensively treated as this is not based on any facts. Alternatively, the ERG should provide all possible explanations for the small differences seen.	is not supported by facts and could be due to several other reasons. The conclusion of a [redacted] increase in ACEi use without data on dose is factually incorrect	statement about the cause of the differences identified; it merely highlights a plausible rationale that *may* be the underlying cause.
Page 57 – The ERG states that the Western Europe subgroup is less severe. However, on Page 56 they conclude that LVEF is similar between Western Europe and the trial population. Also, severity was	The ERG should use consistent and correct terminology when using severe as a descriptor of HF.	We assume that the ERG's conclusion that it is a less severe HF population is based on the [redacted] more patients with NYHA Class II in the Western Europe subgroup. However, symptoms and disease severity/progression are poorly	The ERG thanks the company for highlighting the error. The text on page 56 has been updated so that the conclusion that the Western Europe is a less severe HF population is based on the [redacted] more patients

previously defined using EF by the ERG.		correlated. A patient with mild symptoms does not mean that the underlying disease is controlled. If our assumption of the ERG's interpretation is correct, then this should be explained in the text.	with NYHA Class II in the Western Europe subgroup.
Page 57 – The ERG state that blood pressure at baseline is different between the Western Europe subgroup and the trial population, however, they are all in the range of 121-122 mm HG.	The ERG should remove this statement as it is incorrect.	Blood pressure at baseline is not different between the Western Europe subgroup and trial population, hence this is factually incorrect	CS Table 13, pg 55 shows the absolute numbers (%) of people with hypertension in the PARADIGM-HF trial population to be 2,969 (70.9%) in the sacubitril group vs 2,921 (69.3%) in the enalapril group. By contrast the absolute numbers of patients with hypertension in the Western Europe population are; [redacted]) respectively. The ERG has changed the statement to ".fewer patients having hypertension…"
Page 57/186 – The ERG states that a type II error is less likely because the Western Europe subgroup is 25% of the overall trial population. The ERG also note the significance of the HR in smaller regional subgroups. This is a misleading statement as	The ERG should remove this statement as it is statistically incorrect.	Interpretation of treatment effect in subgroups should be undertaken with caution and a non-significant treatment effect can only be assumed if the p-value of interaction is significant between the subgroups. Please see below for excerpt from Lancet publication regarding this:	Not a factual error. As explained throughout the ERG report, there are several issues pointing to the lack of generalisability of the entire trial population when compared to the UK HFrEF population. Therefore the ERG has chosen the Western

subgroup analysis should be interpreted based on p-value of interaction (which is non-significant for all region-based subgroups in PARADIGM-HF) prior to making conclusion on significance of outcomes.		'Reports of the significance of the effect of treatment in individual subgroups should be ignored, especially reports of lack of benefit in a particular subgroup in a trial in which there is overall benefit, unless there is a significant subgroup treatment effect interaction'.[5]	European subgroup as the most representative population of UK patients (still with caveats to the subgroup generalisability). The ERG makes no statement concerning statistically significant differences between regions but does report the results from the most relevant subgroup.
Page 180-181 – The ERG do not make clear that it was the company who had performed a scenario analysis with the Western Europe-specific subgroup data to estimate hospitalisation costs which resulted in a 1% decrease in ICER.	Wording should be updated to: 'The company performed a scenario analysis with the Western Europe-specific subgroup data to estimate hospitalisation costs which resulted in a 1% decrease in ICER from base case as the reduction in hospitalisations associated with sacubitril valsartan produced greater cost savings compared to the base case.'	To clarify and correct the ERG's assumed wording which implies Novartis did not test the Western Europe subgroup specific data in scenario analysis.	Not a factual error. The ERG disagrees that it is not clear in the report that the company undertook scenario analysis to test Western European hospitalisation data. The first paragraph on Page 180 reads "The company also produced a scenario analysis where the reasons for hospitalisation were derived only from the Western European patient subgroup…" Furthermore, the last paragraph on page 179 states "The scenario analysis included in the CS which increased the hospitalisation rate by 10% yearly, proved the model relatively insensitive to this variation…" Therefore the ERG believes that it is clear in

[5] Rothwell (2005) Subgroup analysis in randomised controlled trials: importance, indications and interpretation. Lancet; 365: 176–86.

			the report that the company conducted scenario analysis using the Western European hospitalisation data.

Issue 21 "Random high" effect

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 49/128/143/144 - The ERG state that there is a 'potential bias arising from the early stop observed in the PARADIGM-HF trial, at which point the data observed might have been a "random high" effect, favouring sacubitril' However, the ERG do not have evidence to support this statement.	The ERG should remove statements throughout the document which suggest a potential 'random high' effect as the ERG do not have data to support this.	[redacted]	Not a factual error.

Issue 22 Generalisability of standard therapy use

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 55/129/131 – The ERG uses different evidence to imply that the standard therapies are not reflective of clinical practice (both lower and higher vs. PARADIGM-HF) using clinical expert opinion and CPRD data. For example, on Page 129, the ERG's clinical expert states that the proportion of patients receiving AA was considered to be lower in PARADIGM-HF compared to clinical practice. However the National HF Audit reports that 49% of the HF population receive AA and the CPRD data show [redacted] of patients on AA, which are both [redacted] than the 56% of patients in PARADIGM-HF on aldosterone antagonists at baseline.	The ERG should defer to high quality published evidence (National Heart Failure Audit) over the opinion of individual clinical experts and use a consistent source throughout the document.	Different sources are being used that show both a higher and lower proportion of standard care therapy use in the UK, compared to PARADIGM-HF.	Not a factual error.

Issue 23 Adverse events

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 58 – The ERG insert a quoted statement in Paragraph 3 ('the rate of adverse reactions was similar…') however this is not a	The ERG should insert the exact quote from the SmPC when using quotation marks. ('the rate of adverse reactions was similar…')	To accurately capture the exact wording of the SmPC when using quotation marks.	The ERG thanks the company for highlighting the error. The text has been updated accordingly.

quote from the SMPC but has been rephrased by the ERG.			
Page 58 – The ERG disagrees with the SmPC that adverse reactions were similar across both treatment arms, and overall frequency was not related to gender, age or race based on one adverse reaction in one subgroup and without supportive data for p-value of interaction in that subgroup.	The ERG should remove this conclusion as it is misleading and not supported by evidence.	No data is provided that justifies the challenge to the SmPC and the number of patients affected by this one adverse event, angioedema, are very small (e.g., 2.5% of black patients equates to 5 patients)	The ERG was advised by its clinical experts that angioedema is a clinical outcome of particular concern to clinicians. The ERG considers this to be a small but important numerical difference between adverse events.
Page 59 – The ERG state that 'there could be an increase in the proportion of patients who experience hypotension with a lower baseline BP than the trial population (e.g. the Western Europe population in PARADIGM-HF)'. Additionally the ERG state a reference to the CS, Page 68, Figure 8 which is incorrect and we are unsure which figure the ERG is referring to.	The ERG should remove this statement as it is incorrect.	Blood pressure at baseline between the Western Europe subgroup and the trial population are all in the range of 121-122 mm HG.	The ERG makes no definitive statement about this, merely that there could be an increase in the proportion of patients who experience hypotension".
Page 71 – The ERG states that 'the occurrence of AEs leading to treatment discontinuation was not reported in the CS'. This is not entirely accurate as the CS did report the number of patients who discontinued due to AEs (p. 98,	Wording should be updated to: "The number of patients who discontinued due to pre-specified AEs included in the model was not reported in the CS."	Corrected wording to accurately describe what was reported in CS and what was not.	Not a factual error.

Table 41).			
Page 141 – The ERG state that the 'investigator-reported AEs in the FAS were not provided by the company'. This implies that there was a request for this data by the ERG which Novartis did not fulfil – however no such request was made by the ERG at the clarification stage.	Wording should be updated to: …investigator-reported AEs in the FAS were not *included in* the company *submission'*.	Corrected wording to avoid implication that the company did not fulfil a request by ERG at clarification stage.	Not a factual error.

Issue 24 Definition of treatment failure and line of therapy

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 60 – The ERG conclude that as PARADIGM-HF includes patients who are symptomatic despite treatment these patients have failed on first-line treatment and as such this should be the eligible patient population. 'The ERG considers the trial to be assessing the effectiveness of sacubitril [valsartan] in patients who have failed on first-line therapy' Chronic, progressive symptomatic disease treatment success is not measured by symptomatic changes, therefore it cannot be concluded that patients who remain symptomatic on treatment have necessarily failed on therapy. Also it	Wording should be updated to: 'The ERG considers the trial to be assessing the effectiveness of sacubitril [valsartan] in patients who have *remained symptomatic* on first-line therapy'	HFrEF is a chronic progressive disease and treatment failure could be defined in several ways, however, simply being symptomatic does not equate to treatment failure. Treatment failure could more accurately be defined as the addition of a new drug for the treatment of worsening HF, IV treatment requirement, or an increase of diuretic dose for example. Even when optimally treated, it is uncommon for patients with HFrEF to be asymptomatic (NYHA I). For example only 5% of patients managed to become asymptomatic based on optimising therapy within	Not a factual error.

is important to note that symptoms and disease severity/progression are poorly correlated. A patient with mild symptoms does not mean that the underlying disease is controlled, and hence being symptomatic does not necessarily indicate treatment failure.		the run-in phase for PARADIGM-HF.	

Issue 25 Referring to individual drugs vs. class

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 69/112 and throughout document – It is not entirely accurate to refer to candesartan as the comparator in the secondary analysis, as only the cost is based on candesartan while the efficacy data is based on the NMA which includes evidence from several ARBs (e.g. candesartan, losartan, telmisartan)	The ERG should refer to the comparator in the secondary analysis as an ARB (with cost of candesartan).	Corrected description of comparator arm in secondary analysis so that it is clear that a broader evidence base supports the efficacy data for that comparator (ARB).	Not a factual error. The ERG reports in page 61 that, “In their base-case analysis, the company presented deterministic and probabilistic results for the comparisons of sacubitril valsartan (hereafter referred to as sacubitril) versus ACEi (more specifically enalapril) and ARB (more specifically candesartan)”.

Issue 26 Distribution selection

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 73 – The ERG has not fully explained the reasons for Novartis selecting the Gompertz distribution. In addition to the Gompertz model	Wording should be updated to: The company selected the Gompertz distribution as:	To fully describe the justification for use of the Gompertz distribution which was not accurately reflected	Not a factual error. On page 72/73 of the ERG report it is stated that, “Upon inspection of the AIC and the BIC the

providing the shortest survival times and therefore the most conservative estimate of the mortality benefit, it was selected because: • Of the remaining models, it was noted that the Gompertz model is especially suited to the modelling of human survival, as mortality is assumed to increase at an increasing rate • Clinical experts confirmed that the extrapolation using the Gompertz model is clinically plausible	• This model provided the shortest survival times and therefore the most conservative estimate of the mortality benefit • Of the remaining models, it was noted that the Gompertz model is especially suited to the modelling of human survival, as mortality is assumed to increase at an increasing rate • Clinical experts confirmed that the extrapolation using the Gompertz model is clinically plausible	in the ERG report.	company considered that these were insufficient to draw a conclusion on the best distribution to use as the values were similar, with the exception of the lognormal which was deemed to perform worse than other distributions. Therefore external validation of the different fitted survival curves was undertaken by company's clinical experts"…" The company selected the Gompertz distribution as it was considered that this model provided the shortest survival times and the most conservative estimate of the mortality benefit."

Issue 27 Drug regimen impact on efficacy outcomes

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 101 – The ERG state that 'Drug regimens were also assumed not to depend on patient characteristics or the occurrence of events such as adverse events or hospitalisations, and to have no impact on the efficacy outcomes or incidence of hospitalisation or adverse events."	Wording should be updated to: 'Drug regimens were also assumed not to depend on patient characteristics or the occurrence of events such as adverse events or hospitalisations'.	Removal of sentence that is incorrect based on information presented in CS.	The ERG thanks the company for highlighting the error. The ERG agrees that BB and lipid lowering drugs have an impact on the efficacy outcomes and has removed this sentence from page 101.

This is not accurate as BB use was included as a covariate in the mortality and hospitalisation statistical models. Use of lipid lowering medications was also included as a covariate in the all-cause hospitalisation model. Therefore, certain background medications affected baseline risk of outcomes as they were included as covariates.			

Issue 28 NICE reference case and Philips checklists

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 111 – The ERG state that PARADIGM-HF did not include therapy with beta blocker and aldosterone antagonist for all patients but only for 93% and 56% of patients, respectively – implying that 100% of patients should have been on beta blocker and aldosterone antagonists when this was not explicitly stated in the NICE scope.	Wording should be updated to: 'standard care in the economic model was based on drug used in the PARADIGM-HF trial, and included therapy with beta blocker and aldosterone antagonist for 93% and 56% of patients, respectively, which aligns with UK clinical practice (National HF Audit)' – see Issue 21.	This response in the checklist should be corrected to accurately reflect what was asked for in the NICE scope.	Not a factual error.
Page 113 – In Section D3: Data incorporation, the ERG statement is misleading as there were multiple scenario analyses performed on quality of life (see	The ERG should remove this statement or modify it so that it accurately reflects that quality of life uncertainty was captured, and that it is highly unlikely resource use uncertainty would have impacted on model results based	Corrected wording to accurately capture the level of uncertainty associated with these inputs based on the evidence presented in the CS.	Not a factual error. In the ERG report it is acknowledged that the uncertainty associated with some parameters was explored; however no structural

Table 99 in company submission). Although specific scenario analyses or alternative data sources were not tested for resource use, they were included in the DSA and were not demonstrated to be strong drivers of model outcomes. Therefore, it is highly unlikely that the 'scarcity of analyses' for resource use and quality of life data for adverse events 'underestimates the amount of uncertainty associated with the model predictions'.	on the DSA.		sensitivity analyses around the QoL model was carried out and data from alternative sources (i.e. identified in the literature reviews) were not considered.

Issue 29 EQ-5D/ KCCQ

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 158 – The utility score from Berg *et. al.* is stated by the ERG to be 0.712[6]	Correct the score to 0.72	The correct score is 0.72	The ERG agrees that the correct value is 0.72 instead of 0.712. The ERG identified other instances where 0.712 was reported instead of 0.72 and has corrected these (Page 21 and Page 200). This does not change any of the additional analysis

[6]Berg et.al. (2015) Determinants of Utility Based on the EuroQol Five-Dimensional Questionnaire in Patients with Chronic Heart Failure and Their Change Over Time: Results from the Swedish Heart Failure Registry. Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research.18(4):439-48

			undertaken by the ERG as the correct value (0.72) was used in the ERG analysis.
Page 159 - EQ-5D data by treatment arm (except for the mean value) were not reported by the company.	The ERG should remove this statement as it is incorrect	This data has been included in the cost-effectiveness model to the ERG.	Not a factual error. The cost-effectiveness model does not include EQ-5D data by treatment arm (except for the mean value).
Page 159/161 and repeated elsewhere– The ERG states 'In summary the ERG cannot be certain if there was a statistically significant difference or not at baseline for patients' EQ-5D scores.'	Wording should be updated to: 'There was no evidence of a difference in mean EQ-5D at baseline'.	As we are interested in comparing means, which is the measure of central tendency preferred in health-economic analyses, the sample size in each arm of the PARADIGM-HF data (>4,000 patients) ensures that a parametric test, such as the t-test performed, would provide correct inference based on the central limit theorem. Both the means and standard deviations from the two samples are almost identical. Although a non-parametric test could have also been provided, we believe that it is highly unlikely that such a test would provide different evidence to support another approach.	Not a factual error. The ERG cannot be certain if there was a statistically significant difference or not at baseline for patients' EQ-5D scores.

Page 160 – The ERG state 'Furthermore the NICE DSU (Longworth et. al.)...(i.e. cross-validation).' The NICE DSU referred to is in case EQ-5D needs to be mapped, however, as EQ-5D data was available from PARADIGM-HF mapping was not required and not undertaken. The NICE reference case recommends use of EQ-5D data from clinical trials.	This should be deleted as the NICE DSU[7] referred to is not relevant for the data provided by the company.	The NICE DSU[7] document is not relevant as it refers to the mapping of EQ-5D data.	Not a factual error. The recommendations made by Longworth *et al.*[7] are generally applicable to all types of regression modelling.
Page 20/159/161/162 –The ERG is concerned that the [redacted], and that this could potentially bias the trial and consequently the model outcomes.	The ERG should rephrase throughout and remove any implication of differences in model outcomes based on KCCQ or [redacted] and therefore would not be expected to impact the trial or model outcomes.	A study by Spertus *et al.*[8] states that a minimal difference of 5 points over time depicts a clinically meaningful difference in heart failure. Even though this is not across treatment this is transferable to this example. [redacted] Additionally the KCCQ analysis in PARADIGM-HF used an ANOVA model which did adjust for baseline KCCQ scores (see footnote of Table 14.2-2.4 of CSR)	Not a factual error. The study by Spertus *et al.*[9] reports a minimal difference of 5 points over time however the [redacted] points mentioned by the ERG represent the [redacted] Therefore the ERG cannot be certain [redacted] would be considered

[7]Longworth et. al. (2013) Mapping to Obtain EQ-5D Utility Values for Use in NICE Health Technology Assessments. Value in Health.16(1):202-10.
[8]Spertus et. al. (2004) Monitoring clinical changes in patients with heart failure: A comparison of methods. American Heart Journal.150:707-15.)
[9]Spertus et. al. (2004) Monitoring clinical changes in patients with heart failure: A comparison of methods. American Heart Journal.150:707-15.)

			clinically meaningful or not.
Page 161 – The ERG concludes there is a lack of robust evidence for sacubitril/ valsartan to have measurable improvement to QoL	The ERG should base their conclusion on all available (published) evidence. So the ERG should either include this data and provide a conclusion why this is or is not leading to improvements in QoL or remove this paragraph.	Published data which is not mentioned by the ERG (and provided to them as part of the CS - Packer 2014) include data on worsening of NYHA class over time, clinical meaningful reduction in KCCQ over time all significantly different with sacubitril/ valsartan. In addition the NYHA shift data as presented in the CS as well as repeated in ERG clarification questions has been ignored	Not a factual error. The ERG has several issues with the measurement of differences in QoL at baseline, which may impact the evolution of QoL over time across treatment arms in the PARADIGM-HF trial.
Page 161 – The ERG state 'Therefore the justification… Additional data in the CS as well as in the ERG response was provided with regards to NYHA class shift 'which the ERG has not taken into consideration in their assessment.	The ERG should remove this statement as additional data was provided but not used or referred to base the justification on.	In the ERG clarification question Novartis stated: 'In addition, improvement in NYHA class was more likely for patients treated with sacubitril valsartan compared with enalapril.'	Not a factual error.

