NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

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

The following documents are made available to the consultees and commentators:

1. **Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)**

2. **Consultee and commentator comments on the Appraisal Consultation Document** from:
   - **Novartis Pharmaceuticals**
   - **Pumping Marvellous Foundation**
   - **British Cardiovascular Society**
   - **British Society for Heart Failure**

   The Royal College of Physicians endorses the British Cardiovascular Society and British Society for Heart Failure responses

   'No comment' response received from the Department of Health

3. **Comments on the Appraisal Consultation Document from experts:**
   - Dr Lisa Anderson – clinical expert, nominated by British Society for Heart Failure

4. **Comments on the Appraisal Consultation Document received through the NICE website**

5. **Appendix of new evidence** prepared by Novartis

6. **Evidence Review Group critique of the company new evidence**

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

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Sacubitril valsartan for treating symptomatic chronic heart failure with reduced ejection fraction

Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)

Definitions:

Consultees – Organisations that accept an invitation to participate in the appraisal including the companies, national professional organisations, national patient organisations, the Department of Health and the Welsh Government and relevant NHS organisations in England. Consultees can make a submission and participate in the consultation on the appraisal consultation document (ACD; if produced). All non-company consultees can nominate clinical experts and/or patient experts to verbally present their personal views to the Appraisal Committee. Company consultees can also nominate clinical experts. Representatives from NHS England and clinical commissioning groups invited to participate in the appraisal may also attend the Appraisal Committee as NHS commissioning experts. All consultees have the opportunity to consider an appeal against the final recommendations, or report any factual errors, within the final appraisal determination (FAD).

Clinical and patient experts and NHS commissioning experts – The Chair of the Appraisal Committee and the NICE project team select clinical experts and patient experts from nominations by consultees and commentators. They attend the Appraisal Committee meeting as individuals to answer questions to help clarify issues about the submitted evidence and to provide their views and experiences of the technology and/or condition. Before they attend the meeting, all experts must either submit a written statement (using a template) or indicate they agree with the submission made by their nominating organisation..

Commentators – Commentators can participate in the consultation on the ACD (if produced), but NICE does not ask them to make any submission for the appraisal. Non-company commentator organisations can nominate clinical experts and patient experts to verbally present their personal views to the Appraisal Committee. Commentator organisations representing relevant comparator technology companies can also nominate clinical experts. These organisations receive the FAD and have opportunity to report any factual errors. These organisations include comparator technology companies, Healthcare Improvement Scotland any relevant National Collaborating Centre (a group commissioned by NICE to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups such as the NHS Confederation, the NHS Commercial Medicines Unit, the Scottish Medicines Consortium, the Medicines and Healthcare Products Regulatory Agency, the Department of Health, Social Services and Public Safety for Northern Ireland).

Public – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but NICE reserves the right to summarise and edit comments received during consultations, or not to publish them at all, where in the reasonable opinion of NICE, the comments are voluminous, publication would be unlawful or publication would be otherwise inappropriate.

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comments received from consultees

Consultee	Comment [sic]	Response
Novartis	Novartis welcomes NICE's provisional recommendation to make sacubitril/valsartan available for the treatment of adult patients with symptomatic heart failure with reduced ejection fraction (HFrEF). However, Novartis would like to challenge the restrictions in the provisional recommendation, in order to prevent discrimination against several groups of patients who would benefit from sacubitril/valsartan, and who are covered by the European Medicines Agency (EMA) marketing authorisation for this medicine. There is a considerable unmet need in HFrEF and sacubitril/valsartan would provide an important treatment option in these patients who would currently be excluded from receiving this medication based on NICE's draft guidance. Novartis would like to thank NICE for the opportunity to submit a small amount of additional clinical evidence to support the ACD response. Our comments and additional evidence are provided in response to the standard four questions on which NICE have stated they are interested in receiving comments (page 1 of the ACD). The table below provides a summary of our response. (Note: see table in Novartis response to ACD).	Comments noted, see FAD sections 3.62 to 3.70.
Novartis	**1 Has all of the relevant evidence been taken into account?** There are several pieces of evidence that Novartis does not believe the Committee adequately considered or requested from the company in order to inform its decision to restrict the recommended population who can be treated with sacubitril/valsartan. These include the following data from PARADIGM-HF: • Subgroup analyses of left ventricular ejection fraction (LVEF) subgroups (particularly patients with LVEF > 35%) • Efficacy and safety in the NYHA Class IV population In Sections 1.1 and 1.2 below, we present evidence from PARADIGM-HF as well as	Comments noted, see FAD sections 3.68, 4.8 and 4.20.

Consultee	Comment [sic]	Response
	additional supporting argumentation to challenge the restrictions based on LVEF and NYHA Class specified in the draft guidance. 1.1 **Restriction to patients with LVEF of 35% or less** The ACD has proposed to restrict treatment with sacubitril/valsartan to those patients with a LVEF of 35% or less on the basis that the LVEF inclusion criterion for the PARADIGM-HF trial was changed from 40% or less initially, to 35% or less (Section 4.8 of ACD). In this section we present evidence for the efficacy of sacubitril/valsartan in patients with LVEF >35% (n=963, 11.4% of patients in the trial). We also present arguments regarding the use of cut-off values for LVEF in clinical practice and resource use implications if this restriction was to be applied in practice. **Efficacy of sacubitril/valsartan in patients with LVEF>35%** Of the 8,442 randomised patients in PARADIGM-HF, a total of 963 patients (11.4%) had a LVEF >35% and ≤40%.The first amendment to LVEF in the PARADIGM-HF protocol, dated 15 December 2010, came into effect after 1,285 patients had been randomised into the study. The main purpose of the first amendment was to modify 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. This change was made in response to an anticipated increase in the use of aldosterone antagonists following the release of results from the EMPHASIS-HF trial in 2011 (1). Increased use of aldosterone antagonists was expected to lower the event rate. Thus, the LVEF cut-off was lowered to offset this anticipated decrease in the event rate so that the targeted number of primary composite events would occur within a reasonable follow-up period. LVEF is one of several clinical measures of HF severity. Additional analyses based on other measures of disease severity, baseline NYHA Functional Classification, N-terminal prohormone B-type natriuretic peptide (NT-proBNP) tertiles, and the Meta-Analysis Global Group in Chronic Heart Failure score (MAGGIC score, which is the most widely accepted and used validated risk score for prediction of mortality in	

Consultee	Comment [sic]	Response
	patients with HF (2), were performed to assess whether benefit associated with sacubitril/valsartan treatment in reducing CV death and HF hospitalisation was consistent in HF patients of various severities. The benefit of sacubitril/valsartan over enalapril for the primary endpoint was similar across the spectrum of risk (p = 0.159) based on the MAGGIC score (3). Regarding efficacy in patients with LVEF >35%, there was a consistent treatment benefit in favour of sacubitril/valsartan over enalapril for the primary endpoint (p-value for interaction p=0.3599), and for cardiovascular death (p-value for interaction p=0.3559) for patients with LVEF >35% (4). Additionally, for tertile subgroups for LVEF at screening (<28%, ≥28 to ≤33%, and ≥33%), there was a consistent treatment benefit in favour of sacubitril/valsartan over enalapril for the primary endpoint (p-value for interaction p=0.9720), and for cardiovascular death, regardless of the screening EF values (see Figure 1,). (Note: see Figure 1, in Novartis response to ACD). Additional analyses of PARADIGM-HF data were performed using 5-point subcategories of LVEF for the primary endpoint and for CV death which demonstrated a consistent treatment benefit in favour of sacubitril/valsartan across all subgroups (See separate Appendix of new evidence, Section 5.1).	
Novartis	***Use of cut-off values for LVEF in clinical practice and resource use implication*** In addition to the consistent treatment effect observed across all LVEF subgroups (including >35%), the use of LVEF in clinical practice should also be considered. The European Public Assessment Report (EPAR) states that cut-off values for ejection fraction were an important part of the inclusion/exclusion of the patient population in the pivotal trial and EF is of diagnostic and prognostic value in HF. However the EPAR also states that the use of EF cut-offs outside of studies has limitations and hence a cut-off is not included in the indication. LVEF is an imprecise measure, which can vary in the clinical setting mainly due to (1) different methodologies for EF measurement, (2) inter- or intra-observer variability, and (3) temporary improvement or deterioration as a result of HF treatment or lifestyle measures (e.g. diet, salt intake, comorbidities, etc.). Per the European Society of Cardiology (ESC) guideline, 'It is important to note that EF values and normal ranges are dependent on the imaging technique employed,	Comments noted, see FAD sections 3.68, 4.8 and 4.20.

Consultee	Comment [sic]	Response
	method of analysis, and operator.' In Section 4.8 of the ACD it is stated that 'The Committee discussed how the EF level will be determined in clinical practice and whether the required tests will be readily available to people who will potentially benefit from sacubitril valsartan. It was aware that EF level is usually demonstrated with an echocardiogram and additional tests will not necessarily be required before initiating sacubitril valsartan.' In the UK, operators who perform echocardiography often do not detail the EF value but just describe the grade of ventricular dysfunction (mild, moderate, severe) according to the qualitative categories as provided in the American Society of Echocardiography and the European Association of Cardiovascular Imaging Recommendations for Cardiac Chamber Quantification by Echocardiography in Adults. Therefore, a precise LVEF value may not be readily available for all patients although reduced ejection fraction or ventricular systolic dysfunction is documented and the LVEF will change over time. A requirement for inclusion of a specific LVEF value for treatment may therefore limit the ability of physicians to prescribe the drug to a patient who could benefit from sacubitril/valsartan. Additionally, physicians might be required to repeat an echocardiogram to provide evidence that a patients EF is below the cut-off value leading to increased NHS resource use. ***Conclusion*** Overall Novartis proposes that NICE refers to "reduced ejection fraction" rather than a specific cut-off for LVEF in the final guidance for sacubitril/valsartan as: • consistent treatment benefit is seen across all subgroups of LVEF in PARADIGM-HF including 963 patients with LVEF >35% and ≤40% • the use of EF cut offs outside of studies has limitations and will likely lead to a greater and unnecessary use of NHS resources. This proposal is in line with the EMA marketing authorisation and would ensure UK patients are able to equally benefit from improved outcomes due to this innovative medicine.	

Consultee	Comment [sic]	Response
Novartis	**Restriction to patients with NYHA Class II-III** The ACD has proposed to restrict the recommendation of sacubitril/valsartan to those patients with NYHA Class II-III based on the limited representation of patients with NYHA Class IV in PARADIGM-HF (Section 4.9 of ACD). In this response we present evidence to support the use of sacubitril/valsartan in patients with NYHA Class IV, specifically with respect to the efficacy and safety of sacubitril/valsartan in patients with NYHA IV. We also consider the impact on patients and prescribers if this restriction is imposed in practice. • ***Efficacy and safety of sacubitril/valsartan in patients with NYHA IV*** Despite a small sample size, post-hoc subgroup analysis for patients with NYHA Class IV at randomisation shows that efficacy and safety are comparable to those of different NYHA Classes in comparison to the enalapril arm. Generally, there are the same trends of improvement in efficacy across different NYHA Classes (See separate Appendix of new evidence, Section 5.2 – Table 4). Regarding safety, in line with results of other NYHA Classes, there is a higher incidence of hypotension and a lower incidence of hyperkalaemia and renal impairment in the sacubitril/valsartan treatment arm for the NYHA Class IV subgroup. (See separate Appendix of new evidence, Section 5.2 – Table 5). The NYHA Functional Classification is one of several clinical measures of HF severity. Additional analyses based on other measures of disease severity, baseline LVEF, NT-proBNP tertiles, and the MAGGIC score were performed to assess whether benefit associated with sacubitril/valsartan treatment in reducing CV death and HF hospitalisation was consistent in HF patients with various severities. Sacubitril/valsartan showed superiority over enalapril across all HFrEF patients including the more severe ones: patients with the highest baseline NT-proBNP tertile, patients with the lowest baseline LVEF tertile, and patients with the highest MAGGIC score.	Comments noted, see FAD sections 1.1, 3.63, 4.9 and 4.20.

Consultee	Comment [sic]	Response
	It is important to note that experience with NYHA Class IV patients in PARADIGM-HF is not only from those patients who were NYHA Class IV at randomisation (N=60), but also from the 323 patients having NYHA Class IV status at any visit during the double-blind period. NYHA class IV is associated with an increased risk of HF hospitalisation. The appropriateness of prescribing sacubitril/valsartan in patients with NYHA Class IV HF is further supported by the efficacy of sacubitril/valsartan in patients who deteriorated to Class IV during the trial by virtue of the fact that they were hospitalised for HF following randomisation. During PARADIGM-HF, 1195 patients (537 in the sacubitril/valsartan group and 658 in the enalapril group) were hospitalised for worsening HF. Even though at time of hospitalisation NYHA Class was not determined, these patients can essentially be considered NYHA Class IV, and subsequently fewer sacubitril/valsartan-treated patients experienced repeat hospitalisations for HF (N=170 of 537, 31.7%) compared to enalapril-treated patients (N=240 of 658, 36.5%), as shown in **Error! Reference source not found.** (please also see Table 18 in the company submission). It should be noted that all HF hospitalisations (first and recurrent) were centrally adjudicated by the Clinical Endpoint Adjudication Committee (CEC). The benefit of sacubitril/valsartan in patients with NYHA Class IV was recognised by the CHMP.	
Novartis	• ***Impact on patients and prescribers*** The number of NYHA Class IV patients randomised in PARADIGM-HF (N=60) was in line with the numbers reported in recently completed HF trials including HEAAL (N=22), CHARM-added (N=78), and SHIFT (N=87) (9-11). All the products studied in the aforementioned trials (e.g. ivabradine) are indicated for the treatment of HF including patients with NYHA Class IV and recommended as such by NICE clinical guidelines. The exclusion of NYHA Class IV patients from the population with HF who can be treated with sacubitril/valsartan would be very confusing for the prescriber, especially in relation to patients who develop transient NYHA Class IV symptoms while taking sacubitril/valsartan. If use of sacubitril/valsartan in NYHA Class IV patients was to be excluded, these “new” Class IV patients should be switched immediately to an ACEi or ARB. The results from PARADIGM-HF on the efficacy and safety in NYHA Class IV patients summarised in this document do not support	Comments noted, see FAD sections 1.1, 3.63, 4.9 and 4.20.

Consultee	Comment [sic]	Response
	this switch. Furthermore, in the event that NYHA Class IV patients improve to NYHA Class III symptoms, their treatment should again be switched to sacubitril/valsartan to enable these patients to have the benefits of improved mortality and reduced hospitalisations. The transient nature of NYHA Class IV symptoms makes it impractical to change treatment in response to each change in the severity of symptoms. This confusion would be the inevitable result if the use of sacubitril/valsartan was restricted to patients with NYHA Class II-III only, for example when patients become dyspnoeic at rest even for short periods of time. Finally it would be counterintuitive and discriminatory not to allow patients with the most severe symptoms who are at higher risk of hospitalisation to benefit from sacubitril/valsartan, especially as this is a relatively small population of approximately 10% of HF patients. Furthermore, an additional aim of therapy is to reduce symptoms. In PARADIGM-HF, a post-hoc analysis of change from randomisation for NYHA was performed. At eight months, NYHA Class was improved for more patients in the sacubitril/valsartan group than in the enalapril group and NYHA Class worsened for fewer patients in the sacubitril/valsartan group than in the enalapril group (Table 23 in the company submission, and **Error! Reference source not found.** below). ***Conclusion*** Overall, Novartis proposes that NICE removes the restriction for NYHA Class IV from the final guidance for sacubitril/valsartan as: • The evidence does not does support this restriction – specifically the data available does not demonstrate any particular efficacy/safety issue in patients with NYHA IV being treated with sacubitril/valsartan • The oscillation of patients between NYHA III to NYHA IV may lead to confusion for the prescriber especially as there would be a requirement to switch therapy. Restricting an innovative drug with likely benefit for subgroup of patients with the most severe symptoms and high risk of hospitalisation is counterintuitive and could lead to inequality of access.	

Consultee	Comment [sic]	Response
Novartis	**1. Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?** For two restrictions specified in Section 1.1 of the draft guidance, we think the Committee has not presented a reasonable interpretation of the available evidence (discussed in Section 0 and 0). These include: • Restriction to patients currently on stable dose of ACEi or ARB • Specification of initiation, titration and monitoring misaligned with NICE chronic HF (CHF) Clinical Guidelines (CG108) With regards to the cost-effectiveness analysis, we welcome the acceptance of the cost-effectiveness model and the conclusion by the Committee that sacubitril/valsartan represents a cost-effective use of NHS resources. However, we feel that some of the assumptions proposed by the ERG and accepted by the NICE committee do not lead to an accurate reflection of the most plausible ICER based on the clinical and cost-effectiveness evidence provided. These specific assumptions (discussed in Section 0 and **Error! Reference source not found.**) include: • The acceptance of the Western Europe subgroup • The concerns raised regarding the quality of life (QoL) modelling and the subsequent acceptance of the ERG's QoL Model approach Finally, Section **Error! Reference source not found.** discusses the impact of both these ERG assumptions on the ICER as well as some issues with replicating the ERG ICER despite the Addendum to the ERG report provided to Novartis on 10 November 2015. **Restriction to patients currently on stable dose of ACEi or ARB** The ACD has proposed to restrict the recommendation of sacubitril/valsartan to those patients who are already taking a stable dose of ACEi or ARBs, based on a lack of evidence for people who were treatment-naïve to ACEi or ARB (Section 4.2 of ACD). In this response we present a series of arguments to support the use of	Comments noted, see FAD sections 3.64 to 3.67, 4.2, 4.5, 4.11 and 4.20.

Consultee	Comment [sic]	Response
	sacubitril/valsartan in ACEi/ARB-naïve patients, which contradicts the interpretation of clinical evidence as reported in the ACD, including the efficacy and safety of sacubitril/valsartan in ACEi/ARB-naïve patients as well as the impact on NHS resource use, burden and risk to patients. • ***Efficacy of sacubitril/valsartan in ACEi/ARB-naïve patients*** There are no data to suggest, nor is there any clinically sound rationale why, patients who have not been previously treated with therapies that block the renin-angiotensin-aldosterone system (RAAS; ACEis/ARBs) receiving sacubitril/valsartan would not receive similar efficacy benefits to patients previously treated with ACEis/ARBs. The pivotal clinical trial for sacubitril/valsartan, PARADIGM-HF, tested the additional benefit of inhibiting neprilysin (sacubitril) over and above that of blocking RAAS (by valsartan/ ARB). PARADIGM-HF showed that neprilysin inhibition on top of RAAS blockade reduced CV death and HF hospitalisation more than RAAS blockade alone. Additionally, there is no evidence that the neurohormonal response to HF is different in ACEI/ARB-naïve patients. The treatment effect of sacubitril/valsartan was preserved in the closest proxy to ACEi/ARB-naïve patients in PARADIGM-HF – patients with a short time since diagnosis of HF (≤3 months, see separate Appendix of new evidence, Section 5.3). Furthermore, the PARADIGM-HF trial showed a consistent efficacy profile for sacubitril/valsartan across the spectrum of HFrEF severity (based on the MAGGIC risk score,) The CHMP discussed the ACEi/ARB-naïve population based on the above points and concluded that a similar benefit of sacubitril/valsartan can be expected in patients not previously treated with ACEi/ARB. • ***Safety of sacubitril/valsartan in ACEi/ARB-naïve patients*** The safety and tolerability findings from the ACEi/ARB-naïve patients with HFrEF in the TITRATION study were very similar to the overall population. The majority of ACEi/ARB-naïve patients were able to achieve and maintain the 200 mg twice daily (bid) target dose of sacubitril/valsartan following gradual up-titration from 50 mg bid. Furthermore, sacubitril/valsartan hypertension studies included a significant number of ACEi/ARB-naïve patients which demonstrated a similar safety profile to the	

Consultee	Comment [sic]	Response
	overall hypertension patient population (See separate Appendix of new evidence, Section 5.4). The limited experience in ACEi/ARB-naïve patients is clearly described in the SmPC and a lower starting dose is recommended. Other than this recommendation, there are no explicit safety concerns highlighted in the SmPC regarding using sacubitril/valsartan in an ACEi/ARB-naïve population. • ***Impact on NHS resource use and burden and risk to patients*** Additionally, the restriction to patients currently on stable dose of ACEi or ARB can also pose a risk to ACEi/ARB-naïve patients and impact NHS resource use. In the event that sacubitril/valsartan therapy could not be immediately initiated in ACEi/ARB-naïve patients, therapy would have to be initiated with an ACEi before the patient could be switched to sacubitril/valsartan (after a 36-hour washout period). This has the potential to double the number of contacts with health care professionals required to establish the patient on what is a superior therapy, adding unnecessary complexity to the process of initiating treatment. Ultimately this leads to additional NHS resource use and a substantial burden and risk to the patient, especially as many patients are frail with multiple co-morbidities and concomitant treatments. Importantly, the treatment benefit of sacubitril/valsartan versus ACEi for the primary composite endpoint and HF hospitalisations in PARADIGM-HF was evident as early as within the first 30 days (See **Error! Reference source not found.**, in Novartis comments on the ACD). In addition, the most common cause of death was sudden death (36.23% of patients who died), with significantly less patients dying of sudden death in the sacubitril/valsartan arm compared to the ACEi arm (See **Error! Reference source not found.** in Novartis comments on the ACD). Therefore, delay in initiating sacubitril/valsartan will discriminate against ACEi/ARB-naïve patients, who will be denied the additional benefits of neprilysin inhibition and will be at increased risk of experiencing a potentially fatal event during the ACEi treatment period.	