Issue 30 Modelling of mortality

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 120 – The ERG statement that if survival is halved for 90-year old patients after 15 years in the model, there could be nearly twice the survival benefits cannot be substantiated with evidence	The ERG should remove or modify this statement to account for the results of the Jhund *et. al.* paper[9] which does not support differential survival benefits with sacubitril valsartan based on age.	The ERG should only make statements that can be backed up by evidence. In this case, a study exists that refutes the claim made by the ERG that there could be differential survival benefits with	Not a factual error. The statement mentioned by the company (page 120) is in support of Figure 12 (page 121) which is a theoretical demonstration of the impact of

and is misleading. The Jhund *et. al.* paper[10] provides evidence that there is no significant difference in treatment effect across age groups, and no statistically significant p-value for interaction across age groups.		sacubitril valsartan based on age.	starting an economic model at different baseline ages.
Page 17/143 – The ERG wrongly make the comparison between the proportion of patients who die from the start of the model and the proportion of patients who die from time of diagnosis from the NICE CG108 prognosis.	The ERG should remove the following statement as it is inaccurate and misleading: 'However, when compared to the NICE CG108 prognosis that 30% to 40% of patients diagnosed with HF die within a year (simulated by the ERG in Figure 18), the observed and predicted mortality in the CS seem substantially different (less than half).(6)'	It is inaccurate and misleading to compare the NICE CG108 prognosis that 30-40% of patients diagnosed with HF die within a year of diagnosis and the observed and predicted mortality in the CS which is not from diagnosis, so this conclusion should be removed.	Not a factual error. The ERG believes this comparison to be relevant and a determinant in explaining the difference in expected mortality between the PARADIGM-HF trial population and a newly diagnosed HFrEF population.

Issue 31 Incorrect description of sacubitril valsartan

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 18/123/124/132/135/206 – The ERG refer to sacubitril valsartan as 'valsartan (given in combination with sacubitril' or a variation thereof. This is not an accurate description, as it implies that valsartan and sacubitril are two separate entities given in combination when in fact sacubitril valsartan is a salt complex comprising two active moieties,	When referring to sacubitril valsartan, the ERG should use 'sacubitril valsartan' and not 'valsartan (given in combination with sacubitril)' throughout the document.	To use the correct name of sacubitril valsartan throughout the document and to confirm that sacubitril valsartan is a salt complex comprising two active moieties, sacubitril and valsartan, which have been co-crystallised in a 1:1 molar ratio.	The ERG carefully acknowledges the full name of sacubitril valsartan at the beginning of the report before using the name sacubitril for reasons of efficiency. This is not factually incorrect.

[10] Jhund et. al. (2015) Efficacy and safety of LCZ696 (sacubitril valsartan) according to age: insights from PARADIGM-HF. European Heart Journal.

sacubitril and valsartan, which have been co-crystallised in a 1:1 molar ratio.			
Page 125 – The ERG refer to valsartan (with sacubitril in PARADIGM-HF) in Table 46. This is an inaccurate description of sacubitril valsartan for same reasons stated above.	The ERG should correct this table and add two rows, one with valsartan and another row with sacubitril valsartan. The CPRD data should be included for valsartan only and the PARADIGM-HF data included for sacubitril valsartan only.	To use the correct name of sacubitril valsartan throughout the document and to confirm that sacubitril valsartan is a salt complex comprising two active moieties, sacubitril and valsartan, which have been co-crystallised in a 1:1 molar ratio.	The ERG carefully acknowledges the full name of sacubitril valsartan at the beginning of the report before using the name sacubitril for reasons of efficiency. This is not factually incorrect.

Issue 32 Target doses and tolerability

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 123/125/132 – The ERG have made an error regarding the 'target dose of valsartan in the trial (in combination with sacubitril)'. Firstly, referring to sacubitril valsartan as 'valsartan in combination with sacubitril' is incorrect as described in Issue 31. More importantly, each 200 mg tablet of sacubitril valsartan contains 97 mg of sacubitril and **103 mg** of valsartan. Therefore, the ERG have incorrectly reported the target dose of sacubitril valsartan (which is 103 mg of valsartan, not 160mg, as part of the 200mg target dose of sacubitril	The target dose of sacubitril valsartan should be referred to as 200 mg BID, of which the valsartan component is 103mg. The ERG should clarify that the 103mg of valsartan in sacubitril valsartan is *equivalent* to a 160mg dose of valsartan – however 160 mg is not the target dose for valsartan as a component of sacubitril valsartan.	To accurately report the target dose of valsartan in sacubitril valsartan in PARADIGM-HF.	The ERG agrees with the company that the equivalence of valsartan doses in sacubitril valsartan and valsartan alone should be reported in the ERG report. Therefore the ERG has included the following sentence in page 61: "The target dose of sacubitril (200mg BID) contains 103mg of valsartan, which is equivalent to a 160mg dose of valsartan given alone (hereafter referred to as valsartan)."

valsartan).			
Page 123/125/132 – The ERG also make the conclusion that it is uncommon for patients to tolerate the evidence-based 160mg dose of valsartan in clinical practice (based on CPRD data) and this could indicate higher tolerability of sacubitril valsartan in the trial versus clinical practice, implying this could impact effectiveness of sacubitril valsartan in clinical practice. It is important to note that not all patients achieve target dose of ACEi in practice, however there is only evidence for the effectiveness of target doses of ACEi in the key clinical trials (e.g. SOLVD, CONSENSUS). Therefore, the same conclusion that the ERG make for the tolerability of the evidence-based dose of valsartan (160 mg), could be made for ACEi tolerability (and potentially impact on effectiveness) in trials versus real-life practice.	The ERG should provide the context of tolerability in trials versus clinical practice and that this does not only apply to the valsartan component of sacubitril valsartan but also to ACEi use in clinical practice.	The ERG's suggestion that the clinical effectiveness of sacubitril valsartan would be impacted by a reduced tolerability in clinical practice versus trial would also apply to ACEi. Therefore, the implication that the relative effectiveness of sacubitril valsartan versus enalapril would not translate to clinical practice due to potentially lower tolerability of sacubitril valsartan cannot be substantiated by the evidence, and this should be made clear.	Not a factual error. The average dose of enalapril tolerated in the PARADIGM-HF trial is considerably closer to the enalapril tolerability reported in the CPRD analysis than is the valsartan dose in the trial compared with CPRD data.
Page 123-124 – The ERG's comparison at the end of this page between the 10 mg *minimum tolerable* daily dose of enalapril and the 16.4 mg *average* daily dose of enalapril from CPRD data	The conclusion the ERG makes 'that the trial (and therefore the model) population presents a higher tolerability to the intervention drugs' cannot be substantiated with evidence regarding tolerability of daily dose and should	Wording should be removed as the comparison is a misleading one and is not based on evidence.	Not a factual error.

is a misleading one, as the average daily dose of enalapril achieved in the PARADIGM-HF trial was 18.9 mg (which is very close to the average daily dose of enalapril from CPRD).	therefore be removed.		

Issue 33 Resource use drug cost

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 165 – The ERG states 'Despite stating that the cost of sacubitril [valsartan] in the model was estimated based on the target dose of sacubitril in the PARADIGM-HF trial, the company used the observed dose of sacubitril to estimate its costs in the economic analysis.' Novartis has explained this clearly including that the cost would be the same.	The ERG should remove this sentence as it is incorrect.	Page 149 of the CS - The daily cost of sacubitril valsartan is based on the observed dose of sacubitril valsartan from PARADIGM-HF (375 mg) (10). A daily cost based on the pre-specified target dose of 200 mg bid is expected to be the same as that of the observed dose, considering the flat pricing structure of sacubitril valsartan.	The ERG thanks the company for highlighting the error. The ERG has amended the sentence to "The cost of sacubitril in the model was estimated based on the observed dose of sacubitril in the PARADIGM-HF trial".
Page 165 – The ERG, based on clinical expert opinion, states that ramipril would be used as a daily dose which is different from the BNF recommended dose.	The NICE methods guide[11] recommends the use of BNF for drugs resource use and given that the data from a large database (CPRD) shows differential dosing for ramipril compared to ERG's clinical expert opinion, the ERG should use the ramipril target dose from the BNF.	CPRD data showed that [redacted] of patients achieve target dose identified as 5 mg BID. Patients who do not achieve target dose could be treated once daily as suggested or might not be able to reach target dose. This indicates	Not a factual error. The ERG's assumption (based on clinical expert opinion) is within the marketing authorisation for ramipril.

[11]National Institute for Health and Care Excellence. Guide to the methods of technology appraisal. 2013. Available at: http://publications.nice.org.uk/guide-to-the-methods-of-technology-appraisal-2013-pmg9

		that there are differences in UK clinical practice and additionally, NICE recommends the use of BNF doses for resource use.	
Page 165 – The ERG states that the choice of the sources used to model the doses of aspirin and warfarin in the model were not clearly reported in the CS.	The ERG should remove this statement as it is incorrect.	Table 63 in the CS reports the reference for the dose of warfarin and aspirin.	Not a factual error. The choice of the sources and of the dosages used in the company's economic analysis was not justified.

Issue 34 Confidential marking

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 172/199 – in Table 63 and Table 83 the Total costs and QALYs need to be marked as CiC.	The ERG should mark this data CiC as the price for sacubitril valsartan has yet to be published	The Total costs and QALYs need to be marked as CiC at this stage to prevent back-calculation of the price of sacubitril valsartan as it is not yet published.	The ERG has marked the total costs and QALYs associated with sacubitril valsartan as CiC.

Issue 35 ERG scenario analysis

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 200-209 – Novartis were not able to exactly replicate the ICER results from the ERG scenario analyses.	Novartis request that the ERG provide a detailed account of changes/amendments to cells in the electronic model which were required to conduct the ERG scenario analyses.	Further detail required on amendments to model so that Novartis is able to replicate the ERG scenario analyses.	Please see, "Sacubitril valsartan for treating chronic heart failure: Addendum to ERG Report".

Issue 36 Typographical errors

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 11 – The ERG state 'In the final scope issued by NICE, the comparators of interest were identified as ACEi with standard care, angiotensin II receptor blocker (ARB) with standard care (for people in whom an ACEi is unsuitable).'	Wording should be updated to: In the final scope issued by NICE, the comparators of interest were identified as ACEi with standard care, *and* angiotensin II receptor blocker (ARB) with standard care (for people in whom an ACEi is unsuitable).'	Typographical error.	Not a factual error.
Page 41 – In the second paragraph the ERG state: 'randomisation took place following after the run-in phase'	The ERG should delete 'after' or 'following' in this sentence.	Typographical error.	The ERG thanks the company for highlighting the error. The text has been amended.
Page 51 – In the third paragraph HFpEF is referred to as HFrEF	Update abbreviation to HFpEF	Typographical error.	The ERG thanks the company for highlighting the error. The text has been amended.
Page 62 – The ERG statement is not clear whether the total 69 cost-effectiveness analyses identified were from the original search or the total number of studies identified.	Wording should be updated to: "A total of 69 cost-effectiveness analyses were identified: 27 studies from the original search, 39 studies from the first search update and 3 studies from the second search update."	To clarify the number of cost-effectiveness studies that were identified at each update.	Not a factual error.
Page 87 – There is no Section 5.5.9.5 referred to in the footnotes of Table 27	The ERG should add the correct Section here.	Typographical error.	The ERG thanks the company for highlighting the error. The ERG agrees that the Section referred to in Table 27 is the

			incorrect reference, and have changed this to read Section 5.5.8.5.
Page 96 – The utility decrements for hypotension and cough have not been described in the right order. Hypotension is associated with a utility decrement of -0.029 and cough is associated with a utility decrement of -0.028	Wording should be updated to: "The utility decrement for hypotension and cough were associated with reductions in QoL equal to ***-0.029*** and ***-0.028*** over an average duration of 64.9 and 73.3 days respectively	Typographical error.	The ERG thanks the company for highlighting the error. The ERG agrees that the utility decrements were not described in the right order and has corrected the sentence as per the company suggestion.
Page 111 – We assume there is a misspelling of 'inconsistencies' as 'inconstancies'	The ERG to correct sentence to '…the ERG found a few inconsistencies…'	Typographical error.	The ERG thanks the company for highlighting the error. The ERG agrees that "inconsistencies" is the correct word as per the company suggestion and has made the according changes.
Page 129 – The ERG have not accurately reproduced the exact NICE scope wording: '*including* treatment with a BB and an AA'	The ERG to correct sentence to reflect NICE scope wording.	Typographical error.	The ERG has changed the sentences in page 129 from (treatment with a BB and AA) to (including treatment with a BB and AA).
Page 138 – The Jhund *et. al.* study results are presented in Figure 15, not Figure 25 as the ERG states.	The ERG to correctly refer to Figure 15 in this sentence.	Typographical error.	The ERG has changed the reference to Figure 25 to Figure 15 in page 138 of the report.
Page 138 – The ERG states that 'none of the hospitalisation HRs for sacubitril [valsartan] versus enalapril are non-statistically	The ERG likely meant to say that '*all* of the hospitalisation HRs for sacubitril [valsartan] versus enalapril are non-statistically significant'.	Typographical error.	The ERG has changed the word "none" to "all" in page 138 of the report.

significant'.			
Page 141 – Correct wording to 'these consisted *of* hypotension…'	The ERG to correct grammar in this sentence.	Typographical error.	Not a factual error.
Page 152 – Correct 'PARDIGM-HF' to 'PARADIGM-HF'	The ERG to correct spelling of PARADIGM-HF.	Typographical error.	The ERG has changed the word "PARDIGM-HF" to "PARADIGM-HF" in page 152 of the report.
Page 154 – Correct 'rip' to 'reap' …'the benefits associated with the drug for longer;	The ERG to correct spelling of 'reap' in this sentence.	Typographical error.	The ERG has changed the word "rip" to "reap" in page 154 of the report.
Page 173 – The ERG state that the 'ICER in Table 65 [£16,678] is slightly higher than the one reported in Table 63 [£17,939], as expected however the ICER for the secondary analysis using the CV mortality approach is slightly lower than the ICER using the all-cause mortality approach, reported in Table 64 [£16,481].' which is incorrect.	Wording should be updated to: 'The ICER in Table 65 is *lower* than the one reported in Table 63, as expected however the ICER for the secondary analysis using the CV mortality approach is slightly *higher* than the ICER using the all-cause mortality approach, reported in Table 64'	Typographical error.	The ERG changed the sentence, "The ICER in Table 65 is slightly higher than the one reported in Table 63, as expected however the ICER for the secondary analysis using the CV mortality approach is slightly lower than the ICER using the all-cause mortality approach, reported in Table 64." to "The ICER in Table 65 is lower than the one reported in Table 63, as expected however the ICER for the secondary analysis using the CV mortality approach is slightly higher than the ICER using the all-cause mortality approach, reported in Table 64".

Page 179 – The ERG statement that 'cost savings caused by patients switching to the cheaper ARB therapy in the sacubitril [valsartan] arm…' is wrong as patients in the sacubitril valsartan arm move to ACEi when they discontinue in this scenario.	Wording should be updated to: 'cost savings caused by patients switching to the cheaper *ACEi* therapy in the sacubitril arm…'	Typographical error.	The ERG agrees that ACEi therapy should replace ARB therapy in the sentence referred to by the company. The ERG has corrected this in page 179 of the report.

Sacubitril valsartan for treating chronic heart failure
ERRATUM

This report was commissioned by the NIHR HTA Programme as project number 15/64/06

BMJ Technology Assessment Group

This document contains errata in respect of the ERG report in response to the company's factual inaccuracy check.