Consultee	Comment [sic]	Response
Novartis	***Conclusion*** Novartis proposes that NICE removes the restriction to patients on a stable dose of ACEi/ARB as: • PARADIGM-HF showed that neprilysin inhibition on top of RAAS blockade reduced CV death and HF hospitalisation more than RAAS blockade alone. • Time since diagnosis as a proxy to duration of exposure to RAAS inhibition showed no difference in treatment benefit with sacubitril/valsartan over ACEi, hence there is no evidence that ACEi/ARB-naïve patients would respond differently than patients on a stable dose of ACEi/ARB. • There are no anticipated safety issues associated with initiating in ACEI/ARB naïve patients (supported by the SmPC and the TITRATION study). • This restriction will result in initiation of an inferior therapy prior to sacubitril/valsartan leading to substantial burden to patients, putting patients at unnecessary risk of hospitalisations and death, and additional NHS resource.	Comments noted, see FAD sections 4.2 and 4.20.
Novartis	**2.2 Treatment should be started by a HF specialist with access to a multidisciplinary HF team. Dose titration and monitoring should be done by the HF specialist, or in primary care by either a GP with a special interest in HF or a HF specialist nurse.** • ***Clinical expert opinion at NICE Committee meeting*** Novartis has noted that in Section 4.10 of ACD, it is stated that the clinical experts at the NICE Committee meeting (held on 18 November 2015) specified the above restrictions to how sacubitril/valsartan should be initiated, titrated and monitored (as detailed in Section 1.2 of ACD). However, that level of detail was not discussed or agreed in the public session of the committee meeting, so we are very concerned that the guidance does not accurately capture the views expressed by the clinical experts at the meeting or the wider clinical community. • ***Alignment with NICE Clinical Guidelines***	Comment noted, see FAD sections 1.2 and 4.11

Consultee	Comment [sic]	Response
	NICE expressed in Section 4.10 of the ACD that it was the intent to align this service recommendation with NICE CHF Clinical Guidelines (CG108). We note that in the NICE Guidelines, roles have not been specified, with regards to types of healthcare professional who should initiate, titrate and monitor HF treatment. NICE CHF Clinical Guidelines (CG108) state that 'HF care should be delivered by a multidisciplinary team with an integrated approach across the healthcare community [...] the team will decide who is the most appropriate team member to address a particular clinical problem'. Therefore, the ACD wording with regards to delivery of HF services is not aligned with the NICE Clinical Guidelines, which state that the HF multidisciplinary team decides the most appropriate team member to manage HF treatment. • ***Inequality of access and adoption of innovation*** Specifying individual roles and types of healthcare professionals to manage sacubitril/valsartan in practice could lead to confusion and unintended inequality of access as there are wide geographical differences across England in how HF multidisciplinary teams are constituted and operated. This heterogeneity is likely to increase further given the new models of care being introduced across the NHS. How sacubitril/valsartan is implemented locally should be left to the multidisciplinary team to decide as indicated by CG108. Specifying a "specialist" in the guidance (even though this could be a HF nurse, GPSI, or HF cardiologist) could lead to lack of clarity and imply that patients must see a HF specialist in secondary care leading to delay and increased risk to patients. Additionally, NICE accepts that sacubitril/valsartan is an innovation in HF (vs ACEis/ARBs), but the ACD proposes service restrictions beyond CG108, which will impair the ability of NHS to adopt this innovation thereby resulting in patients being unable to benefit from the improved outcomes equally. • ***Conclusion*** Novartis proposes that the wording in Section 1.2 of the ACD should be amended in the final guidance for sacubitril/valsartan in order to align with the NICE CHF Guidelines (CG108) with regards to the delivery of HR care. We propose that the	

Consultee	Comment [sic]	Response
	guidance should instead read “Treatment with sacubitril/valsartan should be initiated, titrated and monitored by the multidisciplinary heart failure team, as defined in the NICE CHF Clinical Guidelines (CG108).”	
Novartis	**Western Europe subgroup in cost-effectiveness model** • ***Factual inaccuracy regarding post-hoc analysis*** It is not accurate to state that the Western Europe subgroup presented in the company submission was the post-hoc analysis i.e. excluding Israel and South Africa (pg. 37 of ACD). In fact, the Western Europe subgroup presented in the submission was the pre-specified subgroup (with Israel and South Africa included for operational reasons) (please see Table 13 as well as Section 5.9.3 in the company submission which states that ‘The model was run for 39 subgroups identified a priori in the statistical analysis plan for PARADIGM-HF’). • ***Point estimate hazard ratio from Western Europe subgroup*** The Committee concluded that the Western Europe subgroup was the most representative of clinical practice in England, but that the lack of statistical significance associated with the Western Europe subgroup would not factor in its decision-making and it would therefore focus on the point estimate hazard ratio in this subgroup (0.89 95% CI, 0.74-1.07 for primary composite endpoint) as it is in the same direction and supports the estimates for the overall trial population (0.80 95% CI, 0.73-0.87 for primary composite endpoint). However, it is inappropriate to apply the hazard ratio from a subgroup where there is no evidence of an interaction effect. The article by Rothwell et al. state the correct analysis to consider when assessing subgroups is the test of subgroup-treatment effect interaction. In Section 4.5 of the ACD the Committee considers and accepts evidence which Novartis believes contradicts the appropriateness of using the HR from the Western	Comment noted and factual inaccuracy has been corrected; see FAD sections 4.5, 4.18 and 4.20.

Consultee	Comment [sic]	Response
	Europe subgroup in the ERG's analysis, because: • tests of interaction showing no evidence of treatment-effect modifiers by region (p=0.3737) for the primary composite endpoint. The hazard ratios within subgroup assume independence (of each other). This is a strong assumption and with an interaction p-value that is not significant further indicates that the overall hazard ratio rather than the subgroup hazard ratio should be used as there is no significant difference the subgroups vary (from the overall). • Western Europe subgroup is not powered to detect statistically significant differences in the primary endpoint • across all pre-specified subgroups, sacubitril/valsartan was consistently better than ACEi with regard to the primary endpoint, and all hazard ratio point estimates suggested a benefit in the sacubitril valsartan group; because the results of subgroup analyses were consistently positive, any differential interpretation of treatment effect in subgroups should be undertaken with caution Furthermore, in Section 4.5 it is stated that 'The Committee noted that the ERG had considered the Western Europe subgroup to be the most representative of clinical practice in England. It understood that the ERG based this on the race, age and cardiac device use of the Western Europe subgroup.' The ERG rationale that Western Europe is the most representative of the English population could also be argued for the Caucasian subgroup with the latter subgroup being twice the size of the Western Europe subgroup. A large proportion of patients in the Western Europe subgroup ([redacted], See Question A1 in Novartis response to ERG clarification questions) belong to the Caucasian/White subgroup. The average age in the Caucasian/White subgroup for sacubitril/valsartan is [redacted] years and enalapril [redacted] years (See CSR - Table 14.1-3.1.3) therefore is comparable to the Western Europe subgroup (for sacubitril/valsartan is [redacted] years and enalapril [redacted] years respectively). Face validation of the point estimate HR for the primary endpoint in PARADIGM-HF for the Western Europe subgroup and the Caucasian/White subgroup generates counterintuitive results (0.89 versus 0.80 respectively). The race subgroup analysis also show no p-value for interaction so if the same logic was applied (which we do not support) the Committee should take into account the fact that, the Caucasian subgroup shows a significant benefit for sacubitril/valsartan (CV death HR 0.80 95%	

Consultee	Comment [sic]	Response
	CI, 0.70, 0.93). Caution should always be applied when interpreting subgroup analyses in clinical trials. When the full trial population is split into smaller subgroups which are not powered to detect statistically significant differences in treatment effect, the likelihood of chance findings means it is improbable that the observed point estimate HR between two groups will be the same, even if the true treatment effect is not different between them. ***Conclusion*** Novartis proposes that the Committee should use PARADIGM-HF data from the overall population in the model (including efficacy data) as this would be a more accurate reflection of the treatment effect, and therefore the cost-effectiveness, of sacubitril/valsartan. This would lead to a most plausible ICER of £19,843 vs. the ERG's ICER of £29,478, when applying all other ERG assumptions.[1] • There is no statistical basis for applying a subgroup HR if tests of interaction showed no evidence of treatment-effect modifiers by region. • There is no face validity in concluding that the Western Europe subgroup (including South Africa and Israel) was the most representative of clinical practice in England as other (larger) subgroups that could be as representative (i.e., Caucasian) are not considered.	
Novartis	2.4 **Quality of life (QoL) in cost-effectiveness model** A linear mixed regression model based on EQ-5D trial data from PARADIGM-HF	Comments noted, see FAD section 4.15.

[1] This cost per QALY result maintains all other ERG ICER assumptions (see Table 86 of the ERG report) with the exception of the Western Europe subgroup efficacy, baseline characteristics and hospitalisation data.

Note, that there were issues with replicating the ERG ICER despite the Addendum to the ERG report provided to Novartis on 10 November 2015 - Novartis generated a final ERG ICER of £26,061 per QALY based on this (See Section **Error! Reference source not found.**).

Consultee	Comment [sic]	Response
	was applied in the cost-effectiveness model to predict utility scores. The utility model included a small but highly significant treatment effect in favour of sacubitril/valsartan after controlling for the effects of hospitalisations and adverse events. The baseline utility score was based on patient-level data from PARADIGM-HF. The ERG expressed concerned regarding the validity of the QoL analysis presented in the submission which the Committee agreed with, specifically: • The ERG could not be certain whether there was a baseline statistically significant difference in patients' EQ-5D scores between the 2 treatment groups of sacubitril/valsartan and enalapril. It suggested the statistical test performed by the company (two-sample t-test), that found there was no statistically significant difference, might not be appropriate. • 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 QoL across the treatment groups. The ERG suggested that, assuming patients in a healthier state would have better outcomes, the potential imbalance in disease severity might have favoured the sacubitril/valsartan group. Table 3 below (see Novartis comments on the ACD) presents the differences between the Novartis and ERG QoL modelling approach – both models are largely identical with the exception of the sacubitril/valsartan treatment effect, baseline EQ-5D and calculation in model.	
	The selection of the EQ-5D at baseline from PARADIGM-HF data follows the NICE reference case, which states that EQ-5D should be sourced from the clinical trial, and if not available data can be sourced from the literature. However due to the run-in period in PARADIGM-HF, we accept the exploration of a lower baseline EQ-5D from the literature to understand the potential impact on the ICER (which was minimal). However, the removal of the sacubitril/valsartan EQ-5D treatment effect from the QoL model was based on a scientifically and methodologically incorrect conclusion that there may have been a statistically significant difference in patients' EQ-5D scores at baseline which may have biased the EQ-5D outcomes in favour of sacubitril/valsartan. The below sections provide argumentation against the assumption of differential baseline scores for both EQ-5D and KCCQ measures from PARADIGM-HF.	Comments noted, see FAD sections 4.15 and 4.20.

Consultee	Comment [sic]	Response
Novartis	***EQ-5D*** It is important to note that testing for baseline differences between the intervention and control group in randomised controlled trials is typically not appropriate as differences at baseline across both groups are by definition due to chance given randomisation. Furthermore, the EQ-5D analysis was based on a repeated measures ANCOVA model which includes treatment, region, visit, and treatment-by-visit interaction as fixed effect factors and baseline value as a covariate with a common unstructured covariance for each treatment group. Therefore, any (random) differences or imbalance in baseline EQ-5D have been controlled for and have not affected the results of either the trial or the model. With regards to the ERG's specific concern around the appropriateness of the t-test used to assess similarity of means at baseline, 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 (24). Both the means and standard deviations from the two samples are almost identical. This supports the argument that the t-test is an appropriate statistical test to assess similarity of mean EQ-5D at baseline. Therefore, the ERG's concerns regarding a potential difference in baseline EQ-5D biasing the trial results in favour of sacubitril/valsartan are unfounded and not based on evidence. As such, we argue that the highly statistically significant EQ-5D treatment effect associated with sacubitril/valsartan is valid (and not a product of bias) and should be included in the base case model analysis. The QoL benefit of sacubitril/valsartan compared to enalapril demonstrated with EQ-5D is further supported by NYHA shift and KCCQ outcomes showing benefit of sacubitril/valsartan in terms of symptoms and QoL. More people in sacubitril/valsartan arm were reporting improvement in symptoms as evidenced by KCCQ and NYHA. ***KCCQ*** The ERG expressed concern that a statistically significant difference in KCCQ	Comments noted, see FAD sections 4.15 and 4.20.

Consultee	Comment [sic]	Response
	scores at baseline could be considered clinically meaningful and that this could potentially bias the trial and model outcomes, as well as imply a difference of EQ-5D at baseline in the same PARADIGM-HF population. A study by Spertus et al.(25) states that a minimal difference of 5 points over time depicts a clinically meaningful difference in HF. Even though this is not across treatments, this is transferable to this example. The difference between sacubitril/valsartan and KCCQ at baseline is statistically significant, however not clinically meaningful as it is 1.26 points, substantially below the 5 point mark. Further to the above argument regarding the clinically meaningful difference in KCCQ scores, the ERG did not acknowledge that the KCCQ analysis in PARADIGM-HF was in fact adjusted for at baseline (in contrast to their assumption that KCCQ was not controlled for at baseline in p.161 of ERG report,). The KCCQ analysis was based on a repeated measures ANCOVA model which includes treatment, region, visit, and treatment-by-visit interaction as fixed effect factors and baseline value as a covariate with a common unstructured covariance for each treatment group. Therefore, any (random) differences in baseline KCCQ have been controlled for and have not affected the results of either the trial or the model. ***Conclusion*** Novartis proposes that the Committee should accept the utility gain of 0.011 for sacubitril/valsartan as this is an evidence-based outcome and would be a more accurate reflection of the treatment effect, and therefore the cost-effectiveness, of sacubitril/valsartan. This would lead to a most plausible ICER of £25,607 vs. the ERG's ICER of £29,478 when applying all other ERG assumptions.[2] • The key concern is that the EQ-5D analysis did not adjust for baseline difference. However, this is incorrect as the EQ-5D analysis was based on	

[2]This cost per QALY result maintains all other ERG ICER assumptions (see Table 86 of the ERG report) with the exception of the statistically significant EQ-5D benefit associated with sacubitril/valsartan.

Note, that there were issues with replicating the ERG ICER despite the Addendum to the ERG report provided to Novartis on 10 November 2015 - Novartis generated a final ERG ICER of £26,061 per QALY based on this (See Section **Error! Reference source not found.**).

Consultee	Comment [sic]	Response
	a repeated measures ANCOVA model which controls for any (random) differences or imbalance in baseline EQ-5D and has not affected the results of either the trial or the model. • Additionally, the EQ-5D benefit is supported by other symptom and QoL measures in the trial including KCCQ and NYHA shift some consistent QoL benefit and symptom reduction with sacubitril/valsartan	
Novartis	2.5 **Summary of cost-effectiveness model issues** Please note Novartis was able to replicate the ERG's ICER (£19,843) with all the following modifications incorporated (Table 86 in ERG report): • Mean age at baseline of 75 years • Change in baseline utility to reflect Berg et al utility (0.72) • Change in QoL modelling approach • Change in pharmaceutical costs to reflect drug target dose • Change in pharmaceutical costs to reflect the cost of ramipril However, Novartis was not able to exactly replicate the ERG's ICER with all changes incorporated (£29,478) nor the ICER compared with base case for the Western Europe subgroup (£20,550) in Table 86 of the ERG report, even when precisely following the instructions detailed in the 'Addendum to the ERG report' (received on the 10th November 2015). Following these instructions, Novartis generated a final ERG ICER of £26,061 per QALY and an ICER versus base case for the Western Europe subgroup of £19,948. Novartis noted that the modifications associated with the Western Europe subgroup overrode previous ERG assumptions (i.e. any changes to baseline characteristics), which could explain these discrepancies. However, even when Novartis re-incorporated these previous assumptions around baseline characteristics, the ERG's ICER still could not be exactly replicated. Novartis proposes that the ERG updates the Addendum to the ERG report to be able to replicate all ICERs in Table 86 and that this is reflected in the final guidance.	Comment noted. The detailed instructions to implement ERG's exploratory analyses were provided to the company. The company confirmed that it could replicate the analyses presented in table 86 of the ERG report. Sections 4.20 and 5.1 of the FAD has been updated.

Consultee	Comment [sic]	Response
	Additionally, Novartis proposes that the Committee use PARADIGM-HF data from the overall trial population and accept the utility gain of 0.011 for sacubitril/valsartan (as discussed above in Sections 2.3 and 2.4) to generate the most plausible ICER for sacubitril/valsartan. Implementing the above changes and keeping the remaining ERG ICER assumptions (as per Table 86 of the ERG report) would lead to a most plausible ICER of £19,530 (vs. the ERG's ICER of £29,478). **3 Are the provisional recommendations sound and a suitable basis for guidance to the NHS?** In Section 4.19 of the ACD it is stated that 'the Committee was aware that sacubitril/valsartan has been granted a promising innovative medicine (PIM) designation by the Medicines and Healthcare Products Regulatory Agency. The ACD does not mention that sacubitril/valsartan received a positive opinion for the Early Access to Medicine Scheme (EAMS) by the MHRA. Novartis proposes the following change to the wording to Section 4.19 In addition, the Committee was aware that sacubitril/valsartan has been granted a promising innovative medicine designation and received a positive opinion for the Early Access to Medicine Scheme by the Medicines and Healthcare Products Regulatory Agency. Additionally, Novartis proposes that Section 5.1 states that drugs introduced through EAMS are expected to be introduced prior to the 90 day limit set out in the regulations. CCGs and Trusts will be expected to implement the NICE TA within a 30 day period (https://www.england.nhs.uk/wp-content/uploads/2015/10/eams-letter-oct15.pdf). 4 **Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?** Novartis does not foresee any significant equality issues above associated with the use of sacubitril/valsartan in people with HFrEF, other than the issues we have	

Consultee	Comment [sic]	Response
	highlighted throughout the document that are as a result of the restrictions proposed by NICE.	
British Society for Heart Failure (BSH)	The BSH feels that sacubitril valsartan should be considered the first line drug for patients with heart failure secondary to left ventricular systolic dysfunction LVSD due to the overwhelming benefit seen in the key outcome study (PARADIGM-HF). The consultation document appears to place sacubitril valsartan as second line agent for the treatment of heart failure with LVSD. Data from the PARADIGM-HF study demonstrate the clear superiority of sacubitril valsartan over the current gold standard treatment of angiotensin converting enzyme (ACE) inhibitor (in this study the ACE inhibitor was that with greatest evidence in heart failure, enalapril). Restricted use will inevitably lead to many patients with heart failure being disadvantaged.	Comments noted, see FAD sections 4.2 and 4.20
British Society for Heart Failure (BSH)	**The BSH does not agree with a number of criticisms of data from PARADIGM-HF, including but not restricted to:** (i) Geographical heterogeneity. The ERG analysis using a subgroup of PARADIGM that was not pre-specified made no sense; a subgroup analysis is, by definition, less likely to show a statistically meaningful difference simply due to it containing smaller numbers of patients and events. The ERG uses the fact that a number of the endpoints in its analyses did not reach statistical significance to suggest limiting the use of sacubitril valsartan; and yet it did not demonstrate any heterogeneity in outcomes between geographical regions. The conclusion that patients in western Europe did not benefit from sacubitril valsartan is specious. There is a manuscript submitted indicating there is no geographical variation in the benefit from sacubitril valsartan within this study (ii) Age of the population being different to standard UK heart failure population. This is consistent for trials across all areas of medicine and relates to the whole evidence base upon which we practice clinical medicine. It is inappropriate to focus upon age. The average age is similar to that seen in other key heart failure trials that have established ACE inhibitors, beta blockers, mineracorticoid antagonists, devices	Comments noted, see FAD sections 4.5, 4.13, 4.14 4.16, 4.18 and 4.20.

Consultee	Comment [sic]	Response
	(ICD, CRT), and ivabradine (TA267) in heart failure guidelines (including NICE chronic and acute heart failure guidelines). (iii) The suggestion (section 4.7) that the study is not applicable to England since enalapril was used as the comparator. In a clinical trial, there needs to be a standard comparator across all countries in the study. The United States Food and Drug Administration (FDA) mandated the choice of enalapril as the comparator as the ACE inhibitor with best evidence in chronic heart failure. Indeed as there is no trial of the effectiveness of ramipril in chronic heart failure, current UK practice is inferior by not routinely using enalapril and the magnitude of benefit of sacubitril valsartan over other ACE inhibitors in UK practice might even be greater than that seen in PARADIGM-HF.	
British Society for Heart Failure (BSH)	**The majority of the BSH does not agree that sacubitril valsartan should not be available for patients presenting with newly diagnosed symptomatic LVSD** Whilst acknowledging that PARADIGM-HF did not specifically include newly diagnosed patients, we have major concerns about the potential for mixed messages and prescribing chaos amongst patients, heart failure nurse specialists, GPs and other heart failure specialists if sacubitril valsartan is not permitted for use in patients with newly diagnosed symptomatic LVSD. Firstly, in PARADIGM-HF the clinical superiority of sacubitril valsartan compared to enalapril was evident to be effective within 30 days of initiation of trial therapy. Therefore, failing to start patients on sacubitril valsartan rather than ACE inhibitors will disadvantage patients who are ACE inhibitor naïve. Secondly, the requirement for ACE inhibitor naïve patients to be initiated, and stabilized, on ACE inhibitor will present logistical problems which are likely to expose patients to potential prescribing errors and risk of adverse events. Practical concerns were raised as to how this might be delivered effectively by heart failure services in the NHS. For example, it would be extremely challenging to provide robust education and clinical support for a pathway that focuses on ACE inhibitor	Comments noted, see FAD sections 4.2, 4.18 and 4.20.