The table below lists the page to be replaced in the original document and the nature of the change:

Page No.	Change
12	Wording updated to, "The primary outcome of the PARADIGM-HF trial was a composite of time to first occurrence of either CV death or first hospitalisation for HF".
17	Word "stable" removed.
18	Word "stable" removed.
21, 158, 200	The utility value 0.712 has been changed to 0.72.
24	Wording amended to, "men have a higher prevalence of HFrEF (defined as left ventricular ejection fraction <40%)". Sentence, "The ERG identified published statistics on the epidemiology of CHF that suggest the overall prevalence of CHF is 3% in UK men and 1.7% in women in the UK (15)." Has been removed.
25	Reference in the heading of Table 1 changed to AHA guideline (from reference 20 to 18).
33	Wording updated to, "little evidence to support the use of sacubitril as a first line treatment in treatment-naïve HFrEF patients".
34	Word "stable" removed. Text amended to "the efficacy of sacubitril 200mg BID compared with the ACEi enalapril 10mg BID".
35	Wording amended. "The ERG notes that the primary efficacy variable was time to first occurrence of either CV death or first hospitalisation for HF and these were combined as a composite variable".
36	Wording amended; "the PARADIGM trial had an actual study duration of 51 months".
41	Word "following" removed.
43	The text has been amended to, "were patients with HFrEF (based on LVEF ≤35%), and the observed benefits of treatment with sacubitril would be greater than in patients without reduced ejection fraction."
45	Study schematic changed.
47	The wording has been amended to "The ERG considers the change from LVEF ≤40% to ≤35% means that the population recruited from then would have had more severe HFrEF". Wording amended to "there were no significant differences between groups regarding any of the demographic or baseline characteristics. However, some differences were observed between the English population with HF and the study population".
48	Text amended to "This was pre-planned with the exception of a post-hoc analysis to assess the treatment effect of the subgroup of patients in Western Europe".
51	Updated abbreviation to HFrEF.
55	Removed the statement pertaining to the ERG clinical experts view of the prognostic relevance of gender in HF.
56	Wording amended regarding prognostic effect of baseline characteristics. Wording amended to "with most patients having an NYHA classification of II".
57	Wording changed to "fewer patients having hypertension". Wording updated so the conclusion is that the Western population is less severe based on the 6% more patients with NYHA class II in the Western Europe subgroup.
58	Quotation marks removed.
59	Wording amended, "The primary composite outcome measure of CV death and HF hospitalisation demonstrated statistical significance after a median double-blind follow-up of 27 months".
60	Wording amended to "patients had to have HFrEF (defined as LVEF≤35%) and NYHA class II-IV". Text changed to " The company's inclusion of TITRATION provides limited evidence of the

	effectiveness of sacubitril in treatment naïve patients as only a fraction (6.6%) of patients included in the trial were treatment naïve.
61	The following sentence has been added: “The target dose of sacubitril (200mg BID) contains 103mg of valsartan, which is equivalent to a 160mg dose of valsartan given alone (hereafter referred to as valsartan).”
87	Section 5.5.9.5 has been changed to Section 5.5.8.5.
96	The following sentence has been amended from, “The utility decrement for hypotension and cough were associated with reductions in QoL equal to -0.028 and -0.029 over an average duration of 64.9 and 73.3 days respectively” to “The utility decrement for hypotension and cough were associated with reductions in QoL equal to -0.029 and -0.028 over an average duration of 64.9 and 73.3 days respectively”.
101	The following sentence has been amended from, “Drug regimens were also assumed not to depend on patient characteristics or the occurrence of events such as adverse events or hospitalisations, and to have no impact on the efficacy outcomes or incidence of hospitalisation or adverse events.” to “Drug regimens were also assumed not to depend on patient characteristics or the occurrence of events such as adverse events or hospitalisations.”
111	The word “inconstancies” has been changed to “inconsistencies”.
122	The sentence, “The company only provided the evolution of NYHA for sacubitril patients (total patients and treatment-naïve patients) and did not provide the results for the enalapril arm. Therefore the additional data provided by the company is of limited value given that it does not allow a comparison between treatment arms with respect to this outcome” has been amended to, “The company provided the evolution of NYHA for sacubitril patients only (total patients and treatment-naïve patients) as the TITRATION trial did not include treatment with enalapril. Therefore the additional data from TITRATION are of limited value given that they do not allow a comparison between treatment arms with respect to this outcome.”
123-124	The percentage of patients discontinuing enalapril during the run-in phase has been amended from 11% to 10%.
129	The sentence, “(treatment with a BB and AA)” has been changed to, “(including treatment with a BB and AA)”.
138	The reference made to Figure 25 has been changed to Figure 15. The following sentence has been changed from “none of the hospitalisation HRs for sacubitril versus enalapril are non-statistically significant” to “all of the hospitalisation HRs for sacubitril versus enalapril are non-statistically significant”.
152	“PARDIGM-HF” has been replaced by “PARADIGM-HF”.
154	The word “rip” has been changed to the word “reap”. The reference made to Figure 25 has been changed to Figure 15.
165	The following sentence has been amended from “Despite stating that the cost of sacubitril in the model was estimated based on the target dose of sacubitril in the PARADIGM-HF trial, the company used the observed dose of sacubitril to estimate its costs in the economic analysis” to “The cost of sacubitril in the model was estimated based on the observed dose of sacubitril in the PARADIGM-HF trial”.
173	The following sentence has been amended from “The ICER in Table 65 is slightly higher than the one reported in Table 63, as expected however the ICER for the secondary analysis using the CV mortality approach is slightly lower than the ICER using the all-cause mortality approach, reported in Table 64.” to “The ICER in Table 65 is lower than the one reported in Table 63, as expected however the ICER for the secondary analysis using the CV mortality approach is slightly higher than the ICER using the all-cause mortality approach, reported in Table 64.”
172,199	The total costs and QALYs reported in Table 63 and Table 83 were marked as CiC.
179	The following sentence has been amended from “cost savings caused by patients switching to the cheaper ARB therapy in the sacubitril arm…” to “cost savings caused by patients switching to the cheaper ACEi therapy in the sacubitril arm…”.

1.2 Summary of clinical effectiveness evidence submitted by the company

The primary objective of the PARADIGM-HF trial was to compare the outcomes of patients receiving sacubitril 200mg BID with enalapril 10mg BID in the management of CHF. To be eligible for enrolment patients had to have CHF defined by LVEF below 35% or reported as reduced with a NYHA class II–IV. The PARADIGM-HF trial also produced data to inform the analysis of treatment-related adverse events which affected about 22% of the trial population.

The number of patients randomised (1:1) to either sacubitril or enalapril were 8,442. There were 4,209 patients randomised to sacubitril and 4,233 patients to enalapril. The company reports data from three different analysis sets in the PARADIGM-HF trial; the Full Analysis Set (FAS) consisted of all patients except those who did not meet the eligibility criteria or did not receive a single dose of the study drug and these data were used for the efficacy outcomes (8,399 patients; 4,187 in the sacubitril group and 4,212 in the enalapril group). The safety (SAF) population comprised all patients who received at least one dose of study drug and these data were used for the safety analysis. A per protocol population (PP) was a subset of the FAS that consisted of the patients who do not have major deviations from the protocol procedures and was used to support the primary analysis results.

Regarding comparators, there were no head-to-head comparisons for sacubitril with ARBs – the drugs specified within the NICE scope for those people who could not tolerate ACEis. The company therefore presented:

- A Network Meta-Analysis (NMA) comparing outcomes from placebo, ACEis, ARBs and ARNIs (sacubitril) with sacubitril data connected to placebo and ARBs data via the enalapril arm of the PARADIGM-HF trial;
- An extended NMA to compare the outcomes from trials with placebo, ACEis, ARBs and ARNIs (sacubitril) plus beta blockers (BBs) and aldosterone antagonists (AAs).

The core NMA indicates sacubitril may be better than placebo, ACEis and ARBs for all outcomes (all-cause mortality, CV mortality) however, the NMA comparison of ARB and sacubitril data produced similar estimates for the relative effectiveness in reducing all cause hospitalisation. The ERG notes the company used a random effects model to account for heterogeneity in the NMA. The wide range in drug doses used to manage HF and the differences in NYHA classification of patients recruited to the trials in the NMA are potential sources of clinical heterogeneity. The primary outcome of the PARADIGM-HF trial was a composite of time to first occurrence of either CV death or first hospitalisation for HF. Overall, the results were consistently in favour of sacubitril. The ERG notes the trial ended "early" when the *a priori* statistically difference between enalapril and sacubitril was observed in fewer than anticipated events. The ERG notes there was a protocol amendment in

1.4.2 Strengths of the economic analysis

The company's analysis was based on the PARADIGM-HF trial, a high quality randomised controlled trial. The formulae within the economic model are generally sound and the economic model is a good predictor of the trial outcomes. The company conducted scenario and subgroup analyses which were not requested in the NICE final scope but added value to the submission.

1.4.3 Weaknesses and areas of uncertainty in the clinical analysis

The ERG notes several concerns regarding the generalisability of the evidence for sacubitril in the management of CHF submitted by the company. Firstly, the population of trial participants was younger and comprised of a higher proportion of males than would be seen in routine clinical practice in the UK. The ERG is advised by clinical experts that these patient characteristics are associated with improved outcomes. Secondly, the subgroup analysis of data from the Western Europe population did not reach statistical significance, despite the sample size being almost 25% of trial participants. Thirdly, the small amount of data provided for patients who had never taken an ACEi means there is little evidence to support the use of sacubitril as a first line treatment in newly diagnosed patients.

1.4.4 Weaknesses and areas of uncertainty in the economic analysis

The company's anticipated positioning of sacubitril in the HFrEF pathway is first-line treatment nonetheless the ERG considers that a first-line ICER for sacubitril compared with enalapril cannot be plausibly estimated based solely on the PARADIGM-HF trial data. The extrapolation of sacubitril's effectiveness in the PARADIGM-HF trial to a first-line treatment scenario is inappropriate given that:

- The PARADIGM-HF trial population does not reflect a newly diagnosed HFrEF population. About 78% and 23% of patients had received ACEi or ARB treatment, respectively, before randomisation. Additionally 70% of patients had been diagnosed for over 1 year at baseline and 31% had been diagnosed more than 5 years ago. Clinical opinion sought by the ERG indicates that based on the trial design, population and outcomes, the evidence supports the use of sacubitril in clinical practice is as a second-line treatment option, given to HFrEF patients who are still symptomatic despite being on an ACEi drug therapy. The trial (and therefore the model) population reflects a chronic and symptomatic (95% of patients in the NYHA class II–IV) HFrEF population who has been on ACEi (or ARB) treatment for at least 1 month;

- The mortality in the trial (and in the model) portrays a scenario representative of the use of sacubitril for established patients. Less than 10% of patients in the trial had died by the end of year 1 and only 20% were dead in both treatment arms by the end of the second year. When compared to the NICE CG108 prognosis that 30% to 40% of patients diagnosed with HF die within a year, the observed mortality in the trial is substantially different (less than half)(6);

- Given that the PARADIGM-HF trial's patients are symptomatic, despite having been treated with ARBs and ACEi, the impact of continuing these patients on ACEi is likely to be a misrepresentation compared to what would happen in treatment-naïve patients. Given that, in principle, the ACEi treatment regimen has been demonstrated to not improve these patients' HFrEF symptoms, randomising them to the same treatment regime is unlikely to show any improvements. This has an impact on the observed relative effectiveness of sacubitril, which might be overestimated in the trial population when compared to treatment-naïve patients.

In light of this, the ERG believes that the ICER presented by the company should be considered in the context of second-line treatment for chronic, stable and symptomatic HFrEF patients who have been on ACEi (or ARB) treatment for at least 1 month. Nonetheless the ERG is concerned with the validity of using the ICER presented by the company as an estimate of the cost-effectiveness of sacubitril compared to enalapril as there is too much uncertainty around the relative effectiveness when analysed in the context of UK clinical practice. This uncertainty is related mainly to:

- The lack of representativeness of the trial treatment regimens compared to the UK clinical practice, more specifically with regards to the dose of valsartan (in combination with sacubitril) given to patients. The ERG has reasons to believe that the tolerability to the observed dose of valsartan (in combination with sacubitril) in the PARADIGM-HF trial is overestimated and that patients in real-life clinical practice are unlikely to be able to tolerate, on average, the dose of valsartan received in the trial. Caution should be taken when interpreting the effectiveness outcomes in the PARADIGM-HF trial as it is difficult to understand how the trial could inform the effectiveness of sacubitril if given at a lower mean dose of valsartan;

- The lack of generalisability of the PARADIGM-HF trial population for second-line HFrEF UK patients. Firstly not only the PARADIGM-HF trial portrays a younger HFrEF population compared to the UK HFrEF average, but might also include slightly "different" HFrEF patients, who present with heart problems from a very young age. This could explain the higher CV mortality in younger patients, when compared to slightly older patients, who present with more "typical" HFrEF. Secondly, opinion provided by the ERG's clinical experts advised that the device use at baseline in PARADIGM-HF was lower than what would be expected in UK clinical practice and that this is an important prognostic factor in HFrEF;

The fact that the Western European subgroup analysis in the PARADIGM-HF trial reports a non-statistically significant HR CV mortality. While the PARADIGM-HF trial was not designed to estimate the effectiveness of sacubitril across different regions, and the sample size of the subgroup is smaller than that of the entire trial population, statistically significant.

1. The ERG changed the CV mortality HR in the model to reflect the Jhund *et al.* HR estimates for the 55–64 year category.(7) The HR used was 0.79 (95% CI: 0.64 to 0.98);

    - As the 95% confidence interval for the HR of CV mortality in the 55–64 years population is wide, the ERG also used both limits of the confidence interval;

2. The ERG used the baseline utility score of 0.72 reported by Berg *et al.*(8);

3. The ERG used the baseline utility score of 0.660 reported by Austin *et al.*(9);

4. Given the issues found in the modelling approach of QoL in the model, the ERG adopted a simplified approach, where the impact of sacubitril on patients' QoL was linked to the incidence of AE, hospitalisation events, and disease progression (i.e. time) in both treatment arms. Therefore, the QoL regression model was not used, even though some of its estimates were used as these were validated by clinical experts. The impact of sacubitril on QoL (other than through hospitalisations and AEs) was also removed to reflect the lack of robust evidence to support a measurable improvement in patients' QoL caused by sacubitril other than through hospitalisation, mortality and AEs. The impact of treatment regimens on QoL was assessed by the ERG through :

    - AEs and hospitalisation events: the ERG applied the same utility decrements used by the company to estimate the loss in QoL due to the incidence of AEs and hospitalisation;

    - Disease progression: the ERG applied the same utility decrement used by the company to reflect the loss of QoL as time progresses for HF patients.

5. The ERG changed the drug doses used in the model to reflect a consistent approach to the estimation of drug costs. The re-estimated drug costs are presented in Table 59, Section 5.5.9.1;

6. The ERG included the cost of ramipril (using the ERG drug dose assumption) to reflect clinical practice in the UK;

7. The ERG used the company's option in the economic model to run the ERG corrected model considering treatment discontinuation;

8. The ERG used the company's subgroup analysis results to run the ERG corrected model considering the Western European population. To note is that the mean baseline age for the Western European population is [redacted] years.

The ERG is aware that epidemiological studies show men have higher prevalence of HFrEF (defined as left ventricular ejection fraction ≤40%) than women and the prevalence in both sexes increases with age (13). The ERG notes that the age of onset of CHF differs between men and women: on average, men are admitted to hospital for CHF at an age 5 years younger than women (72.9 years for men vs 77.7 years for women (14)). The incidence of CHF has been estimated to be 0.6% in UK men in the 45–54 years age group and the estimated prevalence of women in the same age group is zero. Prevalence increases with age, rising to 4.9% in men over the age of 75 years and 2.6% in women of the same age (15). Above the age of 75 years, the proportions of men and women with HF are comparable but over the age of 80, women are more likely to have CHF (1).

- The ERG considers the company's description of the underlying health problem could be more fully explained. CHF is considered to be a clinical presentation of particular symptoms and outcomes, not characterised by a single aetiology or pathology but usually caused by coronary artery disease (CAD), which is estimated to account for approximately 2/3 of cases (16). Diabetes and hypertension are also considered to have an important etiological role in heart failure with reduced ejection fraction (HFrEF) (16, 17). However, more transient pathological conditions can also cause HFrEF (such as viral myopericarditis) from which patients may experience a complete recovery of their systolic ventricular function (16).
- The ERG considers the company's description of the symptoms (Box 2) of CHF is broadly accurate but would add that often the diagnosis of CHF is complicated because symptoms in the early stages of the disease can be non-specific. Typical HF symptoms of fatigue, tiredness, increased time to recover after exercise and ankle swelling can be due to other underlying pathologies and CHF is diagnosed using aspects from the patient's history, laboratory investigations and diagnostic tests (6, 16, 17).

Box 2. The symptoms of heart failure (CS, pg 28)

Typical symptoms of chronic HF includes breathlessness, orthopnoea, paroxysmal nocturnal dyspnoea, reduced exercise tolerance, fatigue, tiredness, increased time to recover after exercise and ankle swelling (18). The course of HF includes deterioration in symptoms, which leads to repeated hospitalisations for acute decompensations, and eventually death from progressive pump failure (19).
Abbreviations used in box: HF, heart failure.

The severity of HF is classified according to the New York Heart Scale (NYHA) Functional Classification which places patients in one of four categories according to the extent to which they are limited during physical activity (Table 1).

Table 1. New York Heart Association classification of heart failure(18)

Class	Description
I	No limitation of physical activity: ordinary physical activity does not cause undue fatigue, palpitations, or dyspnoea
II	Slight limitation of physical activity: comfortable at rest but ordinary physical activity results in fatigue, palpitations, or dyspnoea
III	Marked limitation of physical activity: comfortable at rest, but less than ordinary activity causes fatigue, palpitations, or dyspnoea
IV	Unable to carry out any physical activity without discomfort: symptoms of cardiac insufficiency are present at rest and discomfort increases with any physical activity is undertaken

With reference to the association between CHF and left-ventricular systolic dysfunction (LVSD), the ERG considers it relevant to the decision problem to note that LVSD is typically defined in clinical practice as a left-ventricular ejection fraction (LVEF) of <40% of normal ejection fraction. The ERG has adopted the working definitions of CHF terms contained in the guidance from the European Society for Cardiology, tabulated in Table 2 below.

Table 2. Heart failure terms (18)

Term	Definition
Left ventricular ejection fraction (LVEF)	A measurement of how much blood the left ventricle pumps out with each contraction (normal range 55–70%)
Heart failure reduced ejection fraction (HFrEF)	NYHA classification II-IV (symptomatic) with reduced ventricular ejection fraction of ≤35%
Systolic dysfunction	Defined as an LVEF less than 40%.

2.2 Critique of company's overview of current service provision

The algorithm contained in the NICE guideline on the management of CHF recommends that those with symptoms of CHF plus a history of myocardial infarction (MI) should be urgently referred to specialist assessment and transthoracic 2D Doppler echocardiography within two weeks (6). For those people with symptoms of CHF but no history of MI, a blood test to measure levels of serum brain natriuretic peptide (BNP) is the quality standard. A BNP level of >400 pg/mL (116 pmol/litre) or an N-terminal amino acids (NTpro) BNP level above 2000 pg/ml (236 pmol/litre) are indicative of CHF and require an urgent referral to a specialist for assessment and diagnosis (6).

The ERG notes that HF most commonly presents acutely as emergency admissions in hospital and has a poor prognosis, with 30% to 40% of HF patients dying within the first year (Box 3).

Box 3. Mortality associated with heart failure (CS, pg 18)

One-year mortality estimates for English patients diagnosed with HF vary, ranging from 9% (21) to 38% (22). In the NICE quality standard on chronic HF, it is stated that 30% to 40% of patients

Box 10. PARADIGM-HF trial patient eligibility criteria (CS, pg 42)

A summary of the key inclusion and exclusion criteria in PARADIGM HF is provided in table 9. The inclusion criteria for NHYA, LVEF and BNP are summarised below.

NYHA: All patients screened at study admittance were NYHA functional class II-IV, however, a small number of patients had an improvement in their NYHA class between screening and randomisation, and so nearly 5% of randomised patients were NYHA class I (2).

LVEF: An amendment to the study was made to amend the LVEF entry criterion from ≤40% to ≤35%. This modification was essential to ensure an adequate event rate in the study population where use of evidence-based, disease-modifying agents was increasing. 961 patients who were randomised had LVEF ≤35% (2).

BNP: Mildly elevated BNP or NT-proBNP was required as an inclusion criterion to ensure that patients enrolled were at risk for CV events in order to ensure a reasonable event incidence rate over the duration of the trial (2). The patient characteristics were similar to those of study populations in other relevant trials and patients in the community (42-44)

Abbreviations: BNP: Brain Natriuretic Peptide; LVEF; Left Ventricular Ejection Fraction; NHYA: New York Heart Association; NT-proBNP; N-terminal pro hormone of Brain Natriuretic Peptide.

The ERG notes that 89% of participants (n=7,438) in PARADIGM-HF had a CHF classification of ≤35%. The results from the trial are therefore likely to be representative of this more severe CHF patient population.

The ERG's overall opinion of the PARADIGM-HF trial is presented in Section 4 of this report. It should be noted that the ERG's clinical experts have advised that the small amount of data provided for patients who had never taken an ACEi means there is little evidence to support the use of sacubitril as a first line treatment in newly diagnosed patients.

The ERG's clinical experts believe the PARADIGM-HF trial supports the use of sacubitril only in patients that have a profile matching the one in the trial; i.e. chronic patients, who have been maximally titrated on an ACEi (or ARB) but remain symptomatic.

The ERG also notes the CS contains an explanation of differences which exist between patients who are treated for CHF in the NHS in England and Wales and those patients who were recruited into the PARADIGM-HF trial (Box 11).

Box 11. Description of patient characteristics for the PARADIGM-HF trial (CS, pg 18)

The proportion of patients on various HF standard care and background therapies was reflective of English clinical practice. Patient characteristics in PARADIGM-HF were mostly reflective of the English HF population. However, patients were, on average, younger than the average patients in England (approximately 65 versus 75 years) and more patients were male. However, in PARADIGM-HF, 49% of patients were ≥65 years of age (n=4120) and 18.6% of patients were ≥75

years of age (n=1563) with the oldest patient aged 96 at randomisation (45), and 21.8% (n=1,832) were female (2).
Abbreviations used in table: HF, heart failure.

Based on advice from clinical experts the ERG is aware that the data from the PARADIGM-HF trial have been collected from patients who are a chronic HF population. Concerns that the population might not be representative of the UK and the ERG requested subgroup analysis for people recruited from Western Europe and then these are discussed in greater detail in Section 4.

As described in Section 2 the ERG has adopted the CHF terms issued by the European Society for Cardiology.

3.2 Intervention

The named intervention in the NICE final scope is sacubitril valsartan (henceforth referred to as sacubitril). The CS contains an explanation of the pharmacological specification of sacubitril (Box 12).

Box 12. Description of the intervention (CS, pg 22)

Sacubitril valsartan (previously known as LCZ696) is an angiotensin receptor neprilysin inhibitor (ARNI), a salt complex comprising two active moieties, sacubitril and valsartan, which have been co-crystallised in a 1:1 molar ratio. Sacubitril valsartan is a novel first-in-class therapy proposed for the treatment of HFrEF. Following oral administration, sacubitril valsartan dissociates into the pro-drug sacubitril (also known as AHU377), which is further metabolised to the neprilysin inhibitor (LBQ657), and valsartan, an ARB. Sacubitril valsartan has the mechanism of action of an neprilysin inhibitor and an ARB (angiotensin receptor neprilysin inhibitor; ARNI), by simultaneously inhibiting neprilysin via LBQ657 and blocking the angiotensin II type-1 (AT1) receptor via valsartan, resulting in complementary effects on the CV system that are beneficial in HF patients.
Abbreviations used in table: ARB, angiotensin receptor blocker; CV, cardiovascular; HF, heart failure; HFrEF, heart failure reduced ejection fraction.

The ERG notes the innovative nature of sacubitril in the management of HF, the inhibition of neprilysin being a novel development in the pharmacological management of HF. The ERG notes the marketing authorisation application for sacubitril was submitted to the EMA on 16 December 2014. The CHMP has granted accelerated assessment to sacubitril valsartan. An EMA decision on marketing authorisation is expected in December 2015 (CS, pg 22).

Clinical effectiveness data in the CS are derived from one pivotal trial PARADIGM-HF (n = 8,399). The PARADIGM-HF trial is an international multi-centre randomised controlled trial designed to evaluate the efficacy of sacubitril 200mg BID compared with the ACEi enalapril 10mg BID (both in combination with standard care) in patients with HFrEF (New York Heart Association [NYHA]

classifications II to IV) (CS, pg 17). A second trial TITRATION (n = 498) compares different doses of sacubitril. As the TITRATION trial does not address the decision problem it is not discussed further in Section 3. Instead, the ERG's assessment of the TITRATION trial can be found in Appendix 1.

3.3 Comparators

The ERG notes the comparators of interest in the final scope issued by NICE are an ACEi in combination with standard care or an ARB in combination with standard care (for people in whom an ACEi is unsuitable). The ERG acknowledges the definition of standard care in the NICE final scope as including treatment with a BB and an AA. The CS contains data for patients who received the ACEi, enalapril, in conjunction with standard care: a BB and AA. Thus, the comparator in the evidence submitted by the company is relevant to the final scope issued by NICE. However the ERG has been advised by clinical experts that enalapril is not the most commonly prescribed ACEi in the UK; the ERG's clinical experts' opinion is that the most commonly used ACEi is ramipril, which is believed to be better tolerated and appears to be more convenient for patients as it is taken once per day. This issue is considered in further detail in Sections 4 and 5 of the ERG report.

3.4 Outcomes

The company presents direct evidence for sacubitril versus enalapril for all of the outcomes listed in the final scope issued by NICE:

- Symptoms of HF;
- Hospitalisation for HF;
- All-cause mortality;
- Cardiovascular mortality;
- Adverse effects of treatment;
- Health-Related Quality of Life.

The ERG notes that the primary efficacy variable was time to first occurrence of either CV death or first hospitalisation for HF and these were combined and presented as a composite variable. The ERG is advised by clinical experts that this is a standard approach to the analysis of outcome data in trials of drugs for CHF.

The ERG notes that the Kansas City Cardiomyopathy Questionnaire (KCCQ) was used to measure the symptoms of HF. The company states it is clinically meaningful in CV research, patient management and quality assessment (CS, Table 10, pg 43). The CS contains an overview of the domains measured by the KCCQ and an explanation of how the scores are interpreted, "The KCCQ covers physical function, clinical symptoms social function, self- efficacy and knowledge and QoL. Higher scores (on

the scale of 0 to 100) indicate better HRQoL/reduced HF symptoms. KCCQ scores were assessed at baseline 4, 8, 12, 24 and 36 months as well as the end of each study visit." (CS, summary, pg 34). The ERG notes the PARADIGM-HF investigators also used EQ5D, a generic HRQoL outcome measurement tool and the preferred method for eliciting health-related outcomes (46), in combination with the KCCQ and the NYHA Classification to measure NYHA class shift. The ERG believes these are valid and reliable approaches to the measurement of HF symptoms and signs and are likely to capture HRQoL and changes in CHF status.

The ERG notes the company provides data about the safety of sacubitril compared to enalapril in the PARADIGM-HF trial; the CS presents data for 44 different adverse events where ≥2% of patients in any group were affected (Table 42, CS, pg 99 and 100). The ERG provides a narrative of the most important adverse events and reactions in Section 4 (pg 54).

In summary, the ERG considers the CS to be consistent with the final scope by NICE but deviates from the scope with regard to the NYHA classification of CHF.

3.5 Timeframe

The PARADIGM-HF trial had an actual study duration of 51 months (CSR pg 23). The ERG notes that the intended duration of the trial was 43 months (recruitment of 22 months and a follow-up period of 32 months) (trial protocol pg 31). The PARADIGM-HF trial exceeded its target sample size (randomised n=8,442 as opposed to the target n=7,980) and the trial ended after 51 months when [redacted] events were observed. The reason for the termination of the trial was the Data Monitoring Committee (DMC) recommendation based on compelling efficacy of sacubitril in achieving the primary composite end point of CV mortality and CHF-related hospitalisation in 2,031 patients.

Patients aged ≥18 years with CHF (NYHA functional class II-IV) with LVEF ≤40% (changed to ≤35% by an amendment to the protocol) Plasma BNP ≥150 pg/mL (or NT-proBNP ≥600 pg/mL at screening visit or a BNP ≥100 pg/mL (or NT-proBNP ≥400 pg/mL) and a hospitalisation for heart failure within the last 12 months Receiving stable dose of an ACEI or an ARB for at least 4 weeks before entering the study Receiving stable dose of BB for ≥4 weeks before screening visit (unless contraindicated or not tolerated) Receiving stable dose of AA for ≥4 weeks before screening visit (if prescribed) Patients not tolerating enalapril 10 mg bid during the run-in phase were considered run-in failures, did not enter the sacubitril valsartan run-in phase and were withdrawn from study Patients not tolerating sacubitril valsartan 200 mg bid during the run-in phase were considered run-in failures and were withdrawn from the study	Any contraindications to study drugs or other drugs required in the inclusion criteria History of angioedema Treatment requirement for both ACEi and ARB Current acute decompensated HF Symptomatic hypotension or systolic BP <100 mmHg at Visit 1 or <95 mmHg at Visit 3 or 5 eGFR <30 mL/min per 1.73 m2 at Visit 1, 3 or 5 or ≤35% decline in eGFR between Visit 1 and 3 or 5 ACS, stroke, TIA, major CV surgery, PCI or carotid angioplasty within 3 months prior to Visit 1 CAD likely to require surgical or percutaneous intervention within 6 months after Visit 1 CRT device implanted within 3 months of screening visit or plan to implant History of/planned heart transplant History of severe pulmonary disease Peripartum or chemotherapy induced cardiomyopathy (within 12 months) Untreated ventricular arrhythmia with syncopal episodes (within 3 months) Haemodynamically significant obstructive lesions of the LV outflow tract Any surgical or medical condition which might significantly alter the absorption, distribution, metabolism or excretion of study drugs
Abbreviations used in the table: AA, Aldosterone antagonist; ACEi, Angiotensin converting enzyme inhibitor; ACS, Acute coronary syndrome, ARB, Angiotensin II receptor blocker; BB, Beta blocker; bid, twice daily; BNP, B-type natriuretic peptide; BP, Blood pressure; CAD, Coronary artery disease; CRT, Cardiac resynchronisation therapy; CV, cardiovascular; eGFR, Estimated glomerular filtrate; HF, Heart failure; LVEF, Left ventricular ejection fraction; NYHA, New York Heart Association; TIA, Transient ischaemic attack	

The PARADIGM-HF trial was conducted in 985 sites in 47 different countries. A total of 10,513 patients were recruited. The ERG notes that a large number of exclusion criteria were applied. However, the ERG's clinical experts consider the exclusion criteria to be appropriate for the population and therapies under investigation.

In the PARADIGM-HF trial, randomisation took place after the run-in phase. Eligible patients were screened based on criteria in Table 7. After screening, patients entered the run-in phase where patients were switched from the ACE inhibitor or ARB that they had been receiving to single-blind treatment with enalapril (at a dose of 10 mg twice daily) for two weeks followed by single-blind treatment with sacubitril for an additional 4-6 weeks (initially at a dose of 100 mg twice daily, which was increased to 200 mg twice daily) in the absence of unacceptable side effects. Trial participants not able to tolerate the sacubitril or enalapril were excluded from the trial.

Following run-in, patients were randomised to receive either sacubitril (200 mg bid) or enalapril (10 mg bid) in addition to optimal CHF therapy, in a double-blind fashion with the use of a computerised randomisation system involving concealed study-group assignments. As stated in the CSR (pg 31), "at visit 5, the investigator called the interactive voice response system (IVRS), entered the patient's number, and the IVRS assigned a randomisation number to the patient, that was used to link the

Therapies	AA	2,271 (54.2)	2,400 (57.0)
Medical history, n (%)	Hypertension	2,969 (70.9)	2,971 (70.5)
	Diabetes	1,451 (34.7)	1,456 (34.6)
	AF	1,517 (36.2)	1,574 (37.4)
	Hospitalisation for HF	2,607 (62.3)	2,667 (63.3)
	MI	1,818 (43.4)	1,816 (43.1)
	Stroke	355 (8.5)	370 (8.8)
	Pre-trial use of ACEi	3,266 (78.0)	3,266 (77.5)
	Pre-trial use of ARB	929 (22.2)	963 (22.9)

Abbreviations usd in table: AA, aldosterone antagonists; ACEi, angiotensin converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin II receptor blocker; BB, beta blocker; BNP, B-type natriuretic peptide; BMI, body mass index; HF, heart failure; IC, ischaemic cardiomyopathy; IQR, interquartile range; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NT-proBNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association; SBP, systolic blood pressure; SD, standard deviation.

The ERG notes that the PARADIGM-HF trial recruited relatively few patients from England (n=242/10513 [2.3%]) (CS, Table 11, pg 45). The company states (CS, pg 54) that, "compared with the English HFrEF population, patients in PARADIGM-HF were younger, more likely to be male, and that a lower average age is seen in HF trials as a result of clinical trials requiring clear pre-determined eligibility criteria and rigorous follow-up making recruitment of significant numbers of older patients difficult". The ERG's clinical experts advised that typically patients presenting with HF in the UK are older (≥75 years in men and ≥85 years in women) than those in the PARADIGM-HF trial (mean age was 63.8 years) (CS, Table 13 pg 54) but the younger age population in PARADIGM-HF is typical of all HF trials.

PARADIGM-HF initially recruited patients with LVEF ≤40% before the study protocol was amended to ≤35%. According to the company (CS, pg 42), this was to ensure an adequate event rate in the study population. However, the ERG's clinical experts advised that patients in the PARADIGM-HF trial were patients with severe HF (based on LVEF≤35%), and that the observed benefits of treatment with sacubitril would be greater than in patients without reduced ejection fraction. The ERG's clinical experts highlighted that a proportion of patients with severe HF in the UK would have been fitted with cardiac devices. Although no information is presented on clinical effectiveness in the subgroup of people fitted with a cardiac device in the CS, the ERG notes data are presented in the CSR to show around [redacted] of the trial population used devices (CSR, Table 11-14, pg 100). The ERG notes that approximately 25% of the trial population were recruited from sites in Western Europe. The ERG report contains a critique of the generalisability of the Western Europe population in the subgroup analysis in Section 4.

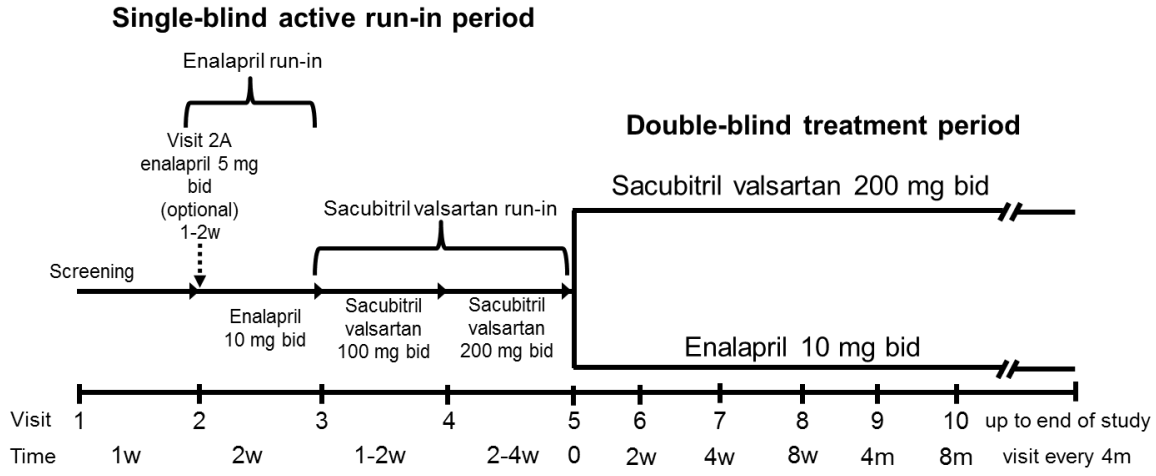
4.2.2 Interventions and comparisons

The primary objective of PARADIGM-HF trial was to compare the ARNI, sacubitril, with the ACEi, enalapril, in patients who had symptomatic HF with a reduced ejection fraction.

The ERG notes the large number of withdrawals/discontinuations during different phases of the PARADIGM-HF trial. [redacted] patients who failed the enalapril run-in period and [redacted] (CSR, pg 87–88 and Tables 10-1 and 10-2). After randomisation, 18 patients (8 in sacubitril group and 10 in enalapril group) discontinued, 4 patients (2 from each group) died, 12 patients were lost to follow-up (5 in sacubitril group and 7 in enalapril group), and one patient from each group requested withdrawal. The ERG's clinical expert believes the number of discontinuations/withdrawals reflects those observed in CHF trials generally.