Consultee	Comment [sic]	Response
	initiation and uptitration for a few weeks to months, followed by an arbitrary period of time to see if the patient remains NHYA II-III (how long; 1 day to 1 year?). These patients will need to be retained in (already overburdened) heart failure services, leading to delays in assessment of new cases or those discharged from hospital as per NICE acute heart failure quality standards. The BSH feels that the requirement to initiate and up-titrate a therapy (ACE inhibitor), with the clear intention of then switching to a superior therapy, conveys mixed messages to patients and carers, as well as to health care professionals. Such a strategy will inevitably lead to the need for additional contacts between patient and health care professional. Moreover, the strategy will require a wash-out period (a period of non treatment) between ACE inhibitor and sacubitril valsartan, leading to a clear risk of overlap of the two therapies and increasing the risk of major adverse events, in particular angioedema. In summary, in clinical practice restriction to patients previously tolerant of ACE inhibitors will lead to significant increase in NHS work and will be demanding on resources. It is likely to disadvantage patients and potentially result in inequitable access depending upon local pathways. Committing the patients to an avoidable wash-out/transfer period may put patients at unnecessary risk.	
British Society for Heart Failure (BSH)	**The BSH does not agree that sacubitril valsartan should be restricted to patients with LVEF<35%** PARADIGM-HF recruited patients with a left ventricular ejection fraction of 40% or lower. There are major variations in cardiology departments with respect to the reporting of echocardiogram assessments of left ventricular function. Due to the challenges of accurate and reproducible documentation of LVEF, many departments report severe, moderate to severe, moderate or mild left ventricular impairment. Data from PARADIGM-HF (see slide) show a consistent benefit of sacubitril valsartan across the range of LVEF with no evidence of lesser benefit in patients with LVEF between 35 and 40%. The BSH feels it would be more appropriate to recommend use in patients with LVSD and either LVEF<40% or LVSD reported as moderate or worse.	Comments noted, see FAD sections 4.8 and 4.20.
Pumping Marvellous Foundations	After considering the appraisal committee's preliminary recommendations please find our response. Point 1.1 Noting the committee recommendations we are surprised and disappointed that NICE may potentially recommend a course of action which involves titrating up on	Comments noted, see FAD sections 1.1, 1.2, 4.2, 4.9, 4.11 and 4.20.

Consultee	Comment [sic]	Response
	less than optimal drugs initially where it seems that patient concerns and their welfare has not been taken into consideration. Considering the timings of when these drugs are prescribed, usually on diagnosis potentially when the patient is at their most vulnerable. Why would you want to prescribe a drug that wasn't the best for the patient? We are concerned with the level knowledge and awareness and therefore usage of the NYHA scale in primary care especially where the NYHA scale is a necessity for consideration of prescribing Sacubitril Valsartan. Point 1.2 Noting the committee's recommendations around the logistics of distributing / prescribing Sacubitril Valsartan through a HF specialist with access to an MDT and with dose and titration monitoring completed either in the acute setting or in primary care through GPSI or HF specialist nurse. We feel this is a rather limited and counter-productive system which will end up with effecting the patients and their families QOL as well as costing the NHS as the up-titration process has to be repeated. The question of resource is a key element to our feedback where 1. We would question the availability of HF nurse prescribers in both acute and community settings? NHS England doesn't know how many HF nurses it employs never mind where 2. We question the availability of GPSI's across the CCG's 3. For instance in the primary care setting in two local adjoining CCG's being served by a DGH where there is a population of 500,000 plus with a high incidence of CHD / HF there is one GPSI and one HF nurse prescriber in the community, this pushes the medicine management question back on the acute system. This would inevitably lead to under prescribing and curtailing patients access to the best drug,; one could assume this creates an underserved population due to lack of access 4. This recommendation fly's in the face of the Steven's plan for the NHS where, if following the recommendations of taking services out of the acute and into the community then this demonstrates the reverse as the primary care management will be overwhelmed due to the lack of resource 5. We would like to understand from the committee their understanding of what an MDT looks like as this seems to be at the HUB of the prescribing process and we know this is not consistent across England and Wales.	

Consultee	Comment [sic]	Response
	In conclusion We feel that the recommendation mirrors the clinical trial data in the Paradigm-HF Trial. However trial conditions don't mirror real world challenges. We are very concerned about patients having to be up titrated on a less than optimal therapy then and only then to be taken off it considering the hard work and effort it takes for the majority of patients to climb the ladder of titration to having to climb the same hill with Sacubitril Valsartan. This is a disservice to the HF patients and their families. We strongly believe that economic pressure has crafted this response which mirrors the ERG's discussion points. We don't feel after analysing the committee papers that the recommendations have taken into account the patient experts or the clinical experts recommendations. The recommendations are clearly aligned with narrowing the patient group which will benefit this new technology therefore reducing the economic impact of a new in class therapy for HF patients. This course of action will lead to the creation of "an underserved class of HF patient" in England and Wales and will, by narrowing the bandwidth not have the desired effect of what by a "lay" person's best guess is a blockbuster therapy. You may forgive me for being direct but as a patient and human and not being emotional about my response I don't think people get heart failure. It is not a sexy condition, count up the amount of times it's mentioned in the press. Heart failure patients had no voice before the Pumping Marvellous Foundation which was formed less than 5 years ago. Just look at NICE and how they have struggled with patient representation for heart failure before the Pumping Marvellous Foundation came along. The patient population estimates vary wildly from 500,000 through to nearly million. I am afraid this decision may put back a clear and present opportunity to impact on the QOL of heart failure patients and their families. Does the committee really think that the decision to pursue a suboptimal treatment as a first line in treating chronic HF is the best the NHS can do? Does the committee really think the NHS has the capacity to achieve this and that individual clinicians will view this as a positive spin on this new drug, does it give them the confidence to pursue a more than normal route of getting the patient optimised on said drug.	
British Cardiovascular Society	**1.1 Sacubitril valsartan is recommended as an option for treating people with heart failure with reduced ejection fraction, only in people:** • **with New York Heart Association (NYHA) class II to III chronic heart**	Comments noted, see FAD sections 1.1, 1.2, 4.2, 4.8, 4.9, 4.11 and 4.20. As sacubitril valsartan was available to the NHS via the granting of an Early Access to Medicines Scheme positive opinion, section 1.3 of the ACD does not apply to the final guidance. Therefore, it

Consultee	Comment [sic]	Response
	failure and • **who are already taking a stable dose of angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor-blockers (ARBs) and** • **with a left ventricular ejection fraction of 35% or less** The licence for sacubitiril valsartan is for symptomatic patients with reduced ejection fraction heart failure. The requirement for a documented EF of < 35% and for NYHA class II and III symptoms only will add an extra layer of complexity in identifying patients who may benefit from this treatment. The accurate assessment of EF is fraught with difficulties and a patient with an EF of 36% will benefit from this drug and not be eligible on the basis of the NICE recommendation. Although accepting that there is limited data, not allowing patients to be initiated on Sacubitril valsartan will lead to significant logistical issues. A new patient with heart failure will be started on an ACE-I or ARB – take several weeks to reach a stable dose, by which time they may have been discharged from hospital care and then will need to be reassessed to swap over. In the case of ACE-I use, the patient will have to stop their drug for 3 days before Sacubitril can be administered. This process will lead to increased hospital visits and increased costs. **1.2 Treatment with sacubitril valsartan should be started by a heart failure specialist with access to a multidisciplinary heart failure team. Dose titration and monitoring should be done by the heart failure specialist, or in primary care by either a GP with a special interest in heart failure or a heart failure specialist nurse.** This recommendation is appropriate initially – but many patients on stable therapy do not necessarily get reviewed by a GPwSI or HF Specialist nurse and so monitoring should be carried out by the patient's GP who may not have a special	has been removed from the FAD.

Consultee	Comment [sic]	Response
	interest in HF. **1.3 People whose treatment with sacubitril valsartan is not recommended in this NICE guidance, but was started within the NHS before this guidance was published, should be able to continue treatment until they and their NHS clinician consider it appropriate to stop.** Agree with this statement Sections 3.5 / 3.34 Patients in clinical trials rarely match routine clinical practice In terms of age or gender. This alone would be insufficient reason to not provide a positive recommendation. Sections 3.10 / 3.37 A subgroup analysis that shows patients in Western Europe gain less benefit from Sacubitril is not valid statistically and should not be used to generate the recommendation. Sections 3.36 Enalapril is the best comparator, as it is the ACE-I with the greatest evidence in chronic heart failure. Although ramipril is most commonly used in the UK, it is often dosed incorrectly (should be given bd rather than od) and only has post-MI data rather than true CHF evidence.	

Comments received from clinical experts and patient experts

Nominating organisation	Comment [sic]	Response
British Society for Heart Failure	I have been asked to comment on the ACD having attended the appraisal meeting on the 18th November as Clinical expert representative from the British Society for Heart Failure. It is important to clarify that the response below is my own and not held by all members of the BSH board. A separate response will be submitted by the BSH board putting forward that viewpoint. My response: I welcome the recommendation for use of sacubitril valsartan as an option for the treatment of heart failure with reduced ejection fraction. I consider that the requirement for previous exposure to ACE inhibitor or ARB is prudent, as we have yet to learn about the safety profile in ACE inhibitor naïve patients. A careful approach, in line with the Paradigm study inclusion criteria appears justified given that, in the US, sacubitril valsartan is subject to two post marketing requirements by the FDA: 1. To conduct a multi centre, randomized, double-blind, active-controlled trial to evaluate the effects of sacubitril valsartan compared to valsartan on cognitive function (as neprilysin is a major beta amyloid-degrading enzyme in the brain). Final report due 2022. 2. To conduct an epidemiologic study using claims or electronic health records data to evaluate the incidence of angioedema in Black patients treated with sacubitril valsartan compared to a control drug. Final report due 2019. The information above was not found in the information pack, but is stored online at http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2015/207620Orig1s000ltr.pdf Therefore I did not consider it as confidential and have submitted this single response. I am happy to submit another with this part removed at NICE's recommendation.	Comments noted, see FAD sections 4.7 and 4.10.

Comments received from commentators

No response received from commentators

Comments received from members of the public

Role*	Section	Comment [sic]	Response
Professor of Cardiovascular Medicine	Comments on individual sections of the ACD:	The document ignores that the PARADIGM trial only enrolled STABLE patients with high BNP levels(>150 pg/ml) or high NT proBNP (>600 pg/ml). Stable patients have mean BNP levels of 93 pg/ml or NT proBNP levels of 953 pg/ml (Cardiovasc Drugs Ther 2008, 22(4) 305-311). Same is true in Am J Card 2006, 98, 1248. Stable patients have lower BNP levels than the BNP level used at the diagnostic stage. In fact mean levels of BNP in PARADIGM were 255 pg/ml and NT pro BNP of 1600 pg/ml. Therefore only stable patients with particularly high BNP levels were recruited in PARADIGM. By ignoring this key entry criterion, your advice will treat more heart failure patients than would be treated in PARADIGM where the benefit lies. The total cost to the country of using this expensive drug in a wider and somewhat milder group of patients than got in to the PARADIGM trial will increase the UK drug bill. Also we cannot be sure that the benefit will outweigh the risk when giving this drug also to milder patients than got in to the PARADIGM trial	Comment noted, see FAD section 4.11.
Professor of Cardiology	Comments on individual sections of the ACD	The Committee noted that the NICE guideline on chronic heart failure in adults: management defined a specialist as a physician with a subspecialty interest in the management of heart failure and who leads a specialist multidisciplinary heart failure team of professionals with appropriate competencies from primary and secondary care.• I feel that consistencies should be employed across different NICE guidelines. The NICE guideline across chronic heart failure defines a HF specialist as either a cardiologist with a HF interest or a HF nurse or physician with a special interest in HF, that would class a GPSI in HF as such a specialist role. Indeed given that several GPs are on the guideline committee for HF (Ivan Bennet, Fuaz Ahmet), I feel that the definition of a HF specialist is far too restrictive. I think that specialist should be defined in a similar manner to other NICE guidance.	Comment noted see, FAD sections 1.2 and 4.11.
Professor of Cardiovascular	Comments on individual	I welcome the positive recommendation for sacubitril valsartan. However aspects of the Assessment Group analysis are very poor, and parts of the	Comments noted, see FAD sections 4.2, 4.5 4.8, 4.18 and 4.20.

* When comments are submitted via the Institute's web site, individuals are asked to identify their role by choosing from a list as follows: 'patent', 'carer', 'general public', 'health professional (within NHS)', 'health professional (private sector)', 'healthcare industry (pharmaceutical)', 'healthcare industry'(other)', 'local government professional' or, if none of these categories apply, 'other' with a separate box to enter a description.

Role*	Section	Comment [sic]	Response
Medicine	sections of the ACD	ACD are unreasonable and are likely to be discriminatory towards large groups of patients with heart failure. 1. Assessment Group report. To base the report upon a subgroup analysis is illogical. While the assessment group stated the wished to make the population more representative of the population in England, the inclusion of patients from South Africa in the "Western Europe" population would appear to make this rather less meaningful. Second, PARADIGM is the largest ever trial in CHF; to place the findings of a subgroup analysis above those of this study is scientifically illogical. Further to this, the assessment group have failed to indicate any regional heterogeneity in the relative benefit of sacubitril valsartan. They have suggested that statistical significance was not reached in Western Europe, but have not attempted to consider whether it was reached in other regions. This renders their analyses meaningless. Further, the Assessment group consideration of ramipril as the more relevant comparator, while based upon UK practice, is misleading: The FAD required the use of enalapril, as this is the ACE inhibitor with the greatest body of evidence in chronic heart failure. The fact that ramipril is used in the UK does not reflect best-practice, and it is crucial that the NICE appraisal committee is aware of this. Sacubitril valsartan is NOT a second line therapy! It is clearly superior to what we currently use and should be regarded as standard-of-care 2. ACD (I) It is unreasonable to restrict use of sacubitril valsartan to patients based upon ejection fraction. LVEF is a highly subjective and poorly reproducible parameter. Moreover, the majority of cardiology services do not report LVEF as a percentage. (II) The PARADIGM HF trial showed clinical superiority of sacubitril valsartan compared to enalapril within 30 days of the start of the study medication. On this basis, to require physicians to prescribe a clinically inferior therapy (ACE inhibitor) and then switch to the superior agent represents poor practice, exposing patients to higher risk of adverse outcome. How can clinicians be expected to explain that to their patients?	
Consultant	Comments	The integrated heart failure service (2 consultant cardiologists, heart failure	Comments noted, see FAD sections 1.1, 4.2,

Role*	Section	Comment [sic]	Response
Cardiologist	on individual sections of the ACD	fellow, heart failure nurse specialists in primary and secondary care) has carefully reviewed the document and has highlighted a number of major concerns and comments in relation to the proposals. 1. Due to the overwhelming benefit seen in the key outcome study (PARADIGM-HF) it was felt that sacubitril valsartan should be considered the first line drug for patients with heart failure secondary to left ventricular systolic dysfunction (LVSD). In contrast the consultation document appears to place sacubitril valsartan as second line agent for the treatment of heart failure with LVSD. Restricted use will inevitably lead to many patients with heart failure being disadvantaged. 2. Furthermore, there was major concern with the proposal that sacubitril valsartan should not be available for patients presenting with newly diagnosed symptomatic LVSD. Acknowledging that PARADIGM-HF did not specifically include newly diagnosed patients, not permitting the use of sacubitril valsartan in such patients would have the potential for mixed messages and prescribing chaos amongst patients, heart failure specialists and GPs. PARADIGM-HF showed clinical superiority of sacubitril valsartan compared to enalapril within 30 days of initiation of trial therapy. It would also represent a major pressure to already overburdened heart failure services. For example, it would be extremely challenging to provide robust education and clinical support for a pathway that focuses on ACE inhibitor initiation and uptitration for a few weeks to months, followed by a period of time to see if the patient remains symptomatic. The requirement to initiate and up-titrate a therapy (ACE inhibitor), with the clear intention of then switching to a superior therapy, conveys mixed messages to patients and carers, as well as to health care professionals. Such a strategy will inevitably lead to the need for additional contacts between patient and health care professional. Moreover, there is a clear risk to patient safety in employing a strategy in which requires a wash-out period (a period of non-treatment) between ACE inhibitor and sacubitril valsartan. Outside the setting of a research study trial there will be a risk of overlap of the two therapies, thus increasing the risk of major	4.5, 4.8, 4.9, 4.18 and 4.20.

Role*	Section	Comment [sic]	Response
		adverse events, in particular angioedema. 3. Concern was also raised in relation to the proposed restriction to patients with LVEF<35%. PARADIGM-HF recruited patients with a left ventricular ejection fraction of 40% or lower. Locally in Portsmouth echocardiograms are generally reported as severe, moderate to severe, moderate or mild left ventricular impairment. Data from PARADIGM-HF show a consistent benefit of sacubitril valsartan across the range of LVEF. We feel it would be more appropriate to recommend use in patients with LVSD and either LVEF<40% or LVSD reported as moderate or worse. 4. Concerns were raised in relation to some of the data presented/analysed by the ERG. This included inappropriate analysis of geographical heterogeneity (no difference seen in a sub group that was not pre-specified), comment regarding the age in PARADIGM-HF (similar to all other heart failure studies that inform NICE heart failure guidelines), and the suggestion (section 4.7) that the study is not applicable to England since enalapril was used as the comparator. The United States Food and Drug Administration (FDA) mandated the choice of enalapril as the comparator as the ACE inhibitor with best evidence in chronic heart failure. 5. Finally concerns were raised in relation to restricting the use of sacubitril valsartan to patients in functional class NYHA II and III. PARADIGM-HF recruited patients in class II to IV, and by randomization, included a small proportion of patients in NYHA I. Unsurprisingly the number of patients in class IV was very small. Sub-group analysis demonstrated that the primary outcome and cardiovascular deaths were in favour of Sacubitril valsartan in all functional classes of heart failure, although for the primary endpoint this reached statistical significance only for patients in NYHA I-II. There doesn't therefore appear to be any clear rationale in restricting the use to patients in NYHA II and III, which will disadvantage patients in other functional	

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Mr M Boysen
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M1 4BT

15 January 2015

Dear Mr Boysen,

Re: Sacubitril valsartan for treating heart failure with systolic dysfunction [ID822] – Appraisal Consultation Document

Thank you for your letter dated 4th December inviting comments on the Appraisal Consultation Document (ACD) for the above appraisal.

Novartis welcomes NICE's provisional recommendation to make sacubitril/valsartan available for the treatment of adult patients with symptomatic heart failure with reduced ejection fraction (HFrEF). However, Novartis would like to challenge the restrictions in the provisional recommendation, in order to prevent discrimination against several groups of patients who would benefit from sacubitril/valsartan, and who are covered by the European Medicines Agency (EMA) marketing authorisation for this medicine. There is a considerable unmet need in HFrEF and sacubitril/valsartan would provide an important treatment option in these patients who would currently be excluded from receiving this medication based on NICE's draft guidance.

Novartis would like to thank NICE for the opportunity to submit a small amount of additional clinical evidence to support the ACD response.

Our comments and additional evidence are provided in response to the standard four questions on which NICE have stated they are interested in receiving comments (page 1 of the ACD). The table below provides a summary of our response.

Issue	NICE recommendation	Novartis response
LVEF	People with LVEF ≤ 35%	Novartis proposes that NICE refers to "reduced ejection fraction" rather than a specific cut-off for LVEF in the final guidance for sacubitril/valsartan as consistent treatment benefit is seen across all subgroups of LVEF in PARADIGM-HF including 963 patients with LVEF >35% and ≤40%.
NYHA	People with NYHA Class II to III	Novartis proposes that NICE removes the restriction for NYHA Class IV as there is oscillation of patients between NYHA III to NYHA IV and restricting an innovative drug will likely discriminate against a severely symptomatic subgroup of patients leading to inequality of access.
ARB/ACEi naïve	People who are already taking a stable dose of ACEi or ARBs	Novartis proposes that NICE removes the restriction to patients on a stable dose of ACEi/ARB as PARADIGM-HF showed that neprilysin inhibition on top of RAAS blockade reduced CV death and HF hospitalisation more than RAAS blockade alone. This restriction will result in initiation of an inferior therapy prior to sacubitril/valsartan leading to substantial burden to patients, putting patients at unnecessary risk of hospitalisations and death, and additional NHS resource.
Treatment setting	Treatment should be started by a HF specialist….. a GP with a special interest in HF or a HF specialist nurse	Novartis agrees with NICE that this statement should be in line with the NICE CHF clinical guidelines (CG108, Section 4.10 of the ACD). However, the wording adopted in the guidance is not fully aligned with the NICE Clinical Guidelines and could lead to inequality of access. We propose that the guidance should instead read "Treatment with sacubitril/valsartan should be initiated, titrated and monitored by the multidisciplinary heart failure team, as defined in the NICE CHF Clinical Guidelines (CG108)."
Cost-effectiveness arguments	NICE accepts the most plausible ICERs generated by the ERG and represented a cost-effective use of NHS resources	Novartis welcomes the conclusion by the Committee that sacubitril/valsartan represents a cost-effective use of NHS resources. However, we feel that some of the assumptions accepted do not lead to an accurate reflection of the most plausible ICER based on the clinical and cost-effectiveness evidence provided. Our rationale for this has been provided in the detailed response. The assumptions that are unfounded are: • The acceptance of the Western Europe subgroup – correcting this assumption lead to a most plausible ICER of £19,843 • The alternative quality of life (QoL) modelling by the ERG – correcting this assumption lead to a most plausible ICER of £ 25,607 Correcting both the above assumptions would lead to a most plausible ICER of £19,530 vs. the ERG's ICER of £29,478.[1]

[1]Note, that there were issues with replicating the ERG ICER despite the Addendum to the ERG report provided to Novartis on 10 November 2015 - Novartis generated a final ERG ICER of £26,061 per QALY based on this.

If you require clarification on any aspects of our response, please do not hesitate to contact me.

Yours sincerely,

Vera Gielen
Health Economics & Outcomes Research Manager
Novartis Pharmaceuticals UK Ltd.

The structure of our response to the NICE Appraisal Consultation Document is detailed in the table of contents below.

Table of Contents

1 Has all of the relevant evidence been taken into account?

There are several pieces of evidence that Novartis does not believe the Committee adequately considered or requested from the company in order to inform its decision to restrict the recommended population who can be treated with sacubitril/valsartan. These include the following data from PARADIGM-HF:

- Subgroup analyses of left ventricular ejection fraction (LVEF) subgroups (particularly patients with LVEF > 35%)
- Efficacy and safety in the NYHA Class IV population

In Sections 1.1 and 1.2 below, we present evidence from PARADIGM-HF as well as additional supporting argumentation to challenge the restrictions based on LVEF and NYHA Class specified in the draft guidance.