Figure 2 summarises the treatment pathways in PARADIGM-HF.

Figure 2. PARADIGM-HF study schematic (from CS Figure 3 pg 41)



4.2.3 Outcomes

The primary outcome in the PARADIGM-HF trial was a composite of death from cardiovascular (CV) causes or a first hospitalisation for HF assessed at every study visit (0 weeks, 2, 4, and 8 weeks, 4 months, and then every 4 months). The target number of primary composite endpoint events was planned to be [redacted] at the end of the study; the target number of CV deaths was planned to be [redacted] (CSR, Section 9.5.2.1, pg 45). In addition to the primary composite endpoint, the CV mortality component was also analysed at each interim efficacy analysis.

The company's rationale for choosing the primary endpoint (CSR, Section 9.2.1, pgs 21–22) is that, "there is a general agreement that the major goal of treating HFrEF is to reduce the major fatal and non-fatal consequences of this illness, i.e. CV death and hospitalization for worsening HF. CV death and HF hospitalization have also been shown to be modifiable by treatments improving this condition. This understanding of HF and its treatment has led to this disease-specific composite endpoint being the most commonly used primary endpoint in recent HF outcomes trials". The ERG's clinical experts agree that PARADIGM-HF used a composite primary outcome which is commonly used in HF trials.

score on the Kansas City Cardiomyopathy Questionnaire (KCCQ), whose scores were assessed at baseline/randomisation visit (visit 5), at four, eight and 12 months (visits 8, 9 and 10), at 24 and 36 months (visits 14 and17), as well as at the end of study visit; time to a new onset of atrial fibrillation (AF) (assessed at all study visits); and time to the first occurrence of a decline in renal function. The ERG's clinical experts note outcomes used in PARADIGM-HF are those typically used in HF trials.

The PARADIGM-HF study protocol was amended four times (CSR, Section 9.8.1, pg 83–83). The key features of the amendments are: change in the LVEF entry criterion from ≤ 40% to ≤ 35% to ensure an adequate event rate in the study population [redacted] Reasons for the amendments are reported in the CSR (Section 9.8.1, pg 83–84). The ERG considers the change from ≤40% to ≤35% LVEF means that the population recruited from then would have more severe HFrEF.

PARADIGM-HF was described as a double-blind, double-dummy study. As stated in Section 4.2, randomisation was performed by computerised Interactive Voice Responsive System (IVRS) in which the IVRS assigned a randomisation number to the patient, that was used to link the patient to a treatment arm and specified unique medication numbers for the packages of the first supply of the study drugs dispensed to the patient. The IVRS provided unique medication numbers for both the sacubitril or its matching placebo and enalapril or its matching placebo. To maintain the double-blind, double dummy design, patients were required to take their assigned active treatment tablet along with matching placebo twice daily (morning and evening dose) in addition to their conventional concomitant therapy. The ERG considers the trial arrangements for the random allocation of the trial drugs and the maintenance of blinding were in accordance with good practice and are adequate.

The company states in the CS (pg 53) that, "there were no significant differences between groups regarding any of the demographic baseline characteristics. However, some differences were observed

between English population with HF and the study population". The ERG was unable to verify this as no measures of statistical significance were reported in the CS (Table 13 pg 54), CSR (Table 11-2, pg 95) or the published PARADIGM-HF trial (2) (Table 1, pgs 996-997).

4.2.5 Description and critique of statistical approach used

The CS contains comprehensive details on the statistical analyses approaches used in the PARADIGM-HF trial. In the PARADIGM-HF trial, it was estimated that the annual rate of the primary outcome in the enalapril group would be 14.5% and the rate of CV death would be 7.0%. Calculation of the sample size was based on CV death in estimating a follow-up of 8,000 patients for 34 months, with 1,229 CV deaths to give the study 80% power to detect a relative reduction of 15% in the risk of CV death in the sacubitril group. On the basis of these power calculations, it was estimated the primary outcome would occur in 2,410 patients and provide 97% power to detect 15% risk reduction (CS, pg 50) (2).

The primary objective of PARADIGM-HF trial was to examine whether the long-term effects of sacubitril on morbidity and mortality were superior to enalapril in patients with CHF and a reduced ejection fraction. To achieve this, the primary efficacy variable (composite outcome of CV death or a first HF hospitalisation) was analysed using Cox's proportional hazards model with treatment and region as fixed factors. The FAS was used for the primary outcome analysis and type I error was set at 2.5%, with a one-sided significance level of alpha (α) used for the final analysis (adjusted for interim analysis).

For secondary efficacy outcomes time to event data (time to all-cause mortality, time to new onset of AF, time to composite renal endpoint) were evaluated using Kaplan-Meier estimates and Cox proportional hazards models with treatment group and region as fixed factors. The estimated hazard ratios and the corresponding 95% Confidence Interval and two-sided p-values were provided for the FAS. Changes in KCCQ scores from baselines were assessed by total score and individual sub-domain scores and analysed as exploratory outcomes. The clinical summary score (CSS) of KCCQ was calculated as the mean of the physical limitation and total HF symptom scores, and changes from baseline were analysed as repeated measures of covariance (ANCOVA) model in which treatment, region, visit, and treatment-by-visit interaction were included as fixed effect factors. Fisher's exact test was used to compare rates of adverse events using the SAF.

A number of pre-specified subgroups including age, gender, race, region NYHA class, diabetes, systolic blood pressure (SBP), LVEF, AF, etc., were analysed to assess the consistency of the treatment effect. This was pre-planned with the exception of a post-hoc analysis to assess the treatment effect of the subgroup of patients in Western Europe.

In addition, (CSR, Section 8.7.13; pg 83) the end of the PARADIGM-HF trial was planned to occur when the pre-specified number of patients [redacted] experienced the primary composite endpoint of cardiovascular deaths or HF hospitalizations, unless the study was terminated early due to critical safety concerns. Accordingly the trial was terminated after a median follow-up of 27 months (actual

• Studies reporting outcomes from drug classes that were not included in the NICE scope as the SR had a broader scope (i.e., ivabradine)

Abbreviations: NMA, network meta-analysis; NICE, National Institute for Health and Care Excellence; SR = systematic review.

The ERG notes the core NMA is based on data from 28 trials of placebo controls, ACEis and ARBs with one ARNI (sacubitril) linked to an ACEi in the PARADIGM-HF trial. The ERG notes that the company NMA focuses on single interventions at the drug class level, i.e. ACEis, ARBs, and sacubitril (ARNI) (CS, pg 72). The inclusion of trials was irrespective of the concomitant therapies being taken by trial patients. The CS cites work (51) reporting an NMA showing no differences in ACEis in 10 trials with outcomes of risk of death, sudden cardiac death, death due to pump failure, re-hospitalisations or drug discontinuation. The CS cites a Cochrane systematic review (49) that assumes a class effect of ACEis and ARBs. The ERG notes the inclusion of data from patients with concomitant therapies is in accordance with the final scope from NICE and therefore considers the company submission is reasonable.

The ERG notes the company has been influenced in its approach to meta-analysis by the Cochrane systematic review which also includes patients with and without concomitant therapies and assumes a drug class effect (49) (CS pg 72).

The CS refers to the evidence from the Cochrane systematic review as to the relative effects of ARBs and ACEis in HF. The ERG understands the Cochrane systematic review includes HF patients in whom the ejection fraction is preserved (HFpEF) (unlike the company's NMA – only data from trial populations with HFrEF were analysed, CS pg 71).

The ERG referred a trial (52), reporting the only direct comparison of an ARB with an ACEi included in a Cochrane systematic review (49). This 3-arm trial compares valsartan with lisinopril versus placebo in patients who had never previously received an ACEi. The main outcomes for this trial were mean pulmonary capillary wedge pressure, systematic vascular resistance and increased cardiac output and no data for hospitalisation were reported. The ERG notes this trial was not included in the NMA and agrees that only some of the studies from the Cochrane systematic review by (49) are applicable to the NICE scope.

The ERG notes the baseline intervention of interest in the NMA is sacubitril (ARNI) which is linked to the other treatments in the network though the ACEi data from the PARADIGM-HF trial. The CS contains NMA for the outcomes of all-cause mortality (CS, Figure 10, pg 76), CV mortality (CS, Figure 11, pg 77) and all-cause hospitalisation (CS, Figure 12, pg 77). The core NMA (all-cause mortality) includes 28 trials, 8 of which are included in the main comparison of interest. The primary outcomes of the trials included in the ACEi versus ARB comparisons are symptoms of HF during exercise, the 6 minute walk test, a bicycle test, clinical status (dyspnoea-fatigue index), treadmill test,

The ERG has concerns about the generalisability of the findings of the PARADIGM-HF trial into UK clinical practice: The trial recruited relatively few patients from England (n=242/10,513 [2.3%]) (CS, Table 11, pg 45) and the company acknowledges that, "compared with the English HFrEF population, patients in PARADIGM-HF were younger, and were more likely to be male". The company's justification of the lower age is, "clinical trials require clear pre-determined eligibility criteria and rigorous follow-up making recruitment of significant numbers of older patients difficult" (CS, pg 54). The ERG's clinical experts advised that patients in the UK presenting with HF are typically older (≥75 years in men and ≥85 years in women) than those in the PARADIGM-HF trial (mean age was 63.8 years) (Table 13 of CS, pg 54).

The higher proportion of men recruited to the trial may be important. However, the ERG notes this effect would be observed across both arms of the trial and would not confer a relative advantage on either of the trial interventional drugs. Rather, the trial population may have exhibited better outcomes than would be observed in clinical practice. However, the ERG's clinical experts have advised that the younger age population in PARADIGM-HF is typical of HF trials.

The ERG notes that the scope from NICE includes standard care as part of the comparisons and the ERG is advised by the clinical experts that most patients in the UK would be taking concomitant therapies; beta blockers (BBs) and an aldosterone antagonist (AAs). The ERG notes that almost all trial patients were taking a BB (>93%) but just over half (~54%) were taking an AA (table 8 ERG report). The ERG's clinical experts highlighted that a proportion of patients with severe HF in the UK would have been fitted with cardiac devices.

The ERG considers that the effect of lowering the trial inclusion criteria from an LVEF of <40% to ≤35% would have led to an increase in the numbers of severe HF patients enrolled in the trial. The protocol amendment was made to increase the event rate and, given the early stopping of the PARADIGM-HF trial, the ERG concludes that this appears to have occurred.

The lack of evidence about the effect of sacubitril in people newly diagnosed with CHF in both the PARADIGM-HF trial and TITRATION trials is problematic and the ERG is unable to comment on what the effectiveness of sacubitril would be in people not previously treated with an ACEi.

4.3.1 Subgroup analyses

The company present tables of results from subgroup analyses of the data collected from patients on the PARADIGM-HF trial (CS, pg 68–70). The ERG discusses the patient characteristics which did

not demonstrate statistically significant effects. The ERG acknowledges that it is possible that some of these comparisons were underpowered to detect a statistically significant difference.

As highlighted in the preceding paragraphs there is a lack of evidence about the effectiveness of sacubitril in newly diagnosed patients. The subgroup analysis from PARADIGM-HF in the 1,867 patients who were considered ACEi naive had no significant benefit in the primary outcome (HR 0.92, 95% CI: 0.76 to 1.10). These data reinforce the ERG's view that the comparative effectiveness of sacubitril vs enalapril in newly diagnosed HF patients is unclear.

The ERG considers the Western Europe population to be the most representative of the UK. The primary outcome in this subpopulation was also non-significant (HR 0.89, 95% CI: 0.74 to 1.07) (CS, pg 68) The ERG therefore requested the characteristics of participants (n= 2,057) for the Western European population from the company and this was supplied during clarification (Table 13).

The ERG notes from this subgroup analysis that the mean age is [redacted], similar to the whole trial population, is predominantly of white race ([redacted] compared to 66% of the total trial population), with most patients having a NYHA classification of II [redacted] vs ~70% of the trial population) an LVEF of [redacted]. The ERG also notes [redacted] had received ACEis at baseline (~78% reported in the total population). [redacted].

However, the ERG notes the differences in the numbers of the Western Europe population who are hypertensive ([redacted] vs 70% of the overall trial population) which may suggest that the Western Europe HF population are in receipt of more intensive "standard care" compared to other regions in the trial.

Table 13. Western Europe subgroup data provided at clarification by the company.

Variable	**Value**	
	Sacubitril valsartan N=1,029	Enalapril N=1,028
Mean age, years (±SD)	[redacted]	[redacted]
Female, n (%)	[redacted]	[redacted]
Race – White, n (%)	[redacted]	[redacted]
Race – Black, n (%)	[redacted]	[redacted]
Race – Asian, n (%)	[redacted]	[redacted]
Race – Other, n (%)	[redacted]	[redacted]
NYHA class I, n (%)	[redacted]	[redacted]
NYHA class II, n (%)	[redacted]	[redacted]
NYHA class III, n (%)	[redacted]	[redacted]
NYHA class IV, n (%)	[redacted]	[redacted]
NYHA class III/IV, n (%)	[redacted]	[redacted]
LVEF %, mean (±SD)	[redacted]	[redacted]
SBP mm HG, mean (±SD)	[redacted]	[redacted]

Heart rate beats/min, mean (±SD)	[redacted]	[redacted]
eGFR (mL/min/1.73m2), mean (±SD)	[redacted]	[redacted]
Median NT-proBNP (IQR), pg/mL	[redacted]	[redacted]
Sodium (mmol/L) mean (±SD)	[redacted]	[redacted]
Potassium (mmol/L) mean (±SD)	[redacted]	[redacted]
QRS duration (ms)	[redacted]	[redacted]
BMI (kg/m2), mean (±SD)	[redacted]	[redacted]
Diabetes (%), n (%)	[redacted]	[redacted]
Hypertension, n (%)	[redacted]	[redacted]
Prior ACEi use, n (%)	[redacted]	[redacted]
Prior ARB use, n (%)	[redacted]	[redacted]
Beta blocker use, n (%)	[redacted]	[redacted]
Mineralocorticoid receptor antagonist use, n (%)	[redacted]	[redacted]
Digoxin use, n (%)	[redacted]	[redacted]
Lipid lowering medication use, n (%)	[redacted]	[redacted]
Allopurinol use, n (%)	[redacted]	[redacted]
≤ 1 year since HF diagnosis, n (%)	[redacted]	[redacted]
1-5 years since HF diagnosis, n (%)	[redacted]	[redacted]
>5 years since HF diagnosis, n (%)	[redacted]	[redacted]
Ischaemic aetiology, n (%)	[redacted]	[redacted]
Prior stroke, n (%)	[redacted]	[redacted]
Prior atrial fibrillation/flutter, n (%) Paroxysmal Permanent	[redacted]	[redacted]
Prior angina, n (%) † Stable angina pectoris Prior unstable angina	[redacted]	[redacted]
Prior cancer, n (%)	[redacted]	[redacted]
Current smoker, n (%)	[redacted]	[redacted]
Prior HF hospitalisation, n (%)	[redacted]	[redacted]
EQ-5D, mean (±SD)	[redacted]	[redacted]
Abbreviations: EQ-5D EuroQol (EQ5D™); HF = heart failure; SD = standard deviation		

The ERG considers that the non-statistically significant effect of sacubitril in the Western Europe population may relate to fewer patients having hypertension, less severe HF and more intensive "standard care" ([redacted]). As the size of the Western Europe population is 25% of the overall trial population a type II error in this analysis is less likely than in other subgroup analyses based on smaller numbers of patients. The ERG notes that regions with smaller numbers of patients did demonstrate a significant difference in the primary outcome measure in favour of sacubitril vs enalapril for example patients in North and Latin America (CS pg 68, figure 9).

4.3.2 Adverse events

The discontinuation rate due to adverse events in the PARADIGM-HF trial were similar being 10.7% in the patients taking sacubitril (n=450) and 12.2% in the patients taking enalapril (n=516).

The ERG notes the company's summary of product characteristics (SmPC) recommends caution in prescribing sacubitril for patients with NYHA class IV due to the limited clinical experience this population and that the company warn that BNP is not a good marker of HF in patients taking sacubitril because of its neprilysin substrate nature.

The SmPC also advises that patients with a history of angioedema were not studied in the PARADIGM-HF trial. As these patients are considered at generally higher risk of angioedema the SmPC recommends caution in the use of sacubitril for this group. The frequency of adverse reactions shows the rate of angioedema was reported on 0.5% of patients in the sacubitril arm of the PARADIGM-HF trial vs 0.2% in the enalapril arm. The SmPC reports a higher incidence of angioedema was observed in black patients and the rate was highest in the sacubitril arm (2.4% vs 0.5%). The ERG therefore disagrees with the statement that, the rate of adverse reactions was similar in the two investigational drugs and the overall frequency was not related to gender, age or race (SmPC, pg 8 (55)).

The SmPC ranks adverse drug reactions by frequency and "very common" equates to ≥1/10. There were three adverse reactions ranked very common; hyperkalaemia (11.6% in the sacubitril arm vs 14% in the enalapril arm), renal impairment (10.1% in the sacubitril arm versus 11.5% in the enalapril arm), hypotension (17.6% in the sacubitril arm vs 11.9% in the enalapril arm). The sacubitril SmPC recommends caution in its use for people with HF who have impaired, worsening renal function or renal artery stenosis.

The ERG notes that sacubitril can influence the ability to drive and use machines and the company advises that occasional dizziness or fatigue may occur during these activities. The company concedes the lack of data to inform the safety of sacubitril for those who drive or use machines.

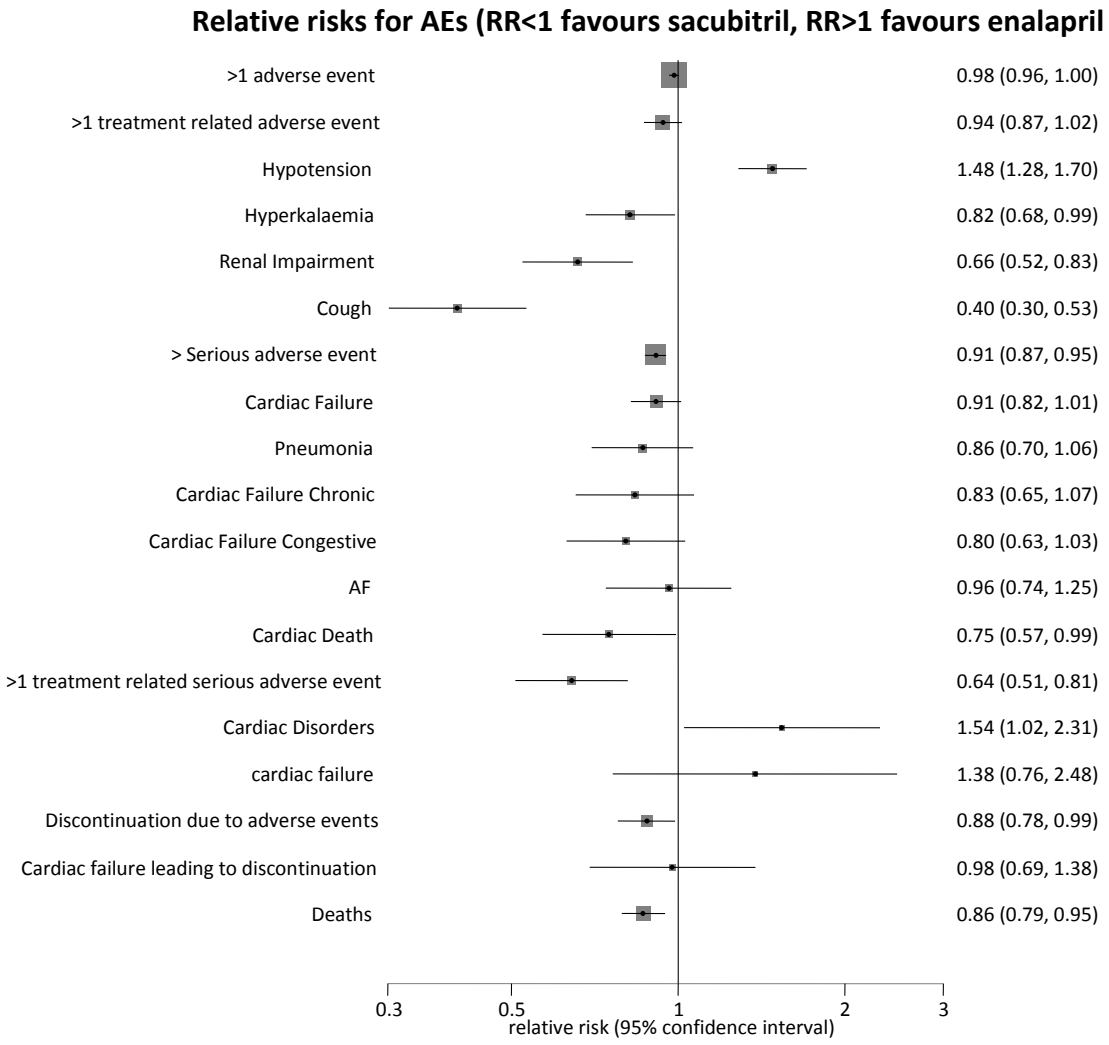
In the CS (Table 41, pg 98) the company reports that the adverse event profile was comparable between sacubitril and enalapril during the double-blind phase of PARADIGM-HF and ~22% of patients experienced a treatment related AE. The CS does not contain tests of statistical significance so the ERG produced a forest plot (Figure 3) with relative risks and 95% CIs for all the adverse events listed in Table 41 of the CS.

The ERG notes there were statistically significant differences in AEs between the two groups with regards to AEs including hypotension and cardiac disorders (from sacubitril) hyperkalaemia, renal

impairment, cough, cardiac death, > 1 treatment related serious adverse event, discontinuation due to adverse events and overall deaths (from enalapril).

The ERG considers it plausible that there could be an increase in the proportion of patients who experience hypotension in a population of patients with a lower baseline BP than the trial population (e.g. the Western Europe population in PARADIGM-HF, (CS pg 68, figure 8).

Figure 3. Forest plot of AEs in the double-blind phase of PARADIGM-HF



4.3.3 Summary of clinical effectiveness

This CS provides evidence for the effectiveness of sacubitril valsartan (200mg BID) compared to enalapril (10mg BID) in patients with chronic stable HF with a HFrEF of ≤35% from a single trial. The primary composite outcome measure of CV death and HF hospitalisation demonstrated statistical significance after a median double-blind follow-up of 27 months (HR 0.80, 95% CI: 0.73 to 0.87,

p-value <0.001). However the ERG notes the PARADIGM-HF includes patients approximately 10years younger than those seen in UK clinical practice and the majority of whom had previously been treated for HF and does not evaluate the effect of sacubitril in patients who are newly diagnosed with HF. The additional trial provided by the company, TITRATION, does not provide evidence of the effects of sacubitril in newly diagnosed patients as only 6.6% were treatment naïve.

The PARADIGM-HF trial includes patients who were still symptomatic despite the majority receiving ACEi/ARB, BB and AA prior to randomisation. As such, the ERG considers the trial to be assessing the effectiveness of sacubitril in patients who have failed on first-line therapy. The subgroup analysis of data from people in Western Europe suggests that the benefits of sacubitril over enalapril observed in the trial population may not be observed in clinical practice in the UK. The ERG is concerned about the small number of UK patients in the PARADIGM-HF trial (n=242) and believes the generalisability of the effect of sacubitril from the trial population to the UK population is unclear.

4.4 Conclusions of the clinical effectiveness section

- The primary objective of the PARADIGM-HF trial was to compare the effectiveness of sacubitril 200mg BID with enalapril 10mgn BID in the management of CHF. To be eligible for enrolment, patients had to have CHF (defined by LVEF below 35% or reported as reduced and NYHA class II–IV;
- The PARADIGM-HF trial also produced data to inform the analysis of treatment-related adverse events which affected ~22% of the population;
- The primary outcome of the PARADIGM-HF trial was a composite outcome of CV mortality or CV hospitalisation. Overall, the results were consistently in favour of sacubitril;
- The ERG considers the trial to be assessing the effectiveness of sacubitril in patients who have failed on first-line therapy.
- The company's inclusion of TITRATION provides limited evidence of the effectiveness of sacubitril in treatment naïve patients as only a fraction (6.6%) of patients included in the trial were treatment naïve;
- The results of the subgroup analyses suggest that the effect of sacubitril observed in the trial population might not be observed when used in clinical practice in the UK due to differences in the baseline characteristics of the Western Europe population;
- A decision on marketing authorisation for sacubitril from the European Medicines Agency is expected in December 2015. The Committee for Medicinal Products for Human Use (CHMP) granted accelerated assessment to sacubitril and a CHMP opinion is due in October 2015.

5 COST EFFECTIVENESS

5.1 Introduction

This section provides a structured description and critique of the systematic literature review and de novo economic evaluation submitted by the company. The company provided a written submission of the economic evidence along with an electronic version of the Microsoft Excel® based economic model. Table 14 summarises the location of the key economic information within the company's submission (CS).

Table 14. Summary of key information within the company's submission

Information	Section (CS)
Details of the systematic review of the economic literature	Section 5.1
Model structure	Section 5.2
Clinical parameters and variables	Section 5.3
Measurement and valuation of health effects and adverse events	Section 5.4
Resource identification, valuation and measurement	Section 5.5
Results	Section 5.7
Sensitivity analysis	Section 5.8
Subgroup analysis	Section 5.9
Validation	Section 5.10
Strengths and weaknesses of economic evaluation	Section 5.11
Abbreviations used in table: CS, company's submission.	

5.2 Summary of the company's key results

In their base-case analysis, the company presented deterministic and probabilistic results for the comparisons of sacubitril valsartan (hereafter referred to as sacubitril) versus ACEi (more specifically enalapril) and ARB (more specifically candesartan) for patients with heart failure with reduced ejection fraction (HFrEF), for a lifetime treatment duration. The target dose of sacubitril (200mg BID) contains 103mg of valsartan, which is equivalent to a 160mg dose of valsartan given alone (hereafter referred to as valsartan). A summary of the base case incremental cost-effectiveness ratios (ICERs) presented by the company is provided in Table 15 for ease of reference. The ERG notes that the results presented are the ones reported after the clarification stage, where the ICER comparing sacubitril with enalapril decreased from £18,187 to £17,939.

5.4.5.2 Overview of QoL within the economic analysis

The company used a linear mixed regression model based on EQ-5D trial data to predict the utility scores for patients in the economic model. Since the economic model did not explicitly include mutually exclusive health states (other than the alive and the dead states), mean utility values over time were calculated for each patient profile (or average cohort). The predictive QoL model took into account:

- Patient baseline characteristics (including EQ-5D index values at baseline);
- The treatment received (i.e. sacubitril or ACEi);
- Time elapsed since beginning of the model;
- Hospitalisation and AEs which were accounted for by including utility decrements based on the average event rate by treatment arm.

The AEs considered in the QoL model were cough and hypertension as the CS (Section 5.4.7) reported that elevated serum potassium and serum creatinine were assumed to have no impact on QoL, and that too few angioedema events were observed to make inference regarding the effects on QoL. Hospitalisation and the AEs experienced (i.e. cough and hypertension) were expressed as function of the treatment received. Event-related disutilities were applied at the time of occurrence of events for simplicity, even though the time-frame for event occurrence was up to 90 days. The mean utility scores predicted by the QoL regression are reported in Table 27. To note is that the values reported below incorporate the ERG corrections made to the QoL analysis and reported in Section 5.5.8.5. The company assumed the utility scores to decrease linearly with time at a rate of -0.008 per year based on the statistical analysis performed.

Table 27.Mean predicted utility scores over time by treatment

Year	Sacubitril valsartan	Enalapril
0	0.79	0.78
10	0.72	0.71
20	0.64	0.63
30	0.56	0.55
Note: the utility scores reported in the table are the half-cycle utility scores for the first and second cycles of the year (or the last cycle for year 30). These are calculated as per the ERG correction of the error found in the utility score estimation (see Section 5.5.8.5).		

5.4.5.3 Analysis of health-related QoL trial data

The PARADIGM-HF trial included several secondary and exploratory objectives aimed at evaluating differential QoL effects between the treatments. The two most relevant exploratory outcomes are:

- The detrimental effect of the entire duration of hospitalisation and AEs managed in the outpatient setting (i.e. cough, hypertension) on QoL was applied in the model cycle in which the patient experienced the event:
    - Hospitalisation was assumed to be associated with a decrement of -0.105 during days 0 to 30, and -0.054 during days 30 to 90;
    - The utility decrement for hypotension and cough were associated with reductions in QoL equal to -0.029 and -0.028 over an average duration of 64.9 and 73.3 days respectively;
- The effect on QoL of serious adverse events requiring hospitalisation was assumed to be captured in the utility decrements associated with hospitalisation.

Table 31. Coefficients of the mixed model with individual-level random effects for utility scores (CS; Table 61)

Covariate	Coefficient	SE	P value	95% CI	
Sacubitril valsartan	0.011	0.003	0.001	0.004	0.017
Age†	-0.001	0.000	0.000	-0.001	0.000
Female	-0.031	0.004	0.000	-0.039	-0.023
Region					
Latin America	0.041	0.007	0.000	0.027	0.055
Western Europe	0.013	0.007	0.063	-0.001	0.026
Central Europe	0.000	0.007	0.969	-0.014	0.013
Asia-Pacific	0.041	0.008	0.000	0.026	0.056
NYHA classification					
II (vs. I)	-0.009	0.008	0.224	-0.024	0.006
III (vs. I)	-0.051	0.008	0.000	-0.067	-0.034
IV (vs. I)	-0.092	0.021	0.000	-0.132	-0.051
Heart rate†	0.000	0.000	0.049	-0.001	0.000
(log) NT-proBNP†	-0.009	0.002	0.000	-0.013	-0.006
Sodium†	0.001	0.001	0.071	0.000	0.002
BMI*	-0.002	0.000	0.000	-0.003	-0.001
Diabetes	-0.014	0.003	0.000	-0.021	-0.007
Time since diagnosis of HF					
1-5 years	-0.017	0.004	0.000	-0.024	-0.009
> 5 years	-0.023	0.004	0.000	-0.031	-0.014
Ischaemic aetiology	-0.007	0.003	0.033	-0.014	-0.001
Prior stroke	-0.012	0.006	0.039	-0.023	-0.001
Current smoker	-0.013	0.005	0.005	-0.022	-0.004
Baseline EQ-5D†	0.488	0.008	0.000	0.473	0.504
Hosp. 0 – 30 days	-0.105	0.006	0.000	-0.116	-0.094
Hosp. 30 – 90 days	-0.054	0.004	0.000	-0.062	-0.045
AE – cough	-0.028	0.007	0.000	-0.041	-0.015

the sacubitril and enalapril (or candesartan) arms of the model also received the standard care therapies.

The observed proportions of patients in the PARADIGM-HF trial receiving BB and AA at baseline (93.00% and 55.61% respectively) were similar to the UK data reported by the British Society for Heart Failure for the treatment of patients with left ventricular systolic disease (LVSD) at discharge (82% and 49% respectively).(1, 90) Based on this similarity, data from the PARADIGM-HF trial were used to define the proportion of patients receiving each drug at baseline. Drug regimens (i.e. the distribution of patients receiving each drug) were assumed not to change over time, irrespective of ageing population and mortality. The proportion of patients on background therapies observed in the trial and applied in the economic model is reported in Table 33. Drug regimens were also assumed not to depend on patient characteristics or the occurrence of events such as adverse events or hospitalisations.

Table 33. Proportion of patients receiving background therapies

Therapy	Proportion of patients	Source
Beta blockers	93.00%	PARADIGM-HF trial(90)
Aldosterone antagonists	55.61%	PARADIGM-HF trial(90)
Digoxin	30.23%	PARADIGM-HF trial(90)
Lipid lowering medications	56.30%	PARADIGM-HF trial(90)
Diuretics	80.22%	PARADIGM-HF trial(90)
Aspirin	51.78%	PARADIGM-HF trial(90)
Anticoagulants	31.97%	PARADIGM-HF trial(90)
ADP antagonists	15.00%	PARADIGM-HF trial(90)
Abbreviations in table: ADP, adenosine diphosphate.		

The daily dose for sacubitril and enalapril in the model was assumed equal to the observed mean dose in the PARADIGM-HF trial, respectively 375 and 18.9 milligrams. (2) (39) (39) (39) (39) (39) (McMurray, Packer et al. 2014) The daily doses for other therapies were based on the British National Formulary (BNF)(94), with the exception of aspirin and warfarin. The CS did not report how the daily doses for aspirin and warfarin were calculated. In the economic analysis, the daily dose of aspirin was referenced from Bermingham *et al.*, but it was not clearly explained (see Section 5.5.9.1).(95) The daily dose of warfarin (5 mg) was referenced from drugs.com, but it was not clearly explained in the CS (see Section 5.5.9.1).(96) The daily doses used in the model and the daily costs for each intervention are reported in Table 34.

The daily cost of sacubitril based on the pre-specified target dose of 200 mg BID is expected to be the same as that of the observed dose in the trial (375 mg daily) as sacubitril has a flat pricing structure.

Technologies	Standard care ivabradine model‡	ACEi arm in sacubitril valsartan model	Absolute difference	Relative difference
Total costs	**£9,446**	£13,286	£3,840	41%
QALYs	3.99	4.46	0.47	12%
Life-years	5.61	6.03	0.42	7%
Survival Year 5	59%	60%	1%	1%
Survival Year 10	22%	27%	5%	23%
† Therapy titration and drug costs; ‡ As reported in manufacturer submission to NICE (57) Abbreviations: ACEi, angiotensin converting enzyme inhibitor; QALY, quality-adjusted life year.				

Despite the validation procedures reported by the company, the ERG found a few inconsistencies in the model inputs and identified problems with the estimation of QALYs in the economic model.

5.5 Critique of the company's economic evaluation

5.5.1 NICE reference case checklist

Table 43 and Table 44 summarise the ERG's quality assessment of the company's economic evaluation. Table 43 summarises the ERGs appraisal of the company's economic evaluation against the requirements set out in the NICE reference case checklist for the base case analysis, with reference to the NICE scope(5) outlined in Section 3 and Table 44 summarises the assessment of the quality of the company's *de novo* economic model using the Philips checklist.(107)

Table 43. NICE reference case checklist for the base case analysis

Attribute	Reference case	Does the *de novo* economic evaluation match the reference case?
Decision problem	The scope developed by NICE	Yes, however some patients experienced an improvement in their NYHA classification between screening and randomisation which led to the inclusion of NYHA class I patients at baseline. NYHA class I was not considered in the NICE scope.
Comparator(s)	Alternative therapies routinely used in the NHS	Yes, however standard care in the economic model was based on drug use in the PARADIGM-HF trial, and did not include therapy with beta blocker and aldosterone antagonist for all patients but only for 93% and 56% of patients, respectively.
Perspective costs	NHS and Personal Social Services	Yes.
Perspective benefits	All health effects on individuals	Yes.
Form of economic evaluation	Cost-utility analysis	Yes.
Time horizon	Sufficient to capture differences in costs and outcomes	Yes.
Synthesis of evidence on outcomes	Systematic review	Yes, a systematic review was carried out. The ERG notes that the synthesis of the clinical data was carried out through a NMA described in Section 4. The ERG also notes that the results of the

not accurately reflect an HFrEF population for whom sacubitril would be given as a first-line treatment. Clinical opinion sought by the ERG indicated that based on the trial design, population and outcomes, the available evidence(in the ERG's clinical experts' views) only supports sacubitril as a second-line treatment option, given to HFrEF patients who are still symptomatic despite being on an ACEi drug therapy.