1.1 Restriction to patients with LVEF of 35% or less

The ACD has proposed to restrict treatment with sacubitril/valsartan to those patients with a LVEF of 35% or less on the basis that the LVEF inclusion criterion for the PARADIGM-HF trial was changed from 40% or less initially, to 35% or less (Section 4.8 of ACD).

In this section we present evidence for the efficacy of sacubitril/valsartan in patients with LVEF >35% (n=963, 11.4% of patients in the trial). We also present arguments regarding the use of cut-off values for LVEF in clinical practice and resource use implications if this restriction was to be applied in practice.

Efficacy of sacubitril/valsartan in patients with LVEF>35%

Of the 8,442 randomised patients in PARADIGM-HF, a total of 963 patients (11.4%) had a LVEF >35% and ≤40%.The first amendment to LVEF in the PARADIGM-HF protocol, dated 15 December 2010, came into effect after 1,285 patients had been randomised into the study. The main purpose of the first amendment was to modify 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. This change was made in response to an anticipated increase in the use of aldosterone antagonists following the release of results from the EMPHASIS-HF trial in 2011 (1). Increased use of aldosterone antagonists was expected to lower the event rate. Thus, the LVEF cut-off was lowered to offset this anticipated decrease in the event rate so that the targeted number of primary composite events would occur within a reasonable follow-up period.

LVEF is one of several clinical measures of HF severity. Additional analyses based on other measures of disease severity, baseline NYHA Functional Classification, N-terminal prohormone B-type natriuretic peptide (NT-proBNP) tertiles, and the Meta-Analysis Global Group in Chronic Heart Failure score (MAGGIC score, which is the most widely accepted and used validated risk

score for prediction of mortality in patients with HF (2), were performed to assess whether benefit associated with sacubitril/valsartan treatment in reducing CV death and HF hospitalisation was consistent in HF patients of various severities. The benefit of sacubitril/valsartan over enalapril for the primary endpoint was similar across the spectrum of risk (p = 0.159) based on the MAGGIC score (3).

Regarding efficacy in patients with LVEF >35%, there was a consistent treatment benefit in favour of sacubitril/valsartan over enalapril for the primary endpoint (p-value for interaction p=0.3599), and for cardiovascular death (p-value for interaction p=0.3559) for patients with LVEF >35% (4). Additionally, for tertile subgroups for LVEF at screening (<28%, ≥28 to ≤33%, and ≥33%), there was a consistent treatment benefit in favour of sacubitril/valsartan over enalapril for the primary endpoint (p-value for interaction p=0.9720), and for cardiovascular death, regardless of the screening EF values (see Figure 1, (5)).

Additional analyses of PARADIGM-HF data were performed using 5-point subcategories of LVEF for the primary endpoint and for CV death which demonstrated a consistent treatment benefit in favour of sacubitril/valsartan across all subgroups (See separate Appendix of new evidence, Section 5.1).

Figure 1: Forest plot for first confirmed primary endpoint (CV death or HF hospitalisation) by EF at screening tertiles (FAS) (5)

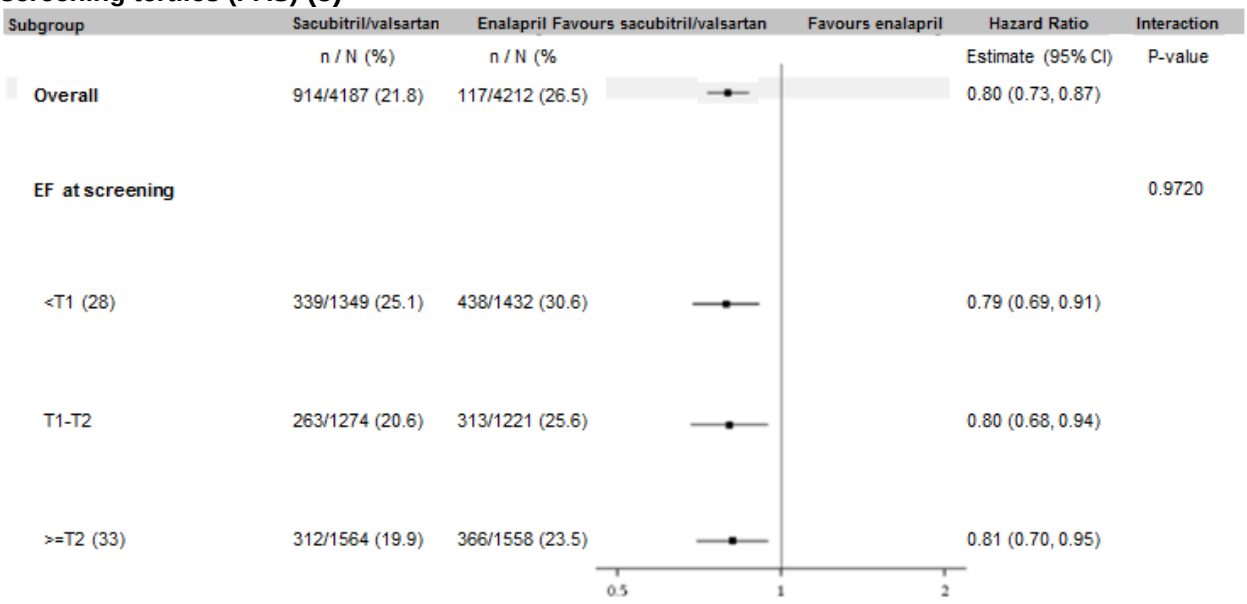


Figure 11-7, page 293 of CSR ('A2 Novartis_2014_CSR_PARADIGM-HF PART 1.pdf' sent to NICE on 25 Sept 2015)

Use of cut-off values for LVEF in clinical practice and resource use implication

In addition to the consistent treatment effect observed across all LVEF subgroups (including >35%), the use of LVEF in clinical practice should also be considered. The European Public Assessment Report (EPAR) states that cut-off values for ejection fraction were an important part

of the inclusion/exclusion of the patient population in the pivotal trial and EF is of diagnostic and prognostic value in HF. However the EPAR also states that the use of EF cut-offs outside of studies has limitations and hence a cut-off is not included in the indication.

LVEF is an imprecise measure, which can vary in the clinical setting mainly due to (1) different methodologies for EF measurement, (2) inter- or intra-observer variability, and (3) temporary improvement or deterioration as a result of HF treatment or lifestyle measures (e.g. diet, salt intake, comorbidities, etc.). Per the European Society of Cardiology (ESC) guideline (6), 'It is important to note that EF values and normal ranges are dependent on the imaging technique employed, method of analysis, and operator.'

In Section 4.8 of the ACD it is stated that 'The Committee discussed how the EF level will be determined in clinical practice and whether the required tests will be readily available to people who will potentially benefit from sacubitril valsartan. It was aware that EF level is usually demonstrated with an echocardiogram and additional tests will not necessarily be required before initiating sacubitril valsartan.' In the UK, operators who perform echocardiography often do not detail the EF value but just describe the grade of ventricular dysfunction (mild, moderate, severe) according to the qualitative categories as provided in the American Society of Echocardiography and the European Association of Cardiovascular Imaging Recommendations for Cardiac Chamber Quantification by Echocardiography in Adults (7).

Therefore, a precise LVEF value may not be readily available for all patients although reduced ejection fraction or ventricular systolic dysfunction is documented and the LVEF will change over time. A requirement for inclusion of a specific LVEF value for treatment may therefore limit the ability of physicians to prescribe the drug to a patient who could benefit from sacubitril/valsartan. Additionally, physicians might be required to repeat an echocardiogram to provide evidence that a patients EF is below the cut-off value leading to increased NHS resource use.

Conclusion

Overall Novartis proposes that NICE refers to "reduced ejection fraction" rather than a specific cut-off for LVEF in the final guidance for sacubitril/valsartan as:

- consistent treatment benefit is seen across all subgroups of LVEF in PARADIGM-HF including 963 patients with LVEF >35% and ≤40%
- the use of EF cut offs outside of studies has limitations and will likely lead to a greater and unnecessary use of NHS resources.

This proposal is in line with the EMA marketing authorisation and would ensure UK patients are able to equally benefit from improved outcomes due to this innovative medicine.

1.2 Restriction to patients with NYHA Class II-III

The ACD has proposed to restrict the recommendation of sacubitril/valsartan to those patients with NYHA Class II-III based on the limited representation of patients with NYHA Class IV in PARADIGM-HF (Section 4.9 of ACD).

In this response we present evidence to support the use of sacubitril/valsartan in patients with NYHA Class IV, specifically with respect to the efficacy and safety of sacubitril/valsartan in patients with NYHA IV. We also consider the impact on patients and prescribers if this restriction is imposed in practice.

Efficacy and safety of sacubitril/valsartan in patients with NYHA IV

Despite a small sample size, post-hoc subgroup analysis for patients with NYHA Class IV at randomisation shows that efficacy and safety are comparable to those of different NYHA Classes in comparison to the enalapril arm.

Generally, there are the same trends of improvement in efficacy across different NYHA Classes (See separate Appendix of new evidence, Section 5.2 – Table 4).

Regarding safety, in line with results of other NYHA Classes, there is a higher incidence of hypotension and a lower incidence of hyperkalaemia and renal impairment in the sacubitril/valsartan treatment arm for the NYHA Class IV subgroup. (See separate Appendix of new evidence, Section 5.2 – Table 5).

The NYHA Functional Classification is one of several clinical measures of HF severity. Additional analyses based on other measures of disease severity, baseline LVEF, NT-proBNP tertiles, and the MAGGIC score (2) were performed to assess whether benefit associated with sacubitril/valsartan treatment in reducing CV death and HF hospitalisation was consistent in HF patients with various severities. Sacubitril/valsartan showed superiority over enalapril across all HFrEF patients including the more severe ones: patients with the highest baseline NT-proBNP tertile, patients with the lowest baseline LVEF tertile, and patients with the highest MAGGIC score (3).

It is important to note that experience with NYHA Class IV patients in PARADIGM-HF is not only from those patients who were NYHA Class IV at randomisation (N=60), but also from the 323 patients having NYHA Class IV status at any visit during the double-blind period. NYHA class IV is associated with an increased risk of HF hospitalisation (8). The appropriateness of prescribing sacubitril/valsartan in patients with NYHA Class IV HF is further supported by the efficacy of sacubitril/valsartan in patients who deteriorated to Class IV during the trial by virtue of the fact that they were hospitalised for HF following randomisation. During PARADIGM-HF, 1195 patients (537 in the sacubitril/valsartan group and 658 in the enalapril group) were hospitalised for worsening HF (5). Even though at time of hospitalisation NYHA Class was not determined, these patients can essentially be considered NYHA Class IV, and subsequently fewer sacubitril/valsartan-treated patients experienced repeat hospitalisations for HF (N=170 of 537,

31.7%) compared to enalapril-treated patients (N=240 of 658, 36.5%), as shown in Table 1 (please also see Table 18 in the company submission). It should be noted that all HF hospitalisations (first and recurrent) were centrally adjudicated by the Clinical Endpoint Adjudication Committee (CEC). The benefit of sacubitril/valsartan in patients with NYHA Class IV was recognised by the CHMP.

Table 1: Rate of hospitalisations for HF (PARADIGM-HF, double-blind period, FAS) (Table 18 in company submission)

	Sacubitril/valsartan N=4187	Enalapril N=4212	P-value (1)
Patients hospitalised, classified by number of hospital admissions for HF - n (%)			0.0001**
0	3650 (87.17)	3554 (84.38)	
1	367 (8.77)	418 (9.92)	
2	110 (2.63)	143 (3.40)	
3	33 (0.79)	53 (1.26)	
≥ 4	27 (0.64)	44 (1.04)	
At least one	537 (12.83)	658 (15.62)	

(1) Wilcoxon rank test for five classes: 0, 1, 2, 3, ≥ 4
*percentage calculated using total number of patients with 2, 3 or ≥ 4hospitalizations as numerator and number of patients with at least one hospitalisation as the denominator.
**indicates 2-sided p-value is significant at alpha = 0.05

Impact on patients and prescribers

The number of NYHA Class IV patients randomised in PARADIGM-HF (N=60) was in line with the numbers reported in recently completed HF trials including HEAAL (N=22), CHARM-added (N=78), and SHIFT (N=87) (9-11). All the products studied in the aforementioned trials (e.g. ivabradine) are indicated for the treatment of HF including patients with NYHA Class IV and recommended as such by NICE clinical guidelines (12, 13).

The exclusion of NYHA Class IV patients from the population with HF who can be treated with sacubitril/valsartan would be very confusing for the prescriber, especially in relation to patients who develop transient NYHA Class IV symptoms while taking sacubitril/valsartan. If use of sacubitril/valsartan in NYHA Class IV patients was to be excluded, these “new” Class IV patients should be switched immediately to an ACEi or ARB. The results from PARADIGM-HF on the efficacy and safety in NYHA Class IV patients summarised in this document do not support this switch.

Furthermore, in the event that NYHA Class IV patients improve to NYHA Class III symptoms, their treatment should again be switched to sacubitril/valsartan to enable these patients to have the benefits of improved mortality and reduced hospitalisations. The transient nature of NYHA Class IV symptoms makes it impractical to change treatment in response to each change in the severity of symptoms. This confusion would be the inevitable result if the use of sacubitril/valsartan was restricted to patients with NYHA Class II-III only, for example when patients become dyspnoeic at rest even for short periods of time.

Finally it would be counterintuitive and discriminatory not to allow patients with the most severe symptoms who are at higher risk of hospitalisation to benefit from sacubitril/valsartan, especially as this is a relatively small population of approximately 10% of HF patients (14). Furthermore, an additional aim of therapy is to reduce symptoms. In PARADIGM-HF, a post-hoc analysis of change from randomisation for NYHA was performed. At eight months, NYHA Class was improved for more patients in the sacubitril/valsartan group than in the enalapril group and NYHA Class worsened for fewer patients in the sacubitril/valsartan group than in the enalapril group (Table 23 in the company submission, and Table 2 below).

Table 2: Between-treatment analysis of change from randomisation for NYHA at Month 8 (FAS) (Table 23 in company submission)

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.

Conclusion

Overall, Novartis proposes that NICE removes the restriction for NYHA Class IV from the final guidance for sacubitril/valsartan as:

- The evidence does not does support this restriction – specifically the data available does not demonstrate any particular efficacy/safety issue in patients with NYHA IV being treated with sacubitril/valsartan
- The oscillation of patients between NYHA III to NYHA IV may lead to confusion for the prescriber especially as there would be a requirement to switch therapy.
- Restricting an innovative drug with likely benefit for subgroup of patients with the most severe symptoms and high risk of hospitalisation is counterintuitive and could lead to inequality of access.

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

For two restrictions specified in Section 1.1 of the draft guidance, we think the Committee has not presented a reasonable interpretation of the available evidence (discussed in Section 2.1 and 2.2). These include:

- Restriction to patients currently on stable dose of ACEi or ARB
- Specification of initiation, titration and monitoring misaligned with NICE chronic HF (CHF) Clinical Guidelines (CG108)

With regards to the cost-effectiveness analysis, we welcome the acceptance of the cost-effectiveness model and the conclusion by the Committee that sacubitril/valsartan represents a cost-effective use of NHS resources. However, we feel that some of the assumptions proposed by the ERG and accepted by the NICE committee do not lead to an accurate reflection of the most plausible ICER based on the clinical and cost-effectiveness evidence provided. These specific assumptions (discussed in Section 2.3 and 2.4) include:

- The acceptance of the Western Europe subgroup
- The concerns raised regarding the quality of life (QoL) modelling and the subsequent acceptance of the ERG's QoL Model approach

Finally, Section 2.5 discusses the impact of both these ERG assumptions on the ICER as well as some issues with replicating the ERG ICER despite the Addendum to the ERG report provided to Novartis on 10 November 2015.

2.1 Restriction to patients currently on stable dose of ACEi or ARB

The ACD has proposed to restrict the recommendation of sacubitril/valsartan to those patients who are already taking a stable dose of ACEi or ARBs, based on a lack of evidence for people who were treatment-naïve to ACEi or ARB (Section 4.2 of ACD).

In this response we present a series of arguments to support the use of sacubitril/valsartan in ACEi/ARB-naïve patients, which contradicts the interpretation of clinical evidence as reported in the ACD, including the efficacy and safety of sacubitril/valsartan in ACEi/ARB-naïve patients as well as the impact on NHS resource use, burden and risk to patients.

Efficacy of sacubitril/valsartan in ACEi/ARB-naïve patients

There are no data to suggest, nor is there any clinically sound rationale why, patients who have not been previously treated with therapies that block the renin-angiotensin-aldosterone system (RAAS; ACEis/ARBs) receiving sacubitril/valsartan would not receive similar efficacy benefits to patients previously treated with ACEis/ARBs. The pivotal clinical trial for sacubitril/valsartan, PARADIGM-HF, tested the additional benefit of inhibiting neprilysin (sacubitril) over and above that of blocking RAAS (by valsartan/ ARB). PARADIGM-HF showed that neprilysin inhibition on

top of RAAS blockade reduced CV death and HF hospitalisation more than RAAS blockade alone.

Additionally, there is no evidence that the neurohormonal response to HF is different in ACEI/ARB-naïve patients. The treatment effect of sacubitril/valsartan was preserved in the closest proxy to ACEi/ARB-naïve patients in PARADIGM-HF – patients with a short time since diagnosis of HF (≤3 months, see separate Appendix of new evidence, Section 5.3). Furthermore, the PARADIGM-HF trial showed a consistent efficacy profile for sacubitril/valsartan across the spectrum of HFrEF severity (based on the MAGGIC risk score, (3))

The CHMP discussed the ACEi/ARB-naïve population based on the above points and concluded that a similar benefit of sacubitril/valsartan can be expected in patients not previously treated with ACEi/ARB (15).

Safety of sacubitril/valsartan in ACEi/ARB-naïve patients

The safety and tolerability findings from the ACEi/ARB-naïve patients with HFrEF in the TITRATION study were very similar to the overall population. The majority of ACEi/ARB-naïve patients were able to achieve and maintain the 200 mg twice daily (bid) target dose of sacubitril/valsartan following gradual up-titration from 50 mg bid (16, 17). Furthermore, sacubitril/valsartan hypertension studies included a significant number of ACEi/ARB-naïve patients which demonstrated a similar safety profile to the overall hypertension patient population (See separate Appendix of new evidence, Section 5.4).

The limited experience in ACEi/ARB-naïve patients is clearly described in the SmPC and a lower starting dose is recommended (15). Other than this recommendation, there are no explicit safety concerns highlighted in the SmPC regarding using sacubitril/valsartan in an ACEi/ARB-naïve population.

Impact on NHS resource use and burden and risk to patients

Additionally, the restriction to patients currently on stable dose of ACEi or ARB can also pose a risk to ACEi/ARB-naïve patients and impact NHS resource use. In the event that sacubitril/valsartan therapy could not be immediately initiated in ACEi/ARB-naïve patients, therapy would have to be initiated with an ACEi before the patient could be switched to sacubitril/valsartan (after a 36-hour washout period). This has the potential to double the number of contacts with health care professionals required to establish the patient on what is a superior therapy, adding unnecessary complexity to the process of initiating treatment. Ultimately this leads to additional NHS resource use and a substantial burden and risk to the patient, especially as many patients are frail with multiple co-morbidities and concomitant treatments.

Importantly, the treatment benefit of sacubitril/valsartan versus ACEi for the primary composite endpoint and HF hospitalisations in PARADIGM-HF was evident as early as within the first 30 days (See Figure 2, (18)). In addition, the most common cause of death was sudden death (36.23% of patients who died (19)), with significantly less patients dying of sudden death in the sacubitril/valsartan arm compared to the ACEi arm (See Figure 3).

Therefore, delay in initiating sacubitril/valsartan will discriminate against ACEi/ARB-naïve patients, who will be denied the additional benefits of neprilysin inhibition and will be at increased risk of experiencing a potentially fatal event during the ACEi treatment period.