The ERG's clinical experts' anticipated positioning of sacubitril matches the trial design and the trial population much more closely than the use of sacubitril as a first-line treatment for newly diagnosed patients, for whom there is no available robust evidence on the effectiveness of sacubitril. To note is that the trial (and therefore the model) population reflects a chronic, stable and symptomatic (95% of patients in the NYHA class II–IV) HFrEF population that has been on ACEi (or ARB) treatment for at least 1 month.

The company also presented the TITRATION study as supporting evidence for the use of sacubitril in treatment-naïve patients.(110) However, only 6.6% of patients in TITRATION were treatment-naïve (i.e had not received ACEi or ARBs in the previous 4 weeks). In the TITRATION CSR the company acknowledges that the small number of naïve patients included in the analysis is not robust enough to draw conclusions about this group of patients.(47) Furthermore, the TITRATION study did not look at the same effectiveness outcomes as PARADIGM-HF as the latter investigated the safety and tolerability of initiating and up-titrating sacubitril but it did look at the evolution of the NYHA in patients (including treatment-naïve patients) across treatment arms. This outcome was not fully reported in the TITRATION CSR therefore the ERG requested that the company provided it during clarification. The company provided the evolution of NYHA for sacubitril patients only (total patients and treatment-naïve patients) as the TITRATION trial did not include treatment with enalapril. Therefore the additional data from TITRATION are of limited value given that they do not allow a comparison between treatment arms with respect to this outcome.

Tolerability of sacubitril

In order to analyse the tolerability of valsartan, the ERG makes several comparisons across the PARADIGM-HF trial and the company's commissioned analysis of the CPRD dataset. The CPRD analysis was undertaken with the goal of characterising the burden of illness of HF in the UK in terms of demographic and clinical characteristics of patients, resource use (inpatient and outpatient), treatment patterns (medications and devices), adherence and persistence with drug therapy. Further details on the company's CPRD analysis and its use in the economic model are provided in Section 5.4.6 of this report.

To note is that the CPRD data analysis included HF patients with substantially different characteristics from the PARADIGM-HF population (Section 5.4.6). [redacted] of the CPRD

patients had confirmed left ventricular dysfunction even though all patients included were HF patients. CPRD patients also presented the average co-morbidities expected for an older population [redacted] such as cancer, diabetes, kidney disease, etc. While the CPRD population presented with serious co-morbidities, one of the PARADIGM-HF inclusion criteria was that patients could not have any co-morbidities associated with a life expectancy of less than 5 years. Therefore the PARADIGM-HF population is not only younger but healthier than the CPRD population, nonetheless the CPRD population can potentially be considered more reflective of the typically presenting HF population in the UK.

The PARADIGM-HF trial included a pre-randomisation run-in phase where all patients included in the study received enalapril (10mg BID) for two weeks followed by a two-week period of sacubitril at 100mg BID which was then increased to 200mg BID for another 2 weeks (i.e. sacubitril was given for 4 weeks before randomisation). During the run-in phase [redacted] of patients in PARADIGM-HF discontinued enalapril (mean follow-up [redacted] days) while [redacted] of patients receiving sacubitril valsartan discontinued the drug (mean follow up [redacted] days). To note is that enalapril patients were already receiving an ACEi (or an ARB) for at least 4 weeks and most likely for over 1 year (70% of patients). During the randomisation phase of the trial (mean follow-up period of [redacted] years), there were 32% of discontinuations in the enalapril arm and 28% of discontinuations in the sacubitril arm of the trial.

Clinical opinion sought by the ERG noted that the discontinuation rates observed in the PARADIGM-HF trial are lower than what would be expected in clinical practice, especially with regards to valsartan (given in combination with sacubitril) and that there are no reasons to expect sacubitril valsartan would present higher tolerability than valsartan given alone. As previously mentioned in Section 4 the target dose of valsartan in the trial (in combination with sacubitril) was 160mg BID which is the maximum dose allowed for valsartan. However it seems to be uncommon for patients to tolerate such high doses of valsartan in clinical practice. According to the ERG's clinical experts' opinion the higher valsartan tolerability in PARADIGM-HF might be related to a pre-selection of patients during the run-in phase of the trial. Additionally, the study eligibility criteria set by the PARADIGM-HF protocol defined the minimum tolerable dose of valsartan to be 160mg, which seems to be higher than the average dose tolerated by patients in clinical practice. As an example, analysis of the CPRD data presented by the company shows that the average dose of valsartan tolerated by patients ([redacted]. As for enalapril, the inclusion criterion for this drug was set to be 10mg as the minimum tolerable daily dose, which seems to be lower than the average dose tolerated by patients in clinical practice. Analysis of the CPRD data presented by the company shows that the average dose of enalapril[redacted]. Therefore, while the

CPRD data shows that the average dose of valsartan tolerated by patients is [redacted] lower than the minimum tolerable dose of valsartan set in the eligibility

criteria of the PARADIGM-HF protocol (106mg), the average dose of enalapril tolerated by patients reported in the CPRD ([redacted]) is higher than the minimum tolerable dose of elaparil set in the eligibility criteria (10mg) of the trial. This issue is further discussed in Section 5.5.4.

Taking this in consideration, it seems that the trial (and therefore the model) population presents a higher tolerability to the intervention drugs, especially valsartan (given in combination with sacubitril) than the typical HFrEF population. This has an impact on the observed discontinuation of study drugs, which is likely to be higher in UK clinical practice than it is in the trial.

The ERG produced Table 46 which presents a summary of the discontinuation rates in the PARADIGM-HF trial and in the CPRD analysis. The ERG estimated the proportion of patients discontinuing study drugs in the run-in phase and in the randomisation phase of the trial by considering all causes for discontinuation (i.e. AEs, protocol deviations, administrative problems, lost to follow-up, death, etc.). To note is that discontinuations in the enalapril run-in (and randomisation) stages need to be interpreted with caution as these patients had been on ACEi or ARB treatment for at least 1 month, and most likely (70% of patients) for over 1 year. The same is true for valsartan (in combination with sacubitril) patients, given that 23% of patients had received an ARB at baseline.

Looking at Table 46 it can be observed that [redacted]. During the run-in phase of the trial [redacted] of patients in PARADIGM-HF had discontinued enalapril (mean follow-up [redacted] days), while [redacted] of patients receiving sacubitril valsartan discontinued the study drug (mean follow-up [redacted] days). Nonetheless, it should be noted that the tolerability in the CPRD dataset and in the trial are in respect of different drug doses. The average dose of the drugs tolerated by patients during the run-in period is not available in the PARADIGM-HF CSR, but given that the target dose for the run-in period was 10mg BID for enalapril and 100mg BID for sacubitril (followed by 200mg BID), it is likely that patients who were receiving ACEi before the start of the run-in period (and who might not have been receiving enalapril, but instead other ACEi) had to adjust to the new study drug and to a higher drug dose, leading to a peak in discontinuations even for patients who were tolerating ACEi before. The same applies to ARBs (i.e. to valsartan).

Comparing the 1 year discontinuation rates in the CPRD patients with the [redacted] discontinuation rates in PARADIGM-HF it is apparent that the trial discontinuation is substantially lower than the CPRD discontinuation (even when the trial follow-up period is twice as much as the CPRD follow-up is). When the 1 year discontinuation rates for valsartan-naïve patients,

[redacted], are compared with the 28% discontinuation in the trial after a mean follow-up of [redacted] years, [redacted] difference is even bigger, with CPRD data presenting much higher discontinuation rates. In terms of

of these agents. The dose is meant to be doubled every 2–4 weeks to the target of 200mg BID, as tolerated by the patient. It is also reported [redacted]

The comparators included in the scope were as follows:

- ACEi in combination with standard care (including treatment with a BB and an AA);
- ARB in combination with standard care (including treatment with a BB and an AA), for whom treatment with ACEi is unsuitable.

The intervention drug considered in the economic model matches the NICE final scope.(3) With regards to the comparators included in the economic analysis:

- The ACEi considered in the economic analysis was enalapril. The inclusion of enalapril is appropriate and consistent with the NICE final scope even though clinical opinion sought by the ERG advised that ramipril is the most commonly used ACEi in the UK. Ramipril was considered in the company's scenario analysis.(3)
- The ARB considered in the economic analysis was candesartan, which appears to be appropriate.
- Standard of care considered in the economic analysis included BB, AA for both intervention and comparator arms of the model, which is appropriate. Nonetheless, according to the ERG's clinical experts' opinion, the proportion of patients receiving AA was considered to be lower than what would be expected in clinical practice.
- In addition to standard care, the company also included background therapies in both treatment and comparator arms of the model. This included digoxin, lipid lowering medications, diuretics, aspirin, anticoagulants and ADP antagonists. This reflects the PARADIGM-HF treatment regimen and was considered to be reflective of UK clinical practice according to the expert opinion provided to the ERG.

5.5.1.2 Modelled treatment regimens

The treatment regimens modelled for sacubitril and the included comparators are outlined in Table 48. Table 49 shows the background therapies modelled together with treatment and comparator drugs. The ERG notes that while the enalapril dose used in the model was based on the average dose observed in the PARADIGM-HF trial, the modelled dose of sacubitril was based on the drug target dose (even though the company reports that the modelled dose of sacubitril was the average daily dose of 375mg observed in the trial).

There were 1,624 (19.3%) patients in the <55 years' category while 2,655 (31.6%) patients were between 55 and 64 years and 2,557 (30.4%) patients were between 65 and 74 years old. There were 1,563 (18.6%) patients in the ≥75 years' category. Overall the study found that there were no significant interactions between all the variables analysed and study outcomes, except for age. Even though the HR for sacubitril compared with enalapril for the primary composite outcome, CV death, HF hospitalisation and all-cause mortality was below 1 in all the age categories, the HRs across different age categories were different and became non-statistically significant for patients above 75 years old.

Clinical expert opinion sought by the ERG confirmed that the assumption of constant hospitalisation over time is not reflective of UK clinical practice. For example, a higher proportion of interventional procedures and shorter length of stay would be expected for younger patients than for older patients. The impact of this assumption on the cost of hospitalisation is explored in Section 5.5.9. The company undertook a scenario analysis in which the baseline annual hospitalisation rate is assumed to increase by 10% of the original baseline rate each year (results are presented in Section 5.6).

5.5.1.4 Starting age in the model

The ERG believes that there are two distinct issues related with the starting age in the economic model. Firstly, there is the issue of the effectiveness of sacubitril in older people. This is particularly relevant as according to the ERG's expert opinion and CPRD data, the average UK HF patient is 75 years old (or older). Secondly there is the issue of running the economic analysis with a younger population, which (even if we assume that the effectiveness of sacubitril remains unchanged with age) lives longer and therefore accrues the benefits associated with the drug for longer. Again, the extent to which this is relevant lies in how representative the starting age (64 years old) of the modelled population is of the average UK patient, and for how long the average HF patient can potentially benefit from the effectiveness of sacubitril. The effectiveness of sacubitril in preventing hospitalisation across different age groups is now discussed, while the starting age in the economic model is discussed in the mortality section (Section 5.5.7.4).

Effectiveness of sacubitril in preventing hospitalisation across different age groups

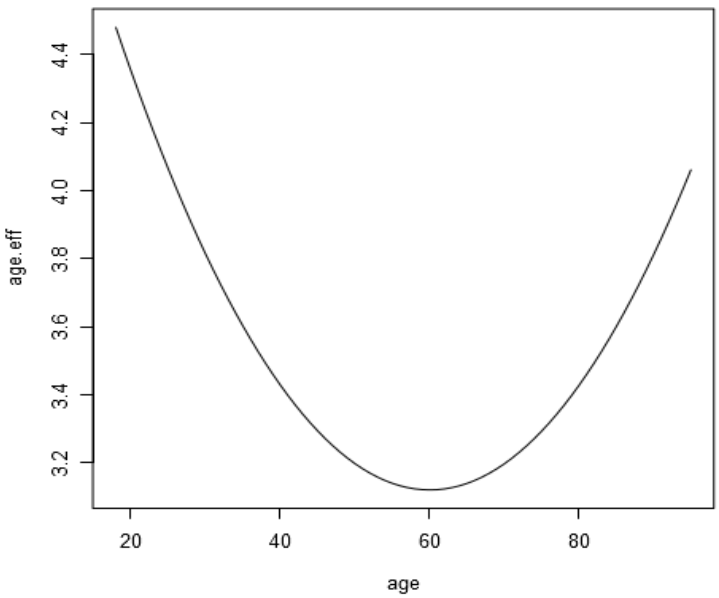
The Jhund *et al.* study results are presented in Figure 15 and these show that for patients in the 65–74 years and ≥75 years' category, all of the hospitalisation HRs for sacubitril versus enalapril are non-statistically significant.(7) In fact, all the HRs reported for the different outcomes in the ≥75 years' category are non-statistically significant. The results of the Jhund *et al.*(7) study need careful interpretation:

1. The HRs presented in the analysis might be reflecting a trend in the effectiveness of sacubitril compared with enalapril. For example, the HF hospitalisation in the 55 to 64 years age group

Even though the modelled effect of age at baseline in CV mortality seems to be appropriate to capture the PARADIGM-HF trial data, the unexpected shape of the curve presented in Figure 22 leads to other issues in the economic analysis, such as the lack of face validity of the predicted life expectancy in the model. In Figure 24 the predicted life expectancy by the mortality survival model indicates that 21-year-old patients have the same life expectancy as 87-year-old patients. Equally implausible, 72-year-old patients have a much higher life expectancy than 18 year olds. The ERG appreciated that this is a direct implication of the modelled effect of age at baseline on CV mortality (Figure 22), which in its turn is a direct consequence of the PARADIGM-HF trial data (Figure 23).

Also worth noting is the slope of the curves in Figure 24. Even though the shape of the curves after 60 years of age is more plausible from a clinical point of view, the slope of the curves is not very steep, as it would be expected with the increasing age of patients. For example, a 64-year-old patient on sacubitril has a life expectancy of approximately 9 years, while a 75-year-old patient has a life-expectancy of 7 years, therefore implying a difference of 2 years in life expectancy between 64 and 75 year-old patients. The UK Life Tables report that on average, 64 year-old patients have a life expectancy of 22 years while 75 year-old patients have a life expectancy of 13 years (a difference of 9 years). Even though it might be argued that HF patients do not exhibit the same life expectancy (thus the same differences in life expectancy) as the average UK population, it seems likely that a difference in life expectancy of 2 years is an underestimation for patients aged 64 or 75 years old. For example, when the ERG changed the starting age of the model from 64 to 75 years, the change in life expectancy and the final ICER is relatively small.

Figure 22. Effect of baseline age on CV mortality in the company's model



replicating the trial data but cannot be changed to portray a population more representative of UK patients. This is particularly true with regards to the starting age of the model population. The trend observed in CV mortality by age group at baseline reinforces the ERG's point that the PARADIGM-HF trial population is not representative of the UK HF population, especially when deviations are made from the mean age trial population (64 years).

To note is that the ERG investigated all-cause mortality data in the PARADIGM-HF trial by age group at baseline and the same issues described here for CV mortality apply to all-cause mortality.

The effect of age at baseline on CV and all-cause mortality is discussed separately for the Western Europe region in Section 5.6.2 of the ERG report.

5.5.1.4 Starting age in the model and impact on mortality

In this section the ERG discusses the effectiveness of sacubitril in reducing mortality in older populations and the issue of running the economic analysis with a younger population, which (even if we assume that the effectiveness of sacubitril remains unchanged with age) lives longer and in theory would reap the benefits associated with the drug for longer.

Effectiveness of sacubitril in reducing mortality across different age groups

The Jhund *et al.* study results are reproduced again in Figure 15 for convenience and these show that for the <55 years' category and the ≥75 years' category the CV mortality HRs for sacubitril versus enalapril are non-statistically significant. However, as discussed in the hospitalisation section (Section 5.5.5.4) the results of the Jhund *et al.* study need to be carefully interpreted.(7) While sacubitril appears to maintain the same direction of effect across age groups, the size of the effect is not as easily established. The authors in Jhund *et al.* conclude that the effect of sacubitril compared with enalapril was consistent across age groups even though HRs were non-statistically-significant in older groups.(7) This is somewhat consistent with the expert opinion provided to the ERG that for patients around 80 years old presenting with HFrEF, clinicians expect treatment (with ACEi or other drugs) to improve patients' QoL and symptoms but improve mortality.

In light of this the ERG has conducted a scenario analysis using the HR obtained in Jhund *et al.* for mortality which was 0.79 (95% CI 0.64 to 0.98) in the 55-64 years' category.(7) As the confidence interval for the HR of CV deaths in the 55–64 years population is wide, the ERG also ran a scenario analysis using both limits of the 95% confidence interval. The ICERs resulting from the ERG analysis are presented in Section 6 of the report.

The ERG has also run a model for an older baseline population (75 year old group). The ERG used the respective HR reported for this category in the Jhund *et al.* study.(7) However and as previously

(Section 5.4.6 of the CS), without producing quantitative and/or qualitative comparisons. Clinical expert opinion sought by the ERG confirmed that the population included in the trial is similar to a stable chronic HFrEF outpatient population. As such, the ERG considers that the studies by Austin *et al.*(9) Iqbal *et al.*(77) and Peters *et al.*(82) to be extremely relevant to the decision problem given that they focused on chronic HFrEF UK patients. Furthermore the studies by Eurich *et al.*(74) and Kraai *et al.*(80) are also relevant as, even though these were carried out in different countries, these based the EQ-5D scoring on UK tariffs, and can therefore be used as comparators. These studies obtained QoL measurements directly from the patients, according to the NICE reference case.(5) The summaries of the studies, together with the observed utility scores, are reported in Table 26.