Figure 2: Kaplan–Meier estimate of the cumulative probability of a first hospitalisation for HF during the first 30 days after randomisation, by treatment (19)

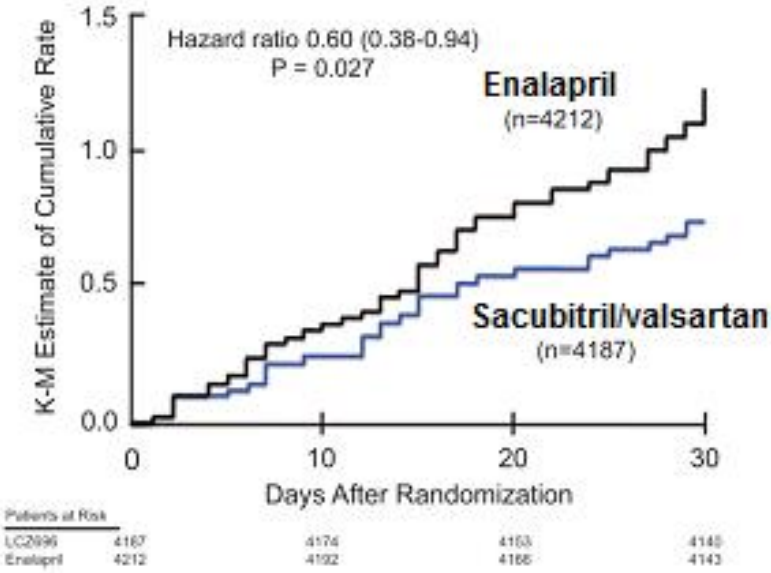
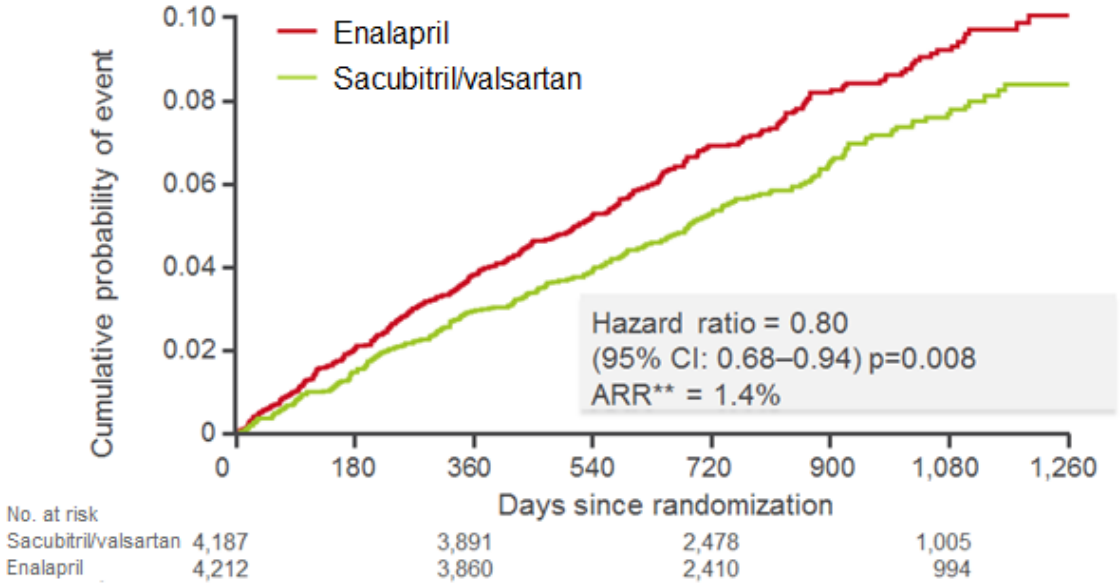


Figure 3: Kaplan–Meier curve for sudden death, by treatment (18)



Conclusion

Novartis proposes that NICE removes the restriction to patients on a stable dose of ACEi/ARB as:

- PARADIGM-HF showed that neprilysin inhibition on top of RAAS blockade reduced CV death and HF hospitalisation more than RAAS blockade alone.
- Time since diagnosis as a proxy to duration of exposure to RAAS inhibition showed no difference in treatment benefit with sacubitril/valsartan over ACEi, hence there is no evidence that ACEi/ARB-naïve patients would respond differently than patients on a stable dose of ACEi/ARB.
- There are no anticipated safety issues associated with initiating in ACEI/ARB naïve patients (supported by the SmPC and the TITRATION study).
- This restriction will result in initiation of an inferior therapy prior to sacubitril/valsartan leading to substantial burden to patients, putting patients at unnecessary risk of hospitalisations and death, and additional NHS resource.

2.2 Treatment should be started by a HF specialist with access to a multidisciplinary HF team. Dose titration and monitoring should be done by the HF specialist, or in primary care by either a GP with a special interest in HF or a HF specialist nurse.

Clinical expert opinion at NICE Committee meeting

Novartis has noted that in Section 4.10 of ACD, it is stated that the clinical experts at the NICE Committee meeting (held on 18 November 2015) specified the above restrictions to how sacubitril/valsartan should be initiated, titrated and monitored (as detailed in Section 1.2 of ACD). However, that level of detail was not discussed or agreed in the public session of the committee meeting, so we are very concerned that the guidance does not accurately capture the views expressed by the clinical experts at the meeting or the wider clinical community.

Alignment with NICE Clinical Guidelines

NICE expressed in Section 4.10 of the ACD that it was the intent to align this service recommendation with NICE CHF Clinical Guidelines (CG108) (12). We note that in the NICE Guidelines, roles have not been specified, with regards to types of healthcare professional who should initiate, titrate and monitor HF treatment. NICE CHF Clinical Guidelines (CG108) state that ‘HF care should be delivered by a multidisciplinary team with an integrated approach across the healthcare community [...] the team will decide who is the most appropriate team member to address a particular clinical problem’. Therefore, the ACD wording with regards to delivery of HF services is not aligned with the NICE Clinical Guidelines, which state that the HF multidisciplinary team decides the most appropriate team member to manage HF treatment.

Inequality of access and adoption of innovation

Specifying individual roles and types of healthcare professionals to manage sacubitril/valsartan in practice could lead to confusion and unintended inequality of access as there are wide geographical differences across England in how HF multidisciplinary teams are constituted and operated. This heterogeneity is likely to increase further given the new models of care being introduced across the NHS. How sacubitril/valsartan is implemented locally should be left to the multidisciplinary team to decide as indicated by CG108.

Specifying a "specialist" in the guidance (even though this could be a HF nurse, GPSI, or HF cardiologist) could lead to lack of clarity and imply that patients must see a HF specialist in secondary care leading to delay and increased risk to patients. Additionally, NICE accepts that sacubitril/valsartan is an innovation in HF (vs ACEis/ARBs), but the ACD proposes service restrictions beyond CG108, which will impair the ability of NHS to adopt this innovation thereby resulting in patients being unable to benefit from the improved outcomes equally.

Conclusion

Novartis proposes that the wording in Section 1.2 of the ACD should be amended in the final guidance for sacubitril/valsartan in order to align with the NICE CHF Guidelines (CG108) with regards to the delivery of HR care. We propose that the guidance should instead read "Treatment with sacubitril/valsartan should be initiated, titrated and monitored by the multidisciplinary heart failure team, as defined in the NICE CHF Clinical Guidelines (CG108)."

2.3 Western Europe subgroup in cost-effectiveness model

Factual inaccuracy regarding post-hoc analysis

It is not accurate to state that the Western Europe subgroup presented in the company submission was the post-hoc analysis i.e. excluding Israel and South Africa (pg. 37 of ACD). In fact, the Western Europe subgroup presented in the submission was the pre-specified subgroup (with Israel and South Africa included for operational reasons) (please see Table 13 as well as Section 5.9.3 in the company submission which states that 'The model was run for 39 subgroups identified a priori in the statistical analysis plan for PARADIGM-HF').

Point estimate hazard ratio from Western Europe subgroup

The Committee concluded that the Western Europe subgroup was the most representative of clinical practice in England, but that the lack of statistical significance associated with the Western Europe subgroup would not factor in its decision-making and it would therefore focus on the point estimate hazard ratio in this subgroup (0.89 95% CI, 0.74-1.07 for primary composite endpoint) as it is in the same direction and supports the estimates for the overall trial population (0.80 95% CI, 0.73-0.87 for primary composite endpoint).

However, it is inappropriate to apply the hazard ratio from a subgroup where there is no evidence of an interaction effect. The article by Rothwell et al. state the correct analysis to consider when assessing subgroups is the test of subgroup-treatment effect interaction (20).

In Section 4.5 of the ACD the Committee considers and accepts evidence which Novartis believes contradicts the appropriateness of using the HR from the Western Europe subgroup in the ERG's analysis, because:

- tests of interaction showing no evidence of treatment-effect modifiers by region (p=0.3737) for the primary composite endpoint. The hazard ratios within subgroup assume independence (of each other). This is a strong assumption and with an interaction p-value that is not significant further indicates that the overall hazard ratio rather than the subgroup hazard ratio should be used as there is no significant difference the subgroups vary (from the overall).
- Western Europe subgroup is not powered to detect statistically significant differences in the primary endpoint
- across all pre-specified subgroups, sacubitril/valsartan was consistently better than ACEi with regard to the primary endpoint, and all hazard ratio point estimates suggested a benefit in the sacubitril valsartan group; because the results of subgroup analyses were consistently positive, any differential interpretation of treatment effect in subgroups should be undertaken with caution

Furthermore, in Section 4.5 it is stated that 'The Committee noted that the ERG had considered the Western Europe subgroup to be the most representative of clinical practice in England. It understood that the ERG based this on the race, age and cardiac device use of the Western Europe subgroup.' The ERG rationale that Western Europe is the most representative of the English population could also be argued for the Caucasian subgroup with the latter subgroup being twice the size of the Western Europe subgroup. A large proportion of patients in the Western Europe subgroup [redacted]See Question A1 in Novartis response to ERG clarification questions) belong to the Caucasian/White subgroup. The average age in the Caucasian/White subgroup for sacubitril/valsartan is [redacted]years and enalapril [redacted]years (See CSR - Table 14.1-3.1.3 (5)) therefore is comparable to the Western Europe subgroup (for sacubitril/valsartan is [redacted]years and enalapril [redacted]years respectively).

Face validation of the point estimate HR for the primary endpoint in PARADIGM-HF for the Western Europe subgroup and the Caucasian/White subgroup generates counterintuitive results (0.89 versus 0.80 respectively). The race subgroup analysis also show no p-value for interaction so if the same logic was applied (which we do not support) the Committee should take into account the fact that, the Caucasian subgroup shows a significant benefit for sacubitril/valsartan (CV death HR 0.80 95% CI, 0.70, 0.93).

Caution should always be applied when interpreting subgroup analyses in clinical trials. When the full trial population is split into smaller subgroups which are not powered to detect statistically significant differences in treatment effect, the likelihood of chance findings means it

is improbable that the observed point estimate HR between two groups will be the same, even if the true treatment effect is not different between them (20, 21).

Conclusion

Novartis proposes that the Committee should use PARADIGM-HF data from the overall population in the model (including efficacy data) as this would be a more accurate reflection of the treatment effect, and therefore the cost-effectiveness, of sacubitril/valsartan. This would lead to a most plausible ICER of £19,843 vs. the ERG's ICER of £29,478, when applying all other ERG assumptions.[2]

- There is no statistical basis for applying a subgroup HR if tests of interaction showed no evidence of treatment-effect modifiers by region.
- There is no face validity in concluding that the Western Europe subgroup (including South Africa and Israel) was the most representative of clinical practice in England as other (larger) subgroups that could be as representative (i.e., Caucasian) are not considered.

2.4 Quality of life (QoL) in cost-effectiveness model

A linear mixed regression model based on EQ-5D trial data from PARADIGM-HF was applied in the cost-effectiveness model to predict utility scores. The utility model included a small but highly significant treatment effect in favour of sacubitril/valsartan after controlling for the effects of hospitalisations and adverse events. The baseline utility score was based on patient-level data from PARADIGM-HF.

The ERG expressed concerned regarding the validity of the QoL analysis presented in the submission which the Committee agreed with, specifically:

- The ERG could not be certain whether there was a baseline statistically significant difference in patients' EQ-5D scores between the 2 treatment groups of sacubitril/valsartan and enalapril. It suggested the statistical test performed by the company (two-sample t-test), that found there was no statistically significant difference, might not be appropriate.

[2] This cost per QALY result maintains all other ERG ICER assumptions (see Table 86 of the ERG report) with the exception of the Western Europe subgroup efficacy, baseline characteristics and hospitalisation data.

Note, that there were issues with replicating the ERG ICER despite the Addendum to the ERG report provided to Novartis on 10 November 2015 - Novartis generated a final ERG ICER of £26,061 per QALY based on this (See Section 2.5).

- 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 QoL across the treatment groups. The ERG suggested that, assuming patients in a healthier state would have better outcomes, the potential imbalance in disease severity might have favoured the sacubitril/valsartan group.

Table 3 below presents the differences between the Novartis and ERG QoL modelling approach – both models are largely identical with the exception of the sacubitril/valsartan treatment effect, baseline EQ-5D and calculation in model.

Table 3: Comparison of Novartis and ERG QoL model features

Features of QoL model	Novartis approach	ERG simplified approach
Assuming treatment benefit of 0.011 with sacubitril/valsartan	Included based on highly significant and persistent improvement with S/V over time for EQ-5D regression models – as well as statistically significant similarity of EQ-5D means at baseline	Excluded based on concern around QoL at baseline
Baseline EQ-5D	0.78 (based on PARADIGM-HF)	0.72 (based on Berg et al.)
Time effect	-0.008	Same as Novartis model
Hospitalisation decrement	-0.21	Same as Novartis model
Hypotension decrement	-0.06	Same as Novartis model
Cough decrement	-0.07	Same as Novartis model
Calculation of EQ-5D in model	EQ-5D predicted at all time points using the model of HRQoL	Estimated decline in EQ-5D, effects of AEs/ hospitalisation are applied to a baseline value (which may be defined/edited by the user)

The selection of the EQ-5D at baseline from PARADIGM-HF data follows the NICE reference case, which states that EQ-5D should be sourced from the clinical trial, and if not available data can be sourced from the literature (22). However due to the run-in period in PARADIGM-HF, we accept the exploration of a lower baseline EQ-5D from the literature to understand the potential impact on the ICER (which was minimal).

However, the removal of the sacubitril/valsartan EQ-5D treatment effect from the QoL model was based on a scientifically and methodologically incorrect conclusion that there may have been a statistically significant difference in patients' EQ-5D scores at baseline which may have biased the EQ-5D outcomes in favour of sacubitril/valsartan. The below sections provide argumentation against the assumption of differential baseline scores for both EQ-5D and KCCQ measures from PARADIGM-HF.

EQ-5D

It is important to note that testing for baseline differences between the intervention and control group in randomised controlled trials is typically not appropriate (23) as differences at baseline across both groups are by definition due to chance given randomisation. Furthermore, the EQ-

5D analysis was based on a repeated measures ANCOVA model which includes treatment, region, visit, and treatment-by-visit interaction as fixed effect factors and baseline value as a covariate with a common unstructured covariance for each treatment group. Therefore, any (random) differences or imbalance in baseline EQ-5D have been controlled for and have not affected the results of either the trial or the model.

With regards to the ERG's specific concern around the appropriateness of the t-test used to assess similarity of means at baseline, 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 (24). Both the means and standard deviations from the two samples are almost identical. This supports the argument that the t-test is an appropriate statistical test to assess similarity of mean EQ-5D at baseline.

Therefore, the ERG's concerns regarding a potential difference in baseline EQ-5D biasing the trial results in favour of sacubitril/valsartan are unfounded and not based on evidence. As such, we argue that the highly statistically significant EQ-5D treatment effect associated with sacubitril/valsartan is valid (and not a product of bias) and should be included in the base case model analysis.

The QoL benefit of sacubitril/valsartan compared to enalapril demonstrated with EQ-5D is further supported by NYHA shift and KCCQ outcomes showing benefit of sacubitril/valsartan in terms of symptoms and QoL. More people in sacubitril/valsartan arm were reporting improvement in symptoms as evidenced by KCCQ and NYHA (19).

KCCQ

The ERG expressed concern that a statistically significant difference in KCCQ scores at baseline could be considered clinically meaningful and that this could potentially bias the trial and model outcomes, as well as imply a difference of EQ-5D at baseline in the same PARADIGM-HF population.

A study by Spertus et al.(25) states that a minimal difference of 5 points over time depicts a clinically meaningful difference in HF. Even though this is not across treatments, this is transferable to this example. The difference between sacubitril/valsartan and KCCQ at baseline is statistically significant, however not clinically meaningful as it is 1.26 points, substantially below the 5 point mark.

Further to the above argument regarding the clinically meaningful difference in KCCQ scores, the ERG did not acknowledge that the KCCQ analysis in PARADIGM-HF was in fact adjusted for at baseline (in contrast to their assumption that KCCQ was not controlled for at baseline in p.161 of ERG report, (5)). The KCCQ analysis was based on a repeated measures ANCOVA model which includes treatment, region, visit, and treatment-by-visit interaction as fixed effect factors and baseline value as a covariate with a common unstructured covariance for each

treatment group. Therefore, any (random) differences in baseline KCCQ have been controlled for and have not affected the results of either the trial or the model.

Conclusion

Novartis proposes that the Committee should accept the utility gain of 0.011 for sacubitril/valsartan as this is an evidence-based outcome and would be a more accurate reflection of the treatment effect, and therefore the cost-effectiveness, of sacubitril/valsartan. This would lead to a most plausible ICER of £25,607 vs. the ERG's ICER of £29,478 when applying all other ERG assumptions.[3]

- The key concern is that the EQ-5D analysis did not adjust for baseline difference. However, this is incorrect as the EQ-5D analysis was based on a repeated measures ANCOVA model which controls for any (random) differences or imbalance in baseline EQ-5D and has not affected the results of either the trial or the model.
- Additionally, the EQ-5D benefit is supported by other symptom and QoL measures in the trial including KCCQ and NYHA shift some consistent QoL benefit and symptom reduction with sacubitril/valsartan

2.5 Summary of cost-effectiveness model issues

Please note Novartis was able to replicate the ERG's ICER (£19,843) with all the following modifications incorporated (Table 86 in ERG report):

- Mean age at baseline of 75 years
- Change in baseline utility to reflect Berg et al utility (0.72)
- Change in QoL modelling approach
- Change in pharmaceutical costs to reflect drug target dose
- Change in pharmaceutical costs to reflect the cost of ramipril

However, Novartis was not able to exactly replicate the ERG's ICER with all changes incorporated (£29,478) nor the ICER compared with base case for the Western Europe subgroup (£20,550) in Table 86 of the ERG report, even when precisely following the instructions detailed in the 'Addendum to the ERG report' (received on the 10th November 2015). Following these instructions, Novartis generated a final ERG ICER of £26,061 per QALY and an ICER versus base case for the Western Europe subgroup of £19,948.

[3]This cost per QALY result maintains all other ERG ICER assumptions (see Table 86 of the ERG report) with the exception of the statistically significant EQ-5D benefit associated with sacubitril/valsartan.

Note, that there were issues with replicating the ERG ICER despite the Addendum to the ERG report provided to Novartis on 10 November 2015 - Novartis generated a final ERG ICER of £26,061 per QALY based on this (See Section 2.5).

Novartis noted that the modifications associated with the Western Europe subgroup overrode previous ERG assumptions (i.e. any changes to baseline characteristics), which could explain these discrepancies. However, even when Novartis re-incorporated these previous assumptions around baseline characteristics, the ERG's ICER still could not be exactly replicated.

Novartis proposes that the ERG updates the Addendum to the ERG report to be able to replicate all ICERs in Table 86 and that this is reflected in the final guidance. Additionally, Novartis proposes that the Committee use PARADIGM-HF data from the overall trial population and accept the utility gain of 0.011 for sacubitril/valsartan (as discussed above in Sections 2.3 and 2.4) to generate the most plausible ICER for sacubitril/valsartan. Implementing the above changes and keeping the remaining ERG ICER assumptions (as per Table 86 of the ERG report) would lead to a most plausible ICER of £19,530 (vs. the ERG's ICER of £29,478).

3 Are the provisional recommendations sound and a suitable basis for guidance to the NHS?

In Section 4.19 of the ACD it is stated that 'the Committee was aware that sacubitril/valsartan has been granted a promising innovative medicine (PIM) designation by the Medicines and Healthcare Products Regulatory Agency. The ACD does not mention that sacubitril/valsartan received a positive opinion for the Early Access to Medicine Scheme (EAMS) by the MHRA.

Novartis proposes the following change to the wording to Section 4.19 In addition, the Committee was aware that sacubitril/valsartan has been granted a promising innovative medicine designation *and received a positive opinion for the Early Access to Medicine Scheme* by the Medicines and Healthcare Products Regulatory Agency.

Additionally, Novartis proposes that Section 5.1 states that drugs introduced through EAMS are expected to be introduced prior to the 90 day limit set out in the regulations. CCGs and Trusts will be expected to implement the NICE TA within a 30 day period (https://www.england.nhs.uk/wp-content/uploads/2015/10/eams-letter-oct15.pdf).

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

Novartis does not foresee any significant equality issues above associated with the use of sacubitril/valsartan in people with HFrEF, other than the issues we have highlighted throughout the document that are as a result of the restrictions proposed by NICE.

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Pumping Marvellous Foundations response to the Single Technology Appraisal (STA) for Sacubitril Valsartan for treating heart failure with systolic dysfunction [ID822]

Appraisal consultation document response

After considering the appraisal committee's preliminary recommendations please find our response.

Point 1.1

Noting the committee recommendations we are surprised and disappointed that NICE may potentially recommend a course of action which involves titrating up on less than optimal drugs initially where it seems that patient concerns and their welfare has not been taken into consideration. Considering the timings of when these drugs are prescribed, usually on diagnosis potentially when the patient is at their most vulnerable. Why would you want to prescribe a drug that wasn't the best for the patient?

We are concerned with the level knowledge and awareness and therefore usage of the NYHA scale in primary care especially where the NYHA scale is a necessity for consideration of prescribing Sacubitril Valsartan.

Point 1.2

Noting the committee's recommendations around the logistics of distributing / prescribing Sacubitril Valsartan through a HF specialist with access to an MDT and with dose and titration monitoring completed either in the acute setting or in primary care through GPSI or HF specialist nurse.

We feel this is a rather limited and counter-productive system which will end up with effecting the patients and their families QOL as well as costing the NHS as the up-titration process has to be repeated.

The question of resource is a key element to our feedback where

I. We would question the availability of HF nurse prescribers in both acute and community settings? NHS England doesn't know how many HF nurses it employs never mind where
II. We question the availability of GPSI's across the CCG's
III. For instance in the primary care setting in two local adjoining CCG's being served by a DGH where there is a population of 500,000 plus with a high incidence of CHD / HF there is one GPSI and one HF nurse prescriber in the community, this pushes the medicine management question back on the acute system. This would inevitably lead to under prescribing and curtailing patients access to the best drug,; one could assume this creates an underserved population due to lack of access

IV. This recommendation fly's in the face of the Steven's plan for the NHS where, if following the recommendations of taking services out of the acute and into the community then this demonstrates the reverse as the primary care management will be overwhelmed due to the lack of resource

V. We would like to understand from the committee their understanding of what an MDT looks like as this seems to be at the HUB of the prescribing process and we know this is not consistent across England and Wales.

In conclusion

We feel that the recommendation mirrors the clinical trial data in the Paradigm-HF Trial. However trial conditions don't mirror real world challenges. We are very concerned about patients having to be up titrated on a less than optimal therapy then and only then to be taken off it considering the hard work and effort it takes for the majority of patients to climb the ladder of titration to having to climb the same hill with Sacubitril Valsartan. This is a disservice to the HF patients and their families.

We strongly believe that economic pressure has crafted this response which mirrors the ERG's discussion points. We don't feel after analysing the committee papers that the recommendations have taken into account the patient experts or the clinical experts recommendations. The recommendations are clearly aligned with narrowing the patient group which will benefit this new technology therefore reducing the economic impact of a new in class therapy for HF patients. This course of action will lead to the creation of "an underserved class of HF patient" in England and Wales and will, by narrowing the bandwidth not have the desired effect of what by a "lay" person's best guess is a blockbuster therapy.