The ERG notes that among the identified studies, utility scores collected in trial-based studies were consistently higher than in other types. This might be explained by the common tendency to have healthier trial patients than the ones observed in clinical practice. In the PARADIGM-HF trial for example, the EQ-5D scores were collected at randomisation, at which point the patients had gone through the inclusion and exclusion criteria selection process at screening and the two run-in periods as per trial design. Therefore the ERG believes that the QoL observed in the trial population at randomisation was higher than the QoL associated with chronic patients seen in the UK outpatient practice.

Given the relationship between the QoL at baseline and the trial outcomes (highlighted by the regression models, which for example show a correlation between EQ-5D scores and mortality), the ERG is concerned that the overestimation of patients' QoL at baseline might impact the benefits observed in the trial when compared with real clinical practice. The ERG conducted a scenario analysis and varied the baseline utility score to match the mean estimates by Berg *et al.*(8) and by Austin *et al.(9)* at baseline, who reported values equal to 0.72 and 0.660, respectively. The impact of this on the ICER is explored in Section 6.

5.5.8.2 Baseline health-related QoL in the intervention and comparator groups

Comparability of health-related QoL at baseline was reported only in a brief study report commissioned by the company (separate from the main submission).(91) These data have been previously described in Section 5.4.5.3.

The document reported that at baseline [redacted] ([redacted]%) and [redacted] ([redacted]%) patients had complete EQ-5D index data in the enalapril and sacubitril arms, respectively. The mean EQ-5D values at baseline were [redacted] (SD [redacted]) for both arms. A two-sample *t* test was performed to compare the two distribution means and [redacted] (p-value = [redacted]). Nonetheless this conclusion needs be considered with caution as the [redacted] shape

of the distribution at baseline might indicate that the mean difference are not sufficient to prove that the two populations were

- HF management resource use and costs;
- AEs resource use and costs.

5.5.9.1 Pharmacological costs

The cost of sacubitril in the model was estimated based on the observed dose of sacubitril in the PARADIGM-HF trial. The company also estimated the daily cost of enalapril per patient based on the average observed drug dose in the PARADIGM-HF trial. Standard care and background therapy use were also based on the PARADIGM-HF trial data. The daily doses for other therapies were based on the BNF (94), with the exception of aspirin and warfarin. The choice of the sources used to model the doses of aspirin and warfarin the model were not clearly reported in the CS.

The ERG notes that the assumptions regarding the daily drug doses were not consistent across different treatments. For some treatments, the doses were estimated as the average between the minimum and maximum dose and for other drugs, the doses were based on maximum doses. The ERG believes that the company should have used drug's target doses or, when the target dose was not available, the maximum dose for the purpose of estimating the treatment cost consistently across all drugs regimens. The ERG undertook additional analysis to reflect consistent drug dose assumptions. The re-estimated drug costs are presented in Table 59, while the impact on the final ICER is presented in Section 6.

As mentioned in Section 5.5.4.2, the most commonly used ACEi in the UK is ramipril. The company undertook scenario analysis where the cost of enalapril was replaced by the cost of ramipril in the economic model. The ERG notes that even though the company took the daily dosage of ramipril from the BNF, this seems to be in conflict with UK general practice. The ERG's clinical experts explained that the key advantage of ramipril over enalapril is the fact that is can be given as a daily dose regimen, which helps with medication adherence. Therefore, even though the BNF recommends administrating ramipril in two daily 5 mg doses (94), the ERG re-estimated the monthly cost of ramipril to better reflect UK clinical practice. The re-estimated cost of ramipril is presented in Table 59, while the impact on the final ICER is presented in Section 6.

Table 59.ERG estimates of the monthly drug costs

Intervention	CS daily dose assumption	ERG daily dose assumptions	CS monthly cost	ERG monthly cost	Notes
Enalapril	18.9 mg	Two 10 mg tabs	£2.10	£2,22	Maximum dose assumed
Ramipril	Two 5 mg tabs	One 10 mg tab	£2.70	£1.45	Clinical experts stated that ramipril is offered as a single daily dose

Finally the ERG notes that CS did not clearly state what preparations of cetirizine and prednisolone were assumed to be used for the management of mild and severe angioedema. The ERG checked the doses and costs against the current guidelines and found them appropriate.

5.6 Results included in company's submission

5.6.1 Base case results

The ERG presents the company's primary and the secondary base case results in Table 63 and Table 64, respectively. The ERG notes that the results presented are for the patient-level model, all-cause mortality approach and post-clarification stage, where the ICER comparing sacubitril with enalapril decreased from £18,187 to £17,939 per QALY gained.

The primary base case results show that sacubitril + standard of care presents a cost per QALY gained of £17,939 compared with enalapril + standard of care. Compared with enalapril, sacubitril results in more QALYs, and is more costly. The secondary base case results compare enalapril with ARB (candesartan). These are presented in Table 64. Sacubitril + standard of care presents a cost per QALY gained of £16,481 compared with candesartan + standard of care.

Table 63.Company's primary base case results

Results per patient	Enalapril+Standard Care (1)	Sacubitril+Standard Care (2)	Incremental value (2-1)
Total costs (£)	£13,287	£20,801	£7,514
QALYs	4.60	5.02	0.42
ICER			**£17,939**

Table 64.Company's secondary base case results

Results per patient	Candesartan+ Standard Care (1)	Sacubitril+ Standard Care (2)	Incremental value (2-1)
Total costs (£)	£12,288	£20,801	£8,513
QALYs	4.50	5.02	0.62
ICER			**£16,481**

The results obtained using the all-cause mortality approach and the mean cohort model are £17,383 per QALY gained for the company's primary results and £15,885 for the secondary analysis.

The company presented modelled survival from month 0 to month 36 (three years) in the economic analysis and compared this with the observed survival in PARADIGM-HF for the same period of

time. Hospitalised rates predicted by the model and observed in the PARADIGM-HF trial were also provided. These results are provided in Section 5.7.2 of the CS.

Table 65 and Table 66 present the ICERs for the company's primary and secondary analysis, respectively, using the CV mortality (instead of all-cause mortality) approach for the patient-level model. The ICER in Table 65 is lower than the one reported in Table 63, as expected however the ICER for the secondary analysis using the CV mortality approach is slightly higher than the ICER using the all-cause mortality approach, reported in Table 64.

Table 65. Company's primary base case results, CV approach

Results per patient	Enalapril+SoC (1)	Sacubitril+SoC (2)	Incremental value (2-1)
Total costs (£)	£14,814	£23,458	£8,644
QALYs	5.08	5.60	0.52
ICER			**£16,678**

Table 66.Company's secondary base case results, CV approach

Results per patient	Candesartan+SoC (1)	Sacubitril+SoC (2)	Incremental value (2-1)
Total costs (£)	£13,835	£23,458	£9,623
QALYs	5.02	5.60	0.58
ICER			**£16,569**

5.6.2 Sensitivity analysis

5.6.2.1 Deterministic sensitivity analysis

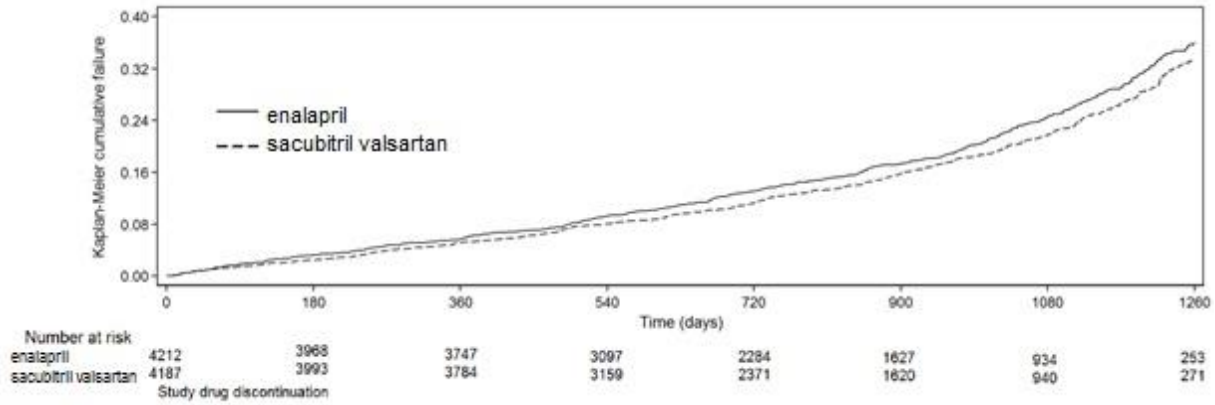
In this section the ERG presents the results for the deterministic sensitivity analysis reported in Sections 5.8.5 to 5.9.5 of the CS. The company performed three distinct types of deterministic sensitivity analyses (DSA): one-way parameter variations, scenario analyses and subgroup analyses. These are reported in the subsections below together with the ERG's commentary.

5.6.2.2 One-way deterministic sensitivity analyses

Univariate one-way DSAs were presented in Sections 5.8.5 and 5.8.6 of the CS. A list of key parameters was identified in the economic model and varied one by one independently and systematically. The values were varied to the upper or lower bounds of the 95% confidence intervals surrounding the point estimate and, when a confidence interval was not available, by increasing or decreasing the parameter value by an arbitrary proportion equal to 25%. The confidence intervals

constant hazard assumption implied by the exponential model specification was considered to be reasonable by the company as it avoids the risk of extrapolating what was considered to be an implausible trend observed at the end of the trial.

Figure 27. Kaplan Meier discontinuation (not caused by death) in PARADIGM-HF (FAS). (reproduced from CS, Figure 41)



Abbreviations used in figure: FAS, full analysis set.

The parametric model used for discontinuation events is reported in Table 98 of the CS. The HR for the reduction in the risk of discontinuation events attributed to sacubitril was 0.89 and significantly different from zero at a confidence level of $1 - \alpha = 0.95$. A substantial variation across geographical areas was observed, with patients in Western Europe and North America being more likely to discontinue treatment than in the other areas of the world. The ERG notes that goodness of fit statistics, visual analyses and alternative model specifications were not reported in the CS.

The scenario analysis does not result in a change in the estimated QALYs for the ACEi arm as no difference is assumed between ACEi and ARBs with the exception of costs and those differ only slightly. The ICER increases from the base case estimate as the cost savings caused by patients switching to the cheaper ACEi therapy in the sacubitril arm are overweighed by a loss in the incremental efficacy compared to ACEi. To also note is that the exponential model is likely to be underestimating the discontinuation rates, [redacted] (Section 5.5.3.2).

Variation in hospitalisation was assessed in several deterministic scenario analyses, looking at changes in event rates, costs and treatment effects. Expert opinion sought by the ERG confirmed that the assumption of a constant rate of hospitalisation was not a reasonable assumption, and that hospitalisation rates, cause and length of stay varies with age (Section 5.5.9). The scenario analysis included in the CS which increased the hospitalisation rate by 10% yearly, proved the model relatively insensitive to this variation (the ICER increased by about £500 per QALY gained).

6 ADDITIONAL WORK UNDERTAKEN BY THE ERG

The ERG carried out minor model corrections (Section 6.1), and several scenario analyses (Section 6.2) on the company's model. In addition, the ERG presents a second-line ICER estimate, which aims to approximate the company's ICER to the second-line HFrEF population in the UK (Section 6.3). The ERG used the mean cohort model and the CV mortality approach for all the additional work undertaken.

6.1 Model corrections

The ERG has corrected the mistake in the half-cycle adjustment found in the estimation of the utility values as explained in Section 5.5.8. The ERG also corrected a mistake found in the company's discontinuation scenario analysis.

After these corrections were applied in the model, the base case ICERs changed from £15,529 per QALY gained for the company's primary results and £15,343 for the secondary analysis to £15,026 and £14,931 for the primary and secondary analysis, respectively, using the mean cohort and the CV mortality approaches. These ICERs are presented in Table 83.

Table 83. ERG corrected ICERs

Results per patient	**Enalapril+SC (1)**	**Sacubitril+SC (2)**	**Candesartan+SC (3)**	**Incremental value (2 – 1)**	**Incremental value (3 – 1)**
Total costs (£)	£22,961	£14,308	£13,335	£8,653	£9,626
QALYs	5.40	4.82	4.76	0.58	0.64
ICER				**£15,026**	**£14,931**

6.2 ERG scenario analysis

The scenario analyses undertaken by the ERG are explained throughout Section 5 of the report and were ran for a population with a mean starting age of 64 years (as per the company's base case) and for a mean starting age of 75 years to reflect the UK HF population. The ERG used the CV mortality approach and the mean cohort model. Results are presented in Table 84.

The additional scenario analysis ran for the 64-year-old population are the following:

1. The ERG changed the CV mortality HR in the model to reflect the Jhund *et al.* HR estimate for the 55**–**64 year category.(7) The HR used was 0.79 (CI 0.64 to 0.98);

    1.1. As the confidence interval for the HR of CV mortality in the 55–64 years population is wide, the ERG also used both limits of the 95% confidence interval;

2. The ERG used the baseline utility score of 0.72 reported by Berg *et al.(8);*

3. The ERG used the baseline utility score of 0.660 reported by Austin *et al.*(9);

4. Given the issues found in the modelling approach of QoL in the model, the ERG adopted a simplified approach, where the impact of sacubitril on patients' QoL was linked to the incidence of AE and hospitalisation events and disease progression (i.e. time) in both treatment arms. Therefore, the QoL regression model was not used, even though some of its estimates were used as these were validated by clinical experts. The impact of sacubitril alone on QoL was also removed to reflect the lack of robust evidence to support a measurable improvement in patients' QoL caused by sacubitril other than through hospitalisation, mortality and AEs. The impact of treatment regimens on QoL was assessed by the ERG through :

    - AEs and hospitalisation events: the ERG applied the same utility decrements used by the company to estimate the loss in QoL due to the incidence of AEs and hospitalisation;

    - Disease progression: the ERG applied the same utility decrement used by the company to reflect the loss of QoL as time progresses for HF patients.

5. The ERG changed the drug doses used in the model to reflect a consistent approach to the estimation of drug costs. The re-estimated drug costs are presented in Table 59, Section 5.5.9.1;

6. The ERG included the cost of ramipril (using the ERG drug dose assumption) as to reflect clinical practice in the UK;

7. The ERG used the option included in the company's economic model to run the ERG corrected model considering treatment discontinuation;

8. The ERG used the company's subgroup analysis results to run the ERG corrected model considering the Western European population. To note is that the mean baseline age for the Western European population is [redacted] years.

Table 84. Results of the ERG's scenario analysis for patients entering the model at 64 years

	Results per patient	**Sacubitril+SoC (1)**	**Enalapril+SoC (2)**	**Incremental value (1-2)**
0	**Base case (CV approach, mean cohort model) with ERG corrections**			
	Total costs (£)	£22,961	£14,308	£8,653

Sacubitril valsartan for treating chronic heart failure
Addendum to ERG Report

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SUMMARY

The ERG has produced Table 1 to summarise the ICERs obtained when different assumptions and data sources are used to model CV or all-cause mortality in the economic analysis. The aim of Table 1 is to reflect the high variability in results obtained when different HRs for all-cause and CV mortality are assumed and to reinforce the ERG's view that the second-line ICER for sacubitril compared with enalapril in the context of UK clinical practice is associated with substantial uncertainty and can range from as low as £14,942 per QALY gained to being dominated (with sacubitril being more expensive and generating less QALYs than enalapril).

The ICERs reported in the third and fourth rows (third column) of Table 1 are the ERG's estimated ICERs for second-line therapy with sacubitril (compared with enalapril), which have been estimated with a CV mortality approach and a mean cohort model. The key assumptions underlying the ICERs (and reported in Section 6 of the ERG's report) are:

- Average age at baseline is 75 years;
- A different baseline utility value for both treatment arms in the model (utility score of 0.72 as reported by Berg *et al*.) (1);
- The effectiveness measures, costs and QoL of the Western European subgroup;
- An alternative, simplified approach for the estimation of QoL in the model.

The second-line ICER estimated by the ERG amounts to £29,478 per QALY gained for sacubitril compared with enalapril. The other ICERs, obtained with different HRs and the all-cause mortality approach, are detailed in Table 1 below.

Table1. Range of second-line ICERs for sacubitril compared with enalapril

Scenario	CV mortality approach HR	ICER	All-cause mortality approach HR	ICER
Second-line ICER estimated by ERG (using Western European HRs)				
[redacted] years	0.86	£30,190	0.94	£53,299
75 years		£29,478		£47,699
HR for CV mortality changed to reflect Jhund *et al.*				
64 years; CV mortality	0.79	£22,025	0.87	£28,851
75 years; CV mortality	0.84	£26,605	0.87	£25,396
HR for CV mortality changed to reflect Jhund *et al.* upper CI limit				
64 years; CV mortality	0.98	£143,265	1.06	Dominated
75 years; CV mortality	1.06	Dominated	1.07	Dominated

HR for CV mortality changed to reflect Jhund *et al.* lower CI limit				
64 years; CV mortality	0.64	£14,942	0.72	£15,959
75 years; CV mortality	0.67	£15,584	0.71	£14,059
HR for CV mortality changed to 1				
64 years	1	£533,646	1	£533,646
75 years		£492,438		£492,438
Western Europe subgroup upper CI limit				
[redacted] years	1.11	Dominated	1.17	Dominated
75 years		Dominated		Dominated
Western Europe subgroup lower CI limit				
[redacted] years	0.67	£15,739	0.76	£17,479
75 years		£15,474		£16,015
Abbreviations: CI, confidence interval; CV, cardiovascular;; HR, hazard ratio; ICER, incremental cost effectiveness ratio; QALY, Quality-adjusted life year.				

REFERENCES

1) Berg J, Lindgren P, Mejhert M, Edner M, Dahlstrom U, Kahan T. Determinants of Utility Based on the EuroQol Five-Dimensional Questionnaire in Patients with Chronic Heart Failure and Their Change Over Time: Results from the Swedish Heart Failure Registry.