You may forgive me for being direct but as a patient and human and not being emotional about my response I don't think people get heart failure. It is not a sexy condition, count up the amount of times it's mentioned in the press. Heart failure patients had no voice before the Pumping Marvellous Foundation which was formed less than 5 years ago. Just look at NICE and how they have struggled with patient representation for heart failure before the Pumping Marvellous Foundation came along. The patient population estimates vary wildly from 500,000 through to nearly million. I am afraid this decision may put back a clear and present opportunity to impact on the QOL of heart failure patients and their families.

Does the committee really think that the decision to pursue a suboptimal treatment as a first line in treating chronic HF is the best the NHS can do? Does the committee really think the NHS has the capacity to achieve this and that individual clinicians will view this as a positive spin on this new drug, does it give them the confidence to pursue a more than normal route of getting the patient optimised on said drug.

Signed

[redacted]

Name – [redacted]

Date – 8th January 2016

British Cardiovascular Society

NICE Single Technology Appraisal (STA)

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

Comments on Appraisal consultation document

[redacted], [redacted] on behalf of the British Cardiovascular Society

5/1/2016

1.1 Sacubitril valsartan is recommended as an option for treating people with heart failure with reduced ejection fraction, only in people:

-with New York Heart Association (NYHA) class II to III chronic heart failure and

-who are already taking a stable dose of angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor-blockers (ARBs) and

-with a left ventricular ejection fraction of 35% or less.

The licence for sacubitiril valsartan is for symptomatic patients with reduced ejection fraction heart failure.

The requirement for a documented EF of < 35% and for NYHA class II and III symptoms only will add an extra layer of complexity in identifying patients who may benefit from this treatment.

The accurate assessment of EF is fraught with difficulties and a patient with an EF of 36% will benefit from this drug and not be eligible on the basis of the NICE recommendation.

Although accepting that there is limited data, not allowing patients to be initiated on Sacubitril valsartan will lead to significant logistical issues. A new patient with heart failure will be started on an ACE-I or ARB – take several weeks to reach a stable dose, by which time they may have been discharged from hospital care and then will need to be reassessed to swap over. In the case of ACE-I use, the patient will have to stop their drug for 3 days before Sacubitril can be administered.

This process will lead to increased hospital visits and increased costs.

1.2 Treatment with sacubitril valsartan should be started by a heart failure specialist with access to a multidisciplinary heart failure team. Dose titration and monitoring should be done by the heart failure specialist, or in primary care by either a GP with a special interest in heart failure or a heart failure specialist nurse.

This recommendation is appropriate initially – but many patients on stable therapy do not necessarily get reviewed by a GPwSI or HF Specialist nurse and so monitoring should be carried out by the patient's GP who may not have a special interest in HF.

1.3 People whose treatment with sacubitril valsartan is not recommended in this NICE guidance, but was started within the NHS before this guidance was published, should be able to continue treatment until they and their NHS clinician consider it appropriate to stop.

Agree with this statement

3.5 / 3.34

Patients in clinical trials rarely match routine clinical practice In terms of age or gender. This alone would be insufficient reason to not provide a positive recommendation

3.10 / 3.37

A subgroup analysis that shows patients in Western Europe gain less benefit from Sacubitril is not valid statistically and should not be used to generate the recommendation

3.36

Enalapril is the best comparator, as it is the ACE-I with the greatest evidence in chronic heart failure. Although ramipril is most commonly used in the UK, it is often dosed incorrectly (should be given bd rather than od) and only has post-MI data rather than true CHF evidence.

Single Technology Appraisal (STA)
Sacubitril valsartan for treating heart failure with systolic dysfunction [ID822]
Appraisal consultation document

BRITISH SOCIETY FOR HEART FAILURE (BSH) RESPONSE TO: the appraisal consultation document (ACD) for the above appraisal.

The Board of the BSH has carefully reviewed the document and the majority of members have highlighted a number of major concerns and comments in relation to the proposals. These are noted below in bold:

The BSH feels that sacubitril valsartan should be considered the first line drug for patients with heart failure secondary to left ventricular systolic dysfunction LVSD due to the overwhelming benefit seen in the key outcome study (PARADIGM-HF).

The consultation document appears to place sacubitril valsartan as second line agent for the treatment of heart failure with LVSD. Data from the PARADIGM-HF study demonstrate the clear superiority of sacubitril valsartan over the current gold standard treatment of angiotensin converting enzyme (ACE) inhibitor (in this study the ACE inhibitor was that with greatest evidence in heart failure, enalapril).

Restricted use will inevitably lead to many patients with heart failure being disadvantaged.

The BSH does not agree with a number of criticisms of data from PARADIGM-HF, including but not restricted to:

(i) Geographical heterogeneity. The ERG analysis using a subgroup of PARADIGM that was not pre-specified made no sense; a subgroup analysis is, by definition, less likely to show a statistically meaningful difference simply due to it containing smaller numbers of patients and events. The ERG uses the fact that a number of the endpoints in its analyses did not reach statistical significance to suggest limiting the use of sacubitril valsartan; and yet it did not demonstrate any heterogeneity in outcomes between geographical regions. The conclusion that patients in western Europe did not benefit from sacubitril valsartan is specious. There is a manuscript submitted indicating there is no geographical variation in the benefit from sacubitril valsartan within this study

(ii) Age of the population being different to standard UK heart failure population. This is consistent for trials across all areas of medicine and relates to the whole evidence base upon which we practice clinical medicine. It is inappropriate to focus upon age. The average age is similar to that seen in other key heart failure trials that have established ACE inhibitors, beta blockers, mineracorticoid antagonists, devices (ICD, CRT), and ivabradine (TA267) in heart failure

guidelines (including NICE chronic and acute heart failure guidelines).

(iii) The suggestion (section 4.7) that the study is not applicable to England since enalapril was used as the comparator. In a clinical trial, there needs to be a standard comparator across all countries in the study. The United States Food and Drug Administration (FDA) mandated the choice of enalapril as the comparator as the ACE inhibitor with best evidence in chronic heart failure. Indeed as there is no trial of the effectiveness of ramipril in chronic heart failure, current UK practice is inferior by not routinely using enalapril and the magnitude of benefit of sacubitril valsartan over other ACE inhibitors in UK practice might even be greater than that seen in PARADIGM-HF.

The majority of the BSH does not agree that sacubitril valsartan should not be available for patients presenting with newly diagnosed symptomatic LVSD

Whilst acknowledging that PARADIGM-HF did not specifically include newly diagnosed patients, we have major concerns about the potential for mixed messages and prescribing chaos amongst patients, heart failure nurse specialists, GPs and other heart failure specialists if sacubitril valsartan is not permitted for use in patients with newly diagnosed symptomatic LVSD.

Firstly, in PARADIGM-HF the clinical superiority of sacubitril valsartan compared to enalapril was evident to be effective within 30 days of initiation of trial therapy. Therefore, failing to start patients on sacubitril valsartan rather than ACE inhibitors will disadvantage patients who are ACE inhibitor naïve.

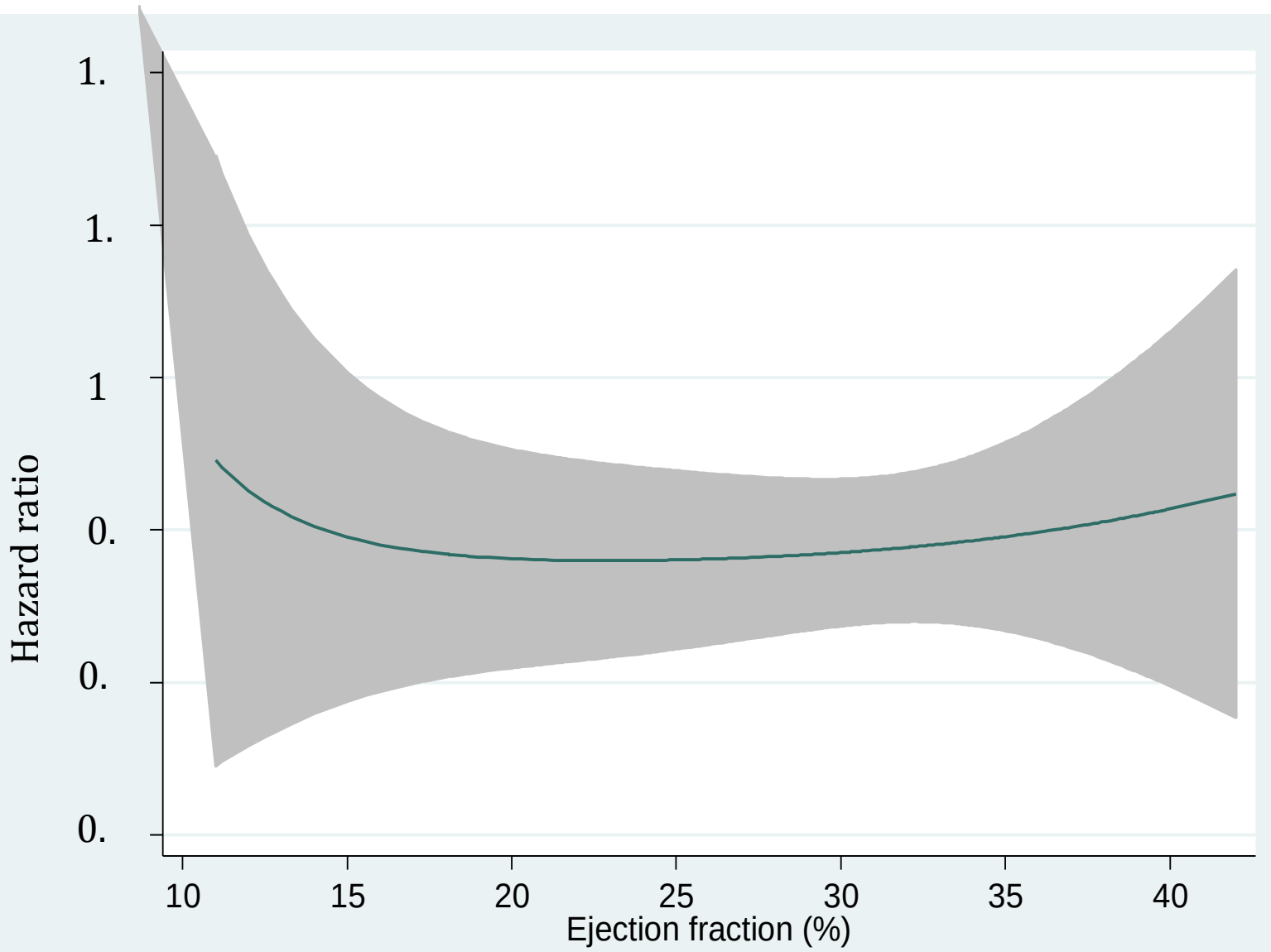
Secondly, the requirement for ACE inhibitor naïve patients to be initiated, and stabilized, on ACE inhibitor will present logistical problems which are likely to expose patients to potential prescribing errors and risk of adverse events. Practical concerns were raised as to how this might be delivered effectively by heart failure services in the NHS. For example, it would be extremely challenging to provide robust education and clinical support for a pathway that focuses on ACE inhibitor initiation and uptitration for a few weeks to months, followed by an arbitrary period of time to see if the patient remains NHYA II-III (how long; 1 day to 1 year?). These patients will need to be retained in (already overburdened) heart failure services, leading to delays in assessment of new cases or those discharged from hospital as per NICE acute heart failure quality standards. The BSH feels that the requirement to initiate and up-titrate a therapy (ACE inhibitor), with the clear intention of then switching to a superior therapy, conveys mixed messages to patients and carers, as well as to health care professionals. Such a strategy will inevitably lead to the need for additional contacts between patient and health care professional. Moreover, the strategy will require a wash-out period (a period of non treatment) between ACE inhibitor and sacubitril valsartan, leading to a clear risk of overlap of the two therapies and increasing the risk of

major adverse events, in particular angioedema.
In summary, in clinical practice restriction to patients previously tolerant of ACE inhibitors will lead to significant increase in NHS work and will be demanding on resources. It is likely to disadvantage patients and potentially result in inequitable access depending upon local pathways. Committing the patients to an avoidable wash-out/transfer period may put patients at unnecessary risk.

The BSH does not agree that sacubitril valsartan should be restricted to patients with LVEF<35%

PARADIGM-HF recruited patients with a left ventricular ejection fraction of 40% or lower. There are major variations in cardiology departments with respect to the reporting of echocardiogram assessments of left ventricular function. Due to the challenges of accurate and reproducible documentation of LVEF, many departments report severe, moderate to severe, moderate or mild left ventricular impairment. Data from PARADIGM-HF (see slide) show a consistent benefit of sacubitril valsartan across the range of LVEF with no evidence of lesser benefit in patients with LVEF between 35 and 40%. The BSH feels it would be more appropriate to recommend use in patients with LVSD and either LVEF<40% or LVSD reported as moderate or worse.

Figure: showing the consistent benefit of sacubitril valsartan (hazard ratio) for the primary end point in PARADIGM-HF across the range of LVEF within the study



Dr Lisa Anderson

Heart Failure Consultant

St George's Hospital London

SW17 0QT

13th Jan 2016

Dear Professor Stevens and the NICE Appraisal Committee

Single Technology Appraisal: Sacubitril valsartan for treating symptomatic chronic heart failure with reduced ejection fraction (ID822). Appraisal Consultation Document (ACD).

I have been asked to comment on the ACD having attended the appraisal meeting on the 18th November as Clinical expert representative from the British Society for Heart Failure.

It is important to clarify that the response below is my own and not held by all members of the BSH board. A separate response will be submitted by the BSH board putting forward that viewpoint.

My response:

I welcome the recommendation for use of sacubitril valsartan as an option for the treatment of heart failure with reduced ejection fraction.

I consider that the requirement for previous exposure to ACE inhibitor or ARB is prudent, as we have yet to learn about the safety profile in ACE inhibitor naïve patients.

A careful approach, in line with the Paradigm study inclusion criteria appears justified given that, in the US, sacubitril valsartan is subject to two post marketing requirements by the FDA:

1. To conduct a multi centre, randomized, double-blind, active-controlled trial to evaluate the effects of sacubitril valsartan compared to valsartan on cognitive function (as neprilysin is a major beta amyloid-degrading enzyme in the brain). Final report due 2022.

2. To conduct an epidemiologic study using claims or electronic health records data to evaluate the incidence of angioedema in Black patients treated with sacubitril valsartan compared to a control drug. Final report due 2019.

The information above was not found in the information pack, but is stored online at

http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2015/207620Orig1s000ltr.pdf.

Therefore I did not consider it as confidential and have submitted this single response. I am happy to submit another with this part removed at NICE's recommendation.

Yours sincerely,

Lisa Anderson

Comments on the ACD Received from the Public through the NICE Website

Name	[redacted]
Role	Professor of Cardiovascular Medicine
Other role	
Organisation	
Location	Scotland
Conflict	No
Notes	I am [redacted]
Comments on individual sections of the ACD: The document ignores that the PARADIGM trial only enrolled STABLE patients with high BNP levels(>150 pg/ml) or high NT proBNP ((>600 pg/ml) . Stable patients have mean BNP levels of 93 pg/ml or NT proBNP levels of 953 pg/ml (Cardiovasc Drugs Ther 2008, 22(4) 305-311). Same is true in Am J Card 2006, 98, 1248. Stable patients have lower BNP levels than the BNP level used at the diagnostic stage. In fact mean levels of BNP in PARADIGM were 255 pg/ml and NT pro BNP of 1600 pg/ml. Therefore only stable patients with particularly high BNP levels were recruited in PARADIGM. By ignoring this key entry criterion , your advice will treat more heart failure patients than would be treated in PARADIGM where the benefit lies. The total cost to the country of using this expensive drug in a wider and somewhat milder group of patients than got in to the PARADIGM trial will increase the UK drug bill. Also we cannot be sure that the benefit will outweigh the risk when giving this drug also to milder patients than got in to the PARADIGM trial	
Section 1 (Appraisal Committee's preliminary recommendations)	
Section 2 (The technology)	
Section 3 (The manufacturer's submission)	
Section 4 (Consideration of the evidence)	
Section 5 (Implementation)	
Section 6 (Related NICE guidance)	
Section 7 (Proposed date of review of guidance)	

Name	[redacted]
Role	Professor of Cardiology
Other role	
Organisation	
Location	
Conflict	No
Notes	
Comments on individual sections of the ACD: The Committee noted that the NICE guideline on chronic heart failure in adults: management defined a specialist as a physician with a subspecialty interest in the management of heart failure and who leads a specialist multidisciplinary heart failure	

team of professionals with appropriate competencies from primary and secondary care•

I feel that consistencies should be employed across different NICE guidelines. The NICE guideline across chronic heart failure defines a HF specialist as either a cardiologist with a HF interest or a HF nurse or physician with a specilai interest in HF, that would class a GPSI in HF as such a specialist role. Indeed given that several GPs are on the guideline committee for HF ([redacted], [redacted]), i feel that the definition of a HF specialist is far too restrictive. I think that specialist should be defined in a similar manner to other NICE guidance

Section 1 (Appraisal Committee's preliminary recommendations)	
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Section 7 (Proposed date of review of guidance)	

Name	[redacted]
Role	Professor of Cardiovascular Medicine
Other role	
Organisation	[redacted]
Location	
Conflict	Yes I was [redacted] the [redacted] in the UK and have [redacted]
Notes	

Comments on individual sections of the ACD:

I welcome the positive recommendation for sacubitril valsartan. However aspects of the Assessment Group analysis are very poor, and parts of the ACD are unreasonable and are likely to be discriminatory towards large groups of patients with heart failure.

1. Assessment Group report. To base the report upon a subgroup analysis is illogical. While the assessment group stated the wished to make the population more representative of the population in England, the inclusion of patients from South Africa in the "Western Europe" population would appear to make this rather less meaningful. Second, PARADIGM is the largest ever trial in CHF; to place the findings of a subgroup analysis above those of this study is scientifically illogical. Further to this, the assessment group have failed to indicate any regional heterogeneity in the relative benefit of sacubitril valsartan. They have suggested that statistical significance was not reached in Western Europe, but have not attempted to consider whether it was reached in other regions. This renders their analyses meaningless. Further, the Assessment group consideration of ramipril as the more relevant comparator, while based upon UK practice, is misleading: The FAD required

the use of enalapril, as this is the ACE inhibitor with the greatest body of evidence in chronic heart failure. The fact that ramipril is used in the UK does not reflect best-practice, and it is crucial that the NICE appraisal committee is aware of this.

Sacubitril valsartan is NOT a second line therapy ! It is clearly superior to what we currently use and should be regarded as standard-of-care

2. ACD

(I) It is unreasonable to restrict use of sacubitril valsartan to patients based upon ejection fraction. LVEF is a highly subjective and poorly reproducible parameter. Moreover, the majority of cardiology services do not report LVEF as a percentage.

(II) The PARADIGM HF trial showed clinical superiority of sacubitril valsartan compared to enalapril within 30 days of the start of the study medication. On this basis, to require physicians to prescribe a clinically inferior therapy (ACE inhibitor) and then switch to the superior agent, represents poor practice, exposing patients to higher risk of adverse outcome. How can clinicians be expected o explain that to their patients ?

Section 1 (Appraisal Committee's preliminary recommendations)	
Section 2 (The technology)	
Section 3 (The manufacturer's submission)	
Section 4 (Consideration of the evidence)	
Section 5 (Implementation)	
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Section 7 (Proposed date of review of guidance)	

Name	[redacted]
Role	Consultant Cardiologist
Other role	
Organisation	[redacted]
Location	England
Conflict	No
Notes	

Comments on individual sections of the ACD:

The integrated heart failure service (2 consultant cardiologists, heart failure fellow, heart failure nurse specialists in primary and secondary care) has carefully reviewed the document and has highlighted a number of major concerns and comments in

relation to the proposals.

1. Due to the overwhelming benefit seen in the key outcome study (PARADIGM-HF) it was felt that sacubitril valsartan should be considered the first line drug for patients with heart failure secondary to left ventricular systolic dysfunction (LVSD). In contrast the consultation document appears to place sacubitril valsartan as second line agent for the treatment of heart failure with LVSD. Restricted use will inevitably lead to many patients with heart failure being disadvantaged.

2. Furthermore, there was major concern with the proposal that sacubitril valsartan should not be available for patients presenting with newly diagnosed symptomatic LVSD.

Acknowledging that PARADIGM-HF did not specifically include newly diagnosed patients, not permitting the use of sacubitril valsartan in such patients would have the potential for mixed messages and prescribing chaos amongst patients, heart failure specialists and GPs.

PARADIGM-HF showed clinical superiority of sacubitril valsartan compared to enalapril within 30 days of initiation of trial therapy. It would also represent a major pressure to already overburdened heart failure services. For example, it would be extremely challenging to provide robust education and clinical support for a pathway that focuses on ACE inhibitor initiation and uptitration for a few weeks to months, followed by a period of time to see if the patient remains symptomatic. The requirement to initiate and up-titrate a therapy (ACE inhibitor), with the clear intention of then switching to a superior therapy, conveys mixed messages to patients and carers, as well as to health care professionals. Such a strategy will inevitably lead to the need for additional contacts between patient and health care professional. Moreover, there is a clear risk to patient safety in employing a strategy in which requires a wash-out period (a period of non-treatment) between ACE inhibitor and sacubitril valsartan. Outside the setting of a research study trial there will be a risk of overlap of the two therapies, thus increasing the risk of major adverse events, in particular angioedema.

3. Concern was also raised in relation to the proposed restriction to patients with LVEF<35%. PARADIGM-HF recruited patients with a left ventricular ejection fraction of 40% or lower. Locally in Portsmouth echocardiograms are generally reported as severe, moderate to severe, moderate or mild left ventricular impairment. Data from PARADIGM-HF (see slide) show a consistent benefit of sacubitril valsartan across the range of LVEF. We feel it would be more appropriate to recommend use in patients with LVSD and either LVEF<40% or LVSD reported as moderate or worse.

4. Concerns were raised in relation to some of the data presented/analysed by the ERG. This included inappropriate analysis of geographical heterogeneity (no difference seen in a sub group that was not pre-specified), comment regarding the age in PARADIGM-HF (similar to all other heart failure studies that inform NICE heart failure guidelines), and the suggestion (section 4.7) that the study is not applicable to England since enalapril was used as the comparator. The United States Food and

Drug Administration (FDA) mandated the choice of enalapril as the comparator as the ACE inhibitor with best evidence in chronic heart failure. 5. Finally concerns were raised in relation to restricting the use of sacubitril valsartan to patients in functional class NYHA II and III. PARADIGM-HF recruited patients in class II to IV, and by randomization, included a small proportion of patients in NYHA I. Unsurprisingly the number of patients in class IV was very small. Sub-group analysis demonstrated that the primary outcome and cardiovascular deaths were in favour of Sacubitril valsartan in all functional classes of heart failure, although for the primary endpoint this reached statistical significance only for patients in NYHA I-II. There doesnt therefore appear to be any clear rationale in restricting the use to patients in NYHA II and III, which will disadvantage patients in other functional classes.	
Section 1 (Appraisal Committee's preliminary recommendations)	
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5 Appendix of new evidence

5.1 LVEF 5-point subcategories

The NICE ACD draft recommendation restricts the population to patients with LVEF ≤35%. Novartis presents additional evidence in the response to the ACD which further supports the consistent efficacy of sacubitril/valsartan in patients with LVEF >35%.

In the company submission and the CSR submitted to NICE, the following data was submitted which demonstrated the consistent treatment effect of sacubitril/valsartan for all patients in the pivotal PARADIGM-HF trial including patients with LVEF >35%:

- Subgroup analysis of patients with LVEF >35%
- Subgroup analysis of tertiles of LVEF at screening of < 28%, ≥ 28 to ≤ 33%, and ≥ 33%

Additional analyses of PARADIGM-HF data were performed as part of the regulatory process using 5-point subcategories and tertiles of LVEF for the primary endpoint and for CV death and are presented in this response to further demonstrate the consistent treatment benefit in favour of sacubitril/valsartan across all subgroups of LVEF.

The 5-point subgroups used were LVEF at screening of ≤ 15%, 16% to ≤ 20%, 21% to ≤25%, 26% to ≤ 30%, 31% to ≤ 35%, and > 35%. There was a consistent treatment benefit in favour of sacubitril/valsartan over enalapril for the primary endpoint (p-value for interaction p=0.9377), and for cardiovascular death (p-value for interaction p=0.3367), regardless of the screening EF values.

The above new 5-point subgroup data presented in the response to the ACD further demonstrates that sacubitril/valsartan has a consistent treatment benefit across all subgroups of LVEF in PARADIGM-HF (including 963 patients with LVEF >35% and ≤40%) and therefore, supports the rationale that the final NICE recommendation wording for sacubitril/valsartan should not include the restriction to patients with LVEF ≤35%.

5.2 NYHA Class IV

The NICE ACD draft recommendation restricts the population to patients with NYHA Class II-III. Novartis presents additional evidence in the response to the ACD which supports consistent efficacy and safety of sacubitril/valsartan in patients with NYHA Class IV compared to NYHA Class II-III.

In the company submission, subgroup analyses were presented for patients with NYHA class I-II and NYHA class III-IV, however analysis of patients with NYHA class IV was not provided.

The below new data presented in the response to the ACD demonstrates similar trends in improved efficacy for the primary endpoint and CV death in the NYHA Class IV subgroup (Table 4) as well as a similar safety profile across NYHA Classes (Table 5) from PARADIGM-HF.

Table 4: Comparison of first primary endpoint and CV death in patients with NYHA Class IV HF at randomisation (FAS)

	Sacubitril/ valsartan n/m (%)	**Enalapril n/m (%)**	**HR (95% CI) (1) sacubitril/valsartan vs. enalapril**
Primary endpoint	10/33 (30.30)	11/27 (40.74)	0.710 (0.298, 1.691)
CV death	6/33 (18.18)	6/27 (22.22)	0.870 (0.278,2.727)

(1) Hazard ratio and its confidence interval are calculated using a Cox model with treatment and region as fixed factors within each subgroup

Table 5: Adverse events during double-blind period, by NYHA Class at randomisation, regardless of study drug relationship (CLCZ696B2314 safety set) (1)

Subgroup	**Sacubitril/valsartan**	**Enalapril**	**Total**
NYHA Class II	N=3002	N=2929	N=5931
Number of patients with ≥1 AE	2465 (82.11)	2461 (84.02)	4926 (83.06)
hypotension	522 (17.39)	357 (12.19)	879 (14.82)
renal impairment	294 (9.79)	346 (11.81)	640 (10.79)
hyperkalaemia	351 (11.69)	416 (14.20)	767 (12.93)
NYHA Class III	N=978	N=1055	N=2033
Number of patients with ≥1 AE	768 (78.53)	838 (79.43)	1606 (79.00)
hypotension	183 (18.71)	118 (11.18)	301 (14.81)
renal impairment	108 (11.04)	114 (10.81)	222 (10.92)
hyperkalaemia	118 (12.07)	155 (14.69)	273 (13.43)
NYHA Class IV	N=33	N=27	N=60
Number of patients with ≥1 AE	24 (72.73)	21 (77.78)	45 (75.00)
hypotension	3 (9.09)	1 (3.70)	4 (6.67)
renal impairment	2 (6.06)	3 (11.11)	5 (8.33)
hyperkalaemia	5 (15.15)	6 (22.22)	11 (18.33)

(1) Analysis is based on Safety set patients who were excluded having missing in NYHA Class at randomisation. A patient with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment.

The above data demonstrates consistent efficacy in patients with NYHA Class IV compared to NYHA Class II-III and that there are no particular safety issues in patients with NYHA IV being treated with sacubitril/valsartan. This supports the rationale that the final NICE recommendation wording for sacubitril/valsartan should not include the restriction to patients with NYHA Class II-III.

5.3 Time since diagnosis < 3 months

The NICE ACD draft recommendation restricts the population to patients on a stable dose of ACEi/ARBs. Novartis presents additional evidence in the response to the ACD to support consistent treatment effect of sacubitril/valsartan in ACEi/ARB-naïve patients.

In the NICE scope, no specific subgroups of interest were identified, however subgroup analyses were still presented in the submission, including subgroups for time since diagnosis (<1 year, 1-5 years, >5 years).

As the subgroup with the shortest time frame since diagnosis presented in the submission was <1 year, Novartis presents further subgroup data with a shorter time frame (< 3 months) since diagnosis, as the closest proxy to ACEi/ARB-naïve patients in PARADIGM-HF. In the subgroup of patients with <3 months since diagnosis, the sacubitril/valsartan treatment effect was preserved. Treatment benefit of sacubitril/valsartan over ACEi was independent of time since diagnosis (p=value of interaction 0.2677) which could be viewed as a proxy to exposure time to RAAS inhibition.

The above data demonstrates similar treatment effect in the closest proxy to an ACEi/ARB-naïve population from PARADIGM-HF (<3 months since diagnosis of HF) and therefore, supports the rationale that the final NICE recommendation wording for sacubitril/valsartan should not include the restriction to patients on a stable dose of ACEi/ARBs.

5.4 Sacubitril/valsartan hypertension studies

The NICE ACD draft recommendation restricts the population to patients on a stable dose of ACEi/ARBs. Novartis presents additional evidence in the response to the ACD to support comparable safety outcomes for sacubitril/valsartan in ACEi/ARB-naïve patients.

Sacubitril/valsartan studies were conducted in hypertension (unpublished) and included a significant number of ACEi/ARB-naïve patients (N=1,012). These patients showed similar safety profiles (AEs SAEs, and AEs that led to discontinuation) to the overall hypertension patient population (See Table 6).

Table 6: Adverse events in sacubitril/valsartan hypertension studies (ACEi/ARB naïve patients)

	Placebo N=145	Sacubitril/ valsartan N=1,012	Olmesartan N=326	Amlodipine N=84	Valsartan N=269
Duration of exposure (days)					
Mean (SD)	56.4 (14.18)	62.5 (17.37)	73.6 (23.70)	56.6 (6.93)	55.9 (14.43)
Adverse events, n (%)					
≥ 1 AEs	46 (31.7)	342 (33.8)	124 (38.0)	19 (22.6)	57 (21.2)
Leading to discontinuation	6 (4.1)	13 (1.3)	7 (2.1)	0 (0.0)	1 (0.4)
≥ 1 SAEs	1 (0.7)	9 (0.9)	6 (1.8)	0 (0.0)	1 (0.4)

The data from sacubitril/valsartan hypertension studies demonstrate a comparable safety profile for sacubitril/valsartan independent of prior treatment with ACEi/ARBs and therefore, supports the rationale that the final NICE recommendation wording for sacubitril/valsartan should not include the restriction to patients on a stable dose of ACEi/ARBs.

Sacubitril valsartan for treating chronic heart failure

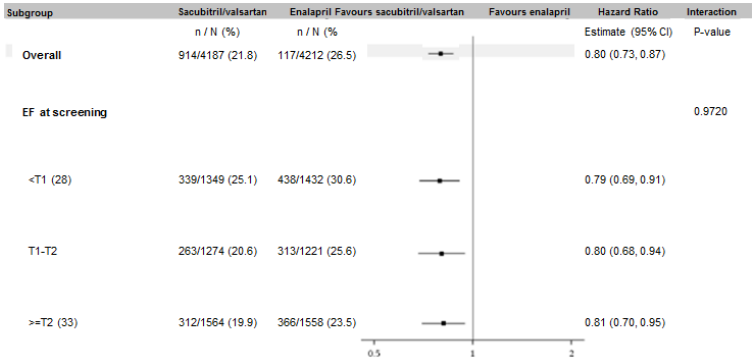
Response to Novartis comments on the ACD

This report was commissioned by the NIHR HTA Programme as project number 15/64/06

BMJ Technology Assessment Group

This document contains the ERG's responses to the comments on the ACD received from Novartis for *Sacubitril valsartan for treating chronic heart failure*.

Company's comment summary	Description of proposed amendment	ERG's response
1.1 Restriction to patients with LVEF of 35% or less Novartis proposes that NICE refers to "reduced ejection fraction" rather than a specific cut-off for LVEF in the final guidance for sacubitril/valsartan as consistent treatment benefit is seen across all subgroups of LVEF in PARADIGM-HF including 963 patients with LVEF >35% and ≤40%. The ACD has proposed to restrict treatment with sacubitril/valsartan to those patients with a LVEF of 35% or less on the basis that the LVEF inclusion criterion for the PARADIGM-HF trial was changed from 40% or less initially, to 35% or less (Section 4.8 of ACD). In this section we present evidence for the efficacy of sacubitril/valsartan in patients with LVEF >35% (n=963, 11.4% of patients in the trial). We also present arguments regarding the use of cut-off values for LVEF in clinical practice and resource use implications if this restriction was to be applied in practice. ***Efficacy of sacubitril/valsartan in patients with LVEF>35%*** Of the 8,442 randomised patients in PARADIGM-HF, a total of 963 patients (11.4%) had a LVEF >35% and ≤40%.The first amendment to LVEF in the PARADIGM-HF protocol, dated 15 December 2010, came into effect after 1,285 patients had been randomised into the study. The main purpose of the first amendment was to modify 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. This change was made in response to an anticipated increase in the use of aldosterone antagonists following the release of results from the EMPHASIS-HF trial in 2011 [(1)]. Increased use of aldosterone antagonists was expected to lower the event rate. Thus, the LVEF cut-off was lowered to offset this anticipated decrease in the event rate so that the targeted number of primary composite events would occur within a reasonable follow-up period. LVEF is one of several clinical measures of HF severity. Additional analyses based on other measures of disease severity, baseline NYHA Functional Classification, N-terminal prohormone B-type natriuretic peptide (NT-proBNP) tertiles, and the Meta-Analysis Global Group in Chronic Heart Failure score (MAGGIC score, which is the most widely accepted and used validated risk score for prediction of mortality in patients with HF [(2)], were performed to assess whether benefit associated with sacubitril/valsartan treatment in reducing CV death and HF hospitalisation was consistent in HF patients of various severities.	Overall Novartis proposes that NICE refers to "reduced ejection fraction" rather than a specific cut-off for LVEF in the final guidance for sacubitril/valsartan as: • consistent treatment benefit is seen across all subgroups of LVEF in PARADIGM-HF including 963 patients with LVEF >35% and ≤40%; • the use of EF cut offs outside of studies has limitations and will likely lead to a greater and unnecessary use of NHS resources. This proposal is in line with the EMA marketing authorisation and would ensure UK patients are able to equally benefit from improved outcomes due to this innovative medicine.	The company presented the results of an analysis of the primary endpoint by EF at screening tertiles. The subgroups were identified by dividing patients into three groups in correspondence of the cut-off EF values 28% and 33%. The analysis shows a consistent effect of sacubitril valsartan over enalapril across the three subgroups. However the ERG does not deem the analysis to be sufficient to prove that the relative effectiveness would be similar in the LVEF>35% subgroup. This is because the LVEF >35% was not compared to the LVEF≤ 35% separately, with only 30.85% of patients being included in the subgroup identified by the upper tertile (i.e. EF>33%). The company also presented results of a 5-point subgroup analysis based on arbitrarily-chosen LVEF at screening, i.e. ≤15%; 16% to ≤20%; 21% to ≤25%; 26% to ≤30%; 31% to ≤35%, and >35%. The company stated that no interaction between subgroup and treatment was found for the primary endpoint (p-value=0.9377) and for cardiovascular death (p-value=0.3367). The company did not provide the number of patients in each subgroup, the estimated effects or any further detail on the analysis. The ERG does not consider the analysis

Company's comment summary	Description of proposed amendment	ERG's response
The benefit of sacubitril/valsartan over enalapril for the primary endpoint was similar across the spectrum of risk (p = 0.159) based on the MAGGIC score [3]. Regarding efficacy in patients with LVEF >35%, there was a consistent treatment benefit in favour of sacubitril/valsartan over enalapril for the primary endpoint (p-value for interaction p=0.3599), and for cardiovascular death (p-value for interaction p=0.3559) for patients with LVEF >35% [4]. Additionally, for tertile subgroups for LVEF at screening (<28%, ≥28 to ≤33%, and ≥33%), there was a consistent treatment benefit in favour of sacubitril/valsartan over enalapril for the primary endpoint (p-value for interaction p=0.9720), and for cardiovascular death, regardless of the screening EF values (see Figure 1, [5]). Additional analyses of PARADIGM-HF data were performed using 5-point subcategories of LVEF for the primary endpoint and for CV death which demonstrated a consistent treatment benefit in favour of sacubitril/valsartan across all subgroups (See separate Appendix of new evidence, Section 5.1). **Figure 1: Forest plot for first confirmed primary endpoint (CV death or HF hospitalisation) by EF at screening tertiles (FAS) [5]**  Figure 11-7, page 293 of CSR ('A2 Novartis_2014_CSR_PARADIGM-HF PART 1.pdf' sent to NICE on 25 Sept 2015)		sufficient to support the statement of an equal relative effectiveness of the two treatment in the LVEF≤35% and >35% subgroups. This is because the analysis presented showed that the 5 subgroups identified do not seem to be different considered at the meantime. Given the lack of details regarding the analysis, it is unclear whether the company tested only for a linear interaction between treatment and subgroup effects. The ERG acknowledges that sacubitril valsartan appears to have consistent treatment benefit across the 5 subgroups identified by the company. However, the company did not prove that the relative benefits observed in LVEF ≤35% patients were not different in the LVEF>35% subgroup.

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Use of cut-off values for LVEF in clinical practice and resource use implication In addition to the consistent treatment effect observed across all LVEF subgroups (including >35%), the use of LVEF in clinical practice should also be considered. The European Public Assessment Report (EPAR) states that cut-off values for ejection fraction were an important part of the inclusion/exclusion of the patient population in the pivotal trial and EF is of diagnostic and prognostic value in HF. However the EPAR also states that the use of EF cut-offs outside of studies has limitations and hence a cut-off is not included in the indication. LVEF is an imprecise measure, which can vary in the clinical setting mainly due to (1) different methodologies for EF measurement, (2) inter- or intra-observer variability, and (3) temporary improvement or deterioration as a result of HF treatment or lifestyle measures (e.g. diet, salt intake, comorbidities, etc.). Per the European Society of Cardiology (ESC) guideline [(6)], 'It is important to note that EF values and normal ranges are dependent on the imaging technique employed, method of analysis, and operator.' In Section 4.8 of the ACD it is stated that 'The Committee discussed how the EF level will be determined in clinical practice and whether the required tests will be readily available to people who will potentially benefit from sacubitril valsartan. It was aware that EF level is usually demonstrated with an echocardiogram and additional tests will not necessarily be required before initiating sacubitril valsartan.' In the UK, operators who perform echocardiography often do not detail the EF value but just describe the grade of ventricular dysfunction (mild, moderate, severe) according to the qualitative categories as provided in the American Society of Echocardiography and the European Association of Cardiovascular Imaging Recommendations for Cardiac Chamber Quantification by Echocardiography in Adults [(7)]. Therefore, a precise LVEF value may not be readily available for all patients although reduced ejection fraction or ventricular systolic dysfunction is documented and the LVEF will change over time. A requirement for inclusion of a specific LVEF value for treatment may therefore limit the ability of physicians to prescribe the drug to a patient who could benefit from sacubitril/valsartan. Additionally, physicians might be required to repeat an echocardiogram to provide evidence that a patients EF is below the cut-off value leading to increased NHS resource use.	As above	The ERG acknowledges that LVEF measurement might be imprecise. However clinical expert opinion sought by the ERG confirmed that in the UK an ejection fraction of less than 35% is considered as a severe systolic dysfunction. The ERG also notes that this cut-off value is used for other analogous treatments, such as aldosterone antagonists. It is true that a repeated test for the measurement of the LVEF might result in an, "increased NHS resource use". However, the burden on the NHS would be markedly lighter than administering a relatively expensive treatment to a proportion of patients (LVEF>35%) who might not benefit from it as much as more severe patients.
1.2 Restriction to patients with NYHA Class II-III The ACD has proposed to restrict the recommendation of sacubitril/valsartan to those patients with NYHA Class II-III based on the limited representation of patients with NYHA Class IV in PARADIGM-HF (Section 4.9 of ACD).	Overall, Novartis proposes that NICE removes the restriction for NYHA Class IV from the final guidance for sacubitril/valsartan	The additional evidence provided by the company was a comparison of the proportion of patients by number of hospitalisations between the two PARADIGM-HF trial arms and analyses

Company's comment summary	Description of proposed amendment	ERG's response
In this response we present evidence to support the use of sacubitril/valsartan in patients with NYHA Class IV, specifically with respect to the efficacy and safety of sacubitril/valsartan in patients with NYHA IV. We also consider the impact on patients and prescribers if this restriction is imposed in practice. Efficacy and safety of sacubitril/valsartan in patients with NYHA IV Despite a small sample size, post-hoc subgroup analysis for patients with NYHA Class IV at randomisation shows that efficacy and safety are comparable to those of different NYHA Classes in comparison to the enalapril arm. Generally, there are the same trends of improvement in efficacy across different NYHA Classes (See separate Appendix of new evidence, Section 5.2 – Table 4). Regarding safety, in line with results of other NYHA Classes, there is a higher incidence of hypotension and a lower incidence of hyperkalaemia and renal impairment in the sacubitril/valsartan treatment arm for the NYHA Class IV subgroup. (See separate Appendix of new evidence, Section 5.2 – Table 5). The NYHA Functional Classification is one of several clinical measures of HF severity. Additional analyses based on other measures of disease severity, baseline LVEF, NT-proBNP tertiles, and the MAGGIC score (2) were performed to assess whether benefit associated with sacubitril/valsartan treatment in reducing CV death and HF hospitalisation was consistent in HF patients with various severities. Sacubitril/valsartan showed superiority over enalapril across all HFrEF patients including the more severe ones: patients with the highest baseline NT-proBNP tertile, patients with the lowest baseline LVEF tertile, and patients with the highest MAGGIC score (3). It is important to note that experience with NYHA Class IV patients in PARADIGM-HF is not only from those patients who were NYHA Class IV at randomisation (N=60), but also from the 323 patients having NYHA Class IV status at any visit during the double-blind period. NYHA class IV is associated with an increased risk of HF hospitalisation (8). The appropriateness of prescribing sacubitril/valsartan in patients with NYHA Class IV HF is further supported by the efficacy of sacubitril/valsartan in patients who deteriorated to Class IV during the trial by virtue of the fact that they were hospitalised for HF following randomisation. During PARADIGM-HF, 1195 patients (537 in the sacubitril/valsartan group and 658 in the enalapril group) were hospitalised for worsening HF (5). Even though at time of hospitalisation NYHA Class was not determined, these patients can essentially be considered NYHA Class IV, and subsequently fewer sacubitril/valsartan-treated patients experienced repeat hospitalisations for HF (N=170 of 537, 31.7%) compared to enalapril-treated patients (N=240 of 658, 36.5%), as shown in Table 1 (please also see Table 18 in the	as: • The evidence does not does support this restriction – specifically the data available does not demonstrate any particular efficacy/safety issue in patients with NYHA IV being treated with sacubitril/valsartan; • The oscillation of patients between NYHA III to NYHA IV may lead to confusion for the prescriber especially as there would be a requirement to switch therapy; • Restricting an innovative drug with likely benefit for subgroup of patients with the most severe symptoms and high risk of hospitalisation is counterintuitive and could lead to inequality of access.	on the primary efficacy endpoint and safety outcomes for NYHA class IV subgroup. The company stated that, "during PARADIGM-HF, 1996 patients (537 in the sacubitril/valsartan group and 658 in the enalapril group) were hospitalised for worsening HF. Even though at time of hospitalisation NYHA Class was not determined, these patients can essentially be considered NYHA Class IV […]". The ERG disagrees with this statement, as the company interpreted the analysis for NYHA IV patients at time of hospitalisation (in correspondence of a likely exacerbation of symptoms), while it should have been based on NYHA IV patients at baseline. This analysis is not considered to contribute with additional relevant evidence for the proposal put forward by the company. The company presented additional evidence in the form of a subgroup analysis of patients by NYHA class IV. The analysis on the primary outcome was based on the 60 out of 8,399 patients in the FAS population. The analysis on the safety endpoints was based on a subgroup analysis of the 60 out of 5,931 patients in the safety set who had a NYHA classification at baseline. A total of 323 patients, the 3.84% of the FAS sample size, were observed to have NYHA IV status in at least one visit during the double-blind period in both trial arms. No data by treatment

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<td>company submission). It should be noted that all HF hospitalisations (first and recurrent) were centrally adjudicated by the Clinical Endpoint Adjudication Committee (CEC). The benefit of sacubitril/valsartan in patients with NYHA Class IV was recognised by the CHMP.

Table 1: Rate of hospitalisations for HF (PARADIGM-HF, double-blind period, FAS) (Table 18 in company submission)

<table>
<tr><th></th><th>Sacubitril/valsartan N=4187</th><th>Enalapril N=4212</th><th>P-value (1)</th></tr>
<tr><td colspan="3">Patients hospitalised, classified by number of hospital admissions for HF - n (%)</td><td>0.0001**</td></tr>
<tr><td>0</td><td>3650 (87.17)</td><td>3554 (84.38)</td><td></td></tr>
<tr><td>1</td><td>367 (8.77)</td><td>418 (9.92)</td><td></td></tr>
<tr><td>2</td><td>110 (2.63)</td><td>143 (3.40)</td><td></td></tr>
<tr><td>3</td><td>33 (0.79)</td><td>53 (1.26)</td><td></td></tr>
<tr><td>≥ 4</td><td>27 (0.64)</td><td>44 (1.04)</td><td></td></tr>
<tr><td>At least one</td><td>537 (12.83)</td><td>658 (15.62)</td><td></td></tr>
</table>
</td>
<td></td>
<td>allocation was provided for this patient subgroup by the company.

The efficacy analysis did not show a significant treatment effect of sacubitril valsartan over enalapril, as expected given the extremely small sample size when compared to the overall number of patients in the FAS. The uncertainty associated with the relative benefits underpinning the cost-effectiveness of sacubitril valsartan was one of the factors leading to the decision; the amount of uncertainty is not reduced by the additional evidence provided by the company.

No justification for the choice of the three AEs included in the subgroup analysis of the safety endpoints was reported by the company. The data showed a similar safety profile for hypotension, renal impairment and hyperkalaemia in the NYHA class IV subgroup between sacubitril valsartan and enalapril. As expected a higher proportion of patients experienced hypotension, but given a relatively low number of patients at risk no conclusions can be taken.</td>
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Impact on patients and prescribers

The number of NYHA Class IV patients randomised in PARADIGM-HF (N=60) was in line with the numbers reported in recently completed HF trials including HEAAL (N=22), CHARM-added (N=78), and SHIFT (N=87) [8-10]. All the products studied in the aforementioned trials (e.g. ivabradine) are indicated for the treatment of HF including patients with NYHA Class IV and recommended as such by NICE clinical guidelines [11, 12].

The exclusion of NYHA Class IV patients from the population with HF who can be treated with sacubitril/valsartan would be very confusing for the prescriber, especially in relation to patients who develop transient NYHA Class IV symptoms while taking sacubitril/valsartan. If use of sacubitril/valsartan in NYHA Class IV patients was to be excluded, these "new" Class IV patients should be switched immediately to an ACEi or ARB. The results from PARADIGM-HF on the efficacy and safety in NYHA Class IV patients summarised in this document do not support this switch.

Furthermore, in the event that NYHA Class IV patients improve to NYHA Class III symptoms, their treatment should again be switched to sacubitril/valsartan to enable these patients to have the benefits of improved mortality and reduced hospitalisations. The transient nature of NYHA Class IV symptoms makes it impractical to change treatment in response to each change in the severity of symptoms. This confusion would be the inevitable result if the use of sacubitril/valsartan was restricted to patients with NYHA Class II-III only, for example when patients become dyspnoeic at rest even for short periods of time.

Finally it would be counterintuitive and discriminatory not to allow patients with the most severe symptoms who are at higher risk of hospitalisation to benefit from sacubitril/valsartan, especially as this is a relatively small population of approximately 10% of HF patients [13]. Furthermore, an additional aim of therapy is to reduce symptoms. In PARADIGM-HF, a post-hoc analysis of change from randomisation for NYHA was performed. At eight months, NYHA Class was improved for more patients in the sacubitril/valsartan group than in the enalapril group and NYHA Class worsened for fewer patients in the sacubitril/valsartan group than in the enalapril group (Table 23 in the company submission, and Table 1 below).

Table 1: Between-treatment analysis of change from randomisation for NYHA at Month 8 (FAS) (Table 23 in company submission)

Measurement	Category	Sacubitril/valsartan n (%)	Enalapril n (%)	p-value
Between-treatment	Patients with data	4,041 (100.00)	4,072 (100.00)	0.0002*

</td>
<td>As above</td>
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The company stated that, "The exclusion of NYHA Class IV patients from the population with HF who can be treated with sacubitril/valsartan would be very confusing for the prescriber, especially in relation to patients who develop transient NYHA Class IV symptoms while taking sacubitril/valsartan".

The ERG does not believe that prescribers would be confused by transient symptoms of patients. Furthermore, the ACD does not specify a stopping rule for patients treated with sacubitril valsartan who would experience NYHA IV symptoms; the preliminary recommendations are based on the patients' chronic, and not acute, characteristics.

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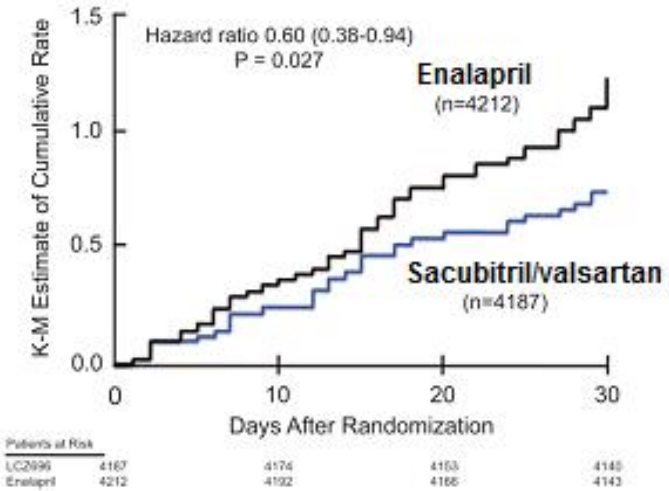
Company's comment summary	Description of proposed amendment	ERG's response
<table><tr><td rowspan="3">analysis of change from randomisation for NYHA†</td><td>Improved</td><td>639 (15.81)</td><td>569 (13.97)</td><td></td></tr><tr><td>Unchanged</td><td>2,989 (73.97)</td><td>2,990 (73.43)</td><td></td></tr><tr><td>Worsened</td><td>413 (10.22)</td><td>513 (12.60)</td><td></td></tr></table> †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.		
1.1 Restriction to patients currently on stable dose of ACEi or ARB The ACD has proposed to restrict the recommendation of sacubitril/valsartan to those patients who are already taking a stable dose of ACEi or ARBs, based on a lack of evidence for people who were treatment-naïve to ACEi or ARB (Section 4.2 of ACD). In this response we present a series of arguments to support the use of sacubitril/valsartan in ACEi/ARB-naïve patients, which contradicts the interpretation of clinical evidence as reported in the ACD, including the efficacy and safety of sacubitril/valsartan in ACEi/ARB-naïve patients as well as the impact on NHS resource use, burden and risk to patients. ***Efficacy of sacubitril/valsartan in ACEi/ARB-naïve patients*** There are no data to suggest, nor is there any clinically sound rationale why, patients who have not been previously treated with therapies that block the renin-angiotensin-aldosterone system (RAAS; ACEis/ARBs) receiving sacubitril/valsartan would not receive similar efficacy benefits to patients previously treated with ACEis/ARBs. The pivotal clinical trial for sacubitril/valsartan, PARADIGM-HF, tested the additional benefit of inhibiting neprilysin (sacubitril) over and above that of blocking RAAS (by valsartan/ ARB). PARADIGM-HF showed that neprilysin inhibition on top of RAAS blockade reduced CV death and HF hospitalisation more than RAAS blockade alone. Additionally, there is no evidence that the neuro-hormonal response to HF is different in ACEI/ARB-naïve patients. The treatment effect of sacubitril/valsartan was preserved in the closest proxy to ACEi/ARB-naïve patients in PARADIGM-HF – patients with a short time since diagnosis of HF (≤3 months, see separate Appendix of new evidence, Section 5.3). Furthermore, the PARADIGM-HF trial showed a consistent efficacy profile for sacubitril/valsartan across the spectrum of HFrEF severity (based on the MAGGIC risk score, [3])	Novartis proposes that NICE removes the restriction to patients on a stable dose of ACEi/ARB as: • PARADIGM-HF showed that neprilysin inhibition on top of RAAS blockade reduced CV death and HF hospitalisation more than RAAS blockade alone. • Time since diagnosis as a proxy to duration of exposure to RAAS inhibition showed no difference in treatment benefit with sacubitril/valsartan over ACEi, hence there is no evidence that ACEi/ARB-naïve patients would respond differently than patients on a stable dose of ACEi/ARB. • There are no anticipated safety issues associated with initiating in ACEI/ARB naïve patients (supported by the SmPC and the TITRATION study). • This restriction will result in initiation of an inferior therapy	The company stated that, "There are no data to suggest, nor is there any clinically sound rationale why, patients who have not been previously treated with therapies that block the renin-angiotensin-aldosterone system receiving sacubitril/valsartan would not receive similar efficacy benefits to patients previously treated with ACEis/ARBs". The ERG disagrees with this statement, as pre-specified subgroup analyses were indicative of a potential difference in the relative effectiveness of sacubitril valsartan compared to enalapril in treatment-naïve and experienced patients to treatment with ACEi and aldosterone antagonists.[4] These effects were tested on patients who were already taking a stable dose of ACEis or ARBs. The PARADIGM-HF trial was designed to demonstrate the superiority of sacubitril valsartan over enalapril in patients who would be able to tolerate a stable dose of ACEi/ARB therapy, and the patient selection is highlighted by the

Company's comment summary	Description of proposed amendment	ERG's response
The CHMP discussed the ACEi/ARB-naïve population based on the above points and concluded that a similar benefit of sacubitril/valsartan can be expected in patients not previously treated with ACEi/ARB [14]. ***Safety of sacubitril/valsartan in ACEi/ARB-naïve patients*** The safety and tolerability findings from the ACEi/ARB-naïve patients with HFrEF in the TITRATION study were very similar to the overall population. The majority of ACEi/ARB-naïve patients were able to achieve and maintain the 200 mg twice daily (bid) target dose of sacubitril/valsartan following gradual up-titration from 50 mg bid [15, 16]. Furthermore, sacubitril/valsartan hypertension studies included a significant number of ACEi/ARB-naïve patients which demonstrated a similar safety profile to the overall hypertension patient population (See separate Appendix of new evidence, Section 5.4). The limited experience in ACEi/ARB-naïve patients is clearly described in the SmPC and a lower starting dose is recommended [14]. Other than this recommendation, there are no explicit safety concerns highlighted in the SmPC regarding using sacubitril/valsartan in an ACEi/ARB-naïve population. ***Impact on NHS resource use and burden and risk to patients*** Additionally, the restriction to patients currently on stable dose of ACEi or ARB can also pose a risk to ACEi/ARB-naïve patients and impact NHS resource use. In the event that sacubitril/valsartan therapy could not be immediately initiated in ACEi/ARB-naïve patients, therapy would have to be initiated with an ACEi before the patient could be switched to sacubitril/valsartan (after a 36-hour washout period). This has the potential to double the number of contacts with health care professionals required to establish the patient on what is a superior therapy, adding unnecessary complexity to the process of initiating treatment. Ultimately this leads to additional NHS resource use and a substantial burden and risk to the patient, especially as many patients are frail with multiple co-morbidities and concomitant treatments. Importantly, the treatment benefit of sacubitril/valsartan versus ACEi for the primary composite endpoint and HF hospitalisations in PARADIGM-HF was evident as early as within the first 30 days (See Figure 2, [17]). In addition, the most common cause of death was sudden death (36.23% of patients who died [18]), with significantly less patients dying of sudden death in the sacubitril/valsartan arm compared to the ACEi arm (See Figure 3). Therefore, delay in initiating sacubitril/valsartan will discriminate against ACEi/ARB-naïve patients, who will be denied the additional benefits of neprilysin inhibition and will be at increased risk of experiencing a potentially fatal event during the ACEi treatment period.	prior to sacubitril/valsartan leading to substantial burden to patients, putting patients at unnecessary risk of hospitalisations and death, and additional NHS resource.	relatively high proportion of patients enrolled in the trial not accessing the double-blind phase. In conclusion, the ERG acknowledges the lack of data to suggest that patients not treated with ACEis or ARBs receiving sacubitril valsartan would not receive similar efficacy benefits to patients previously treated with these therapies. However, the company failed to provide data proving the opposite, i.e. patients not treated with ACEis or ARBs receiving sacubitril valsartan would receive similar efficacy benefits to patients previously treated with these therapies. The data presented by the company are not considered additional evidence by the ERG.

Company's comment summary	Description of proposed amendment	ERG's response
Figure 2: Kaplan–Meier estimate of the cumulative probability of a first hospitalisation for HF during the first 30 days after randomisation, by treatment [18]  **Figure 3: Kaplan–Meier curve for sudden death, by treatment [17]**		

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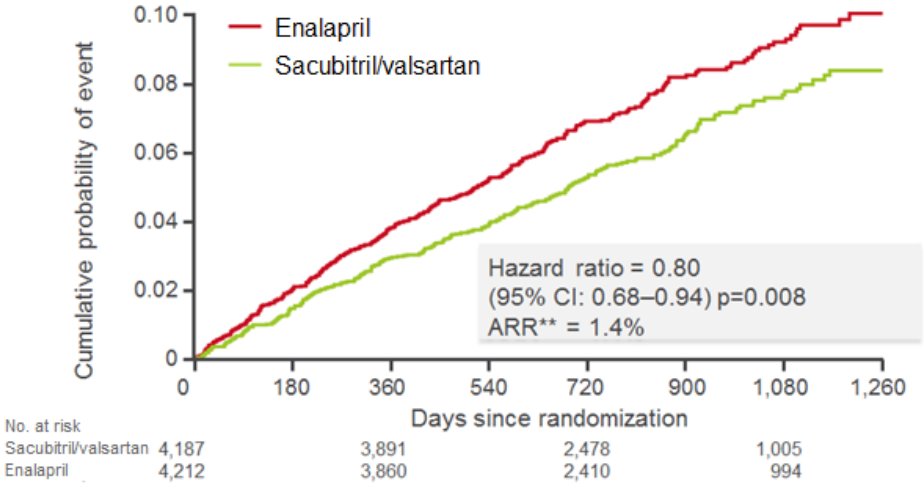		

Company's comment summary	Description of proposed amendment	ERG's response
1.2 Treatment should be started by a HF specialist with access to a multidisciplinary HF team. Dose titration and monitoring should be done by the HF specialist, or in primary care by either a GP with a special interest in HF or a HF specialist nurse. ***Clinical expert opinion at NICE Committee meeting*** Novartis has noted that in Section 4.10 of ACD, it is stated that the clinical experts at the NICE Committee meeting (held on 18 November 2015) specified the above restrictions to how sacubitril/valsartan should be initiated, titrated and monitored (as detailed in Section 1.2 of ACD). However, that level of detail was not discussed or agreed in the public session of the committee meeting, so we are very concerned that the guidance does not accurately capture the views expressed by the clinical experts at the meeting or the wider clinical community. ***Alignment with NICE Clinical Guidelines*** NICE expressed in Section 4.10 of the ACD that it was the intent to align this service recommendation with NICE CHF Clinical Guidelines (CG108) [(11)]. We note that in the NICE Guidelines, roles have not been specified, with regards to types of healthcare professional who should initiate, titrate and monitor HF treatment. NICE CHF Clinical Guidelines (CG108) state that 'HF care should be delivered by a multidisciplinary team with an integrated approach across the healthcare community [...] the team will decide who is the most appropriate team member to address a particular clinical problem'. Therefore, the ACD wording with regards to delivery of HF services is not aligned with the NICE Clinical Guidelines, which state that the HF multidisciplinary team decides the most appropriate team member to manage HF treatment. ***Inequality of access and adoption of innovation*** Specifying individual roles and types of healthcare professionals to manage sacubitril/valsartan in practice could lead to confusion and unintended inequality of access as there are wide geographical differences across England in how HF multidisciplinary teams are constituted and operated. This heterogeneity is likely to increase further given the new models of care being introduced across the NHS. How sacubitril/valsartan is implemented locally should be left to the multidisciplinary team to decide as indicated by CG108. Specifying a "specialist" in the guidance (even though this could be a HF nurse, GPSI, or HF cardiologist) could lead to lack of clarity and imply that patients must see a HF specialist in secondary care leading to delay and increased risk to patients. Additionally, NICE accepts that sacubitril/valsartan is an innovation in HF (vs ACEis/ARBs), but the ACD proposes service restrictions beyond CG108, which will impair the ability of NHS to adopt this	Novartis proposes that the wording in Section 1.2 of the ACD should be amended in the final guidance for sacubitril/valsartan in order to align with the NICE CHF Guidelines (CG108) with regards to the delivery of HR care. We propose that the guidance should instead read, "Treatment with sacubitril/valsartan should be initiated, titrated and monitored by the multidisciplinary heart failure team, as defined in the NICE CHF Clinical Guidelines (CG108)."	No additional evidence provided; this is a consideration for the NICE Appraisal Committee.

Company's comment summary	Description of proposed amendment	ERG's response
innovation thereby resulting in patients being unable to benefit from the improved outcomes equally.		

Company's comment summary	Description of proposed amendment	ERG's response
1.3 Western Europe subgroup in cost-effectiveness model ***Factual inaccuracy regarding post-hoc analysis*** It is not accurate to state that the Western Europe subgroup presented in the company submission was the post-hoc analysis i.e. excluding Israel and South Africa (pg. 37 of ACD). In fact, the Western Europe subgroup presented in the submission was the pre-specified subgroup (with Israel and South Africa included for operational reasons) (please see Table 13 as well as Section 5.9.3 in the company submission which states that 'The model was run for 39 subgroups identified a priori in the statistical analysis plan for PARADIGM-HF'). ***Point estimate hazard ratio from Western Europe subgroup*** The Committee concluded that the Western Europe subgroup was the most representative of clinical practice in England, but that the lack of statistical significance associated with the Western Europe subgroup would not factor in its decision-making and it would therefore focus on the point estimate hazard ratio in this subgroup (0.89 95% CI, 0.74-1.07 for primary composite endpoint) as it is in the same direction and supports the estimates for the overall trial population (0.80 95% CI, 0.73-0.87 for primary composite endpoint). However, it is inappropriate to apply the hazard ratio from a subgroup where there is no evidence of an interaction effect. The article by Rothwell et al. state the correct analysis to consider when assessing subgroups is the test of subgroup-treatment effect interaction [(19)]. In Section 4.5 of the ACD the Committee considers and accepts evidence which Novartis believes contradicts the appropriateness of using the HR from the Western Europe subgroup in the ERG's analysis, because: • tests of interaction showing no evidence of treatment-effect modifiers by region (p=0.3737) for the primary composite endpoint. The hazard ratios within subgroup assume independence (of each other). This is a strong assumption and with an interaction p-value that is not significant further indicates that the overall hazard ratio rather than the subgroup hazard ratio should be used as there is no significant difference the subgroups vary (from the overall). • Western Europe subgroup is not powered to detect statistically significant differences in the primary endpoint • across all pre-specified subgroups, sacubitril/valsartan was consistently better than ACEi with regard to the primary endpoint, and all hazard ratio point estimates suggested a benefit in the sacubitril valsartan group; because the results of subgroup analyses were consistently positive, any differential interpretation of	Novartis proposes that the Committee should use PARADIGM-HF data from the overall population in the model (including efficacy data) as this would be a more accurate reflection of the treatment effect, and therefore the cost-effectiveness, of sacubitril/valsartan. This would lead to a most plausible ICER of £19,843 vs the ERG's ICER of £29,478, when applying all other ERG assumptions. • There is no statistical basis for applying a subgroup HR if tests of interaction showed no evidence of treatment-effect modifiers by region. • There is no face validity in concluding that the Western Europe subgroup (including South Africa and Israel) was the most representative of clinical practice in England as other (larger) subgroups that could be as representative (i.e., Caucasian) are not considered.	The ERG acknowledges the warnings issued by the company and considers that the Appraisal Committee has used the necessary caution when interpreting the subgroup analyses. The Western European subgroup accounted for approximately 25% of the total trial population, including 2,057 patients in total. The ERG does not consider the inclusion of Israel and South African patients to have biased the results. The ERG disagrees with the substitution of the Western European subgroup with the Caucasian subgroup as a more appropriate subgroup proposed by the company. Clinical expert opinion sought by the ERG confirmed that HF aetiology (e.g. ischaemic aetiology), management (e.g. ICD, follow-up) and outcomes (e.g. hospitalisations for non-HF reasons) vary substantially across the world; in the ERG's opinion the varying relative effectiveness of sacubitril valsartan over enalapril observed in different regions is likely to be a direct consequence of these differences.

Company's comment summary	Description of proposed amendment	ERG's response
treatment effect in subgroups should be undertaken with caution Furthermore, in Section 4.5 it is stated that 'The Committee noted that the ERG had considered the Western Europe subgroup to be the most representative of clinical practice in England. It understood that the ERG based this on the race, age and cardiac device use of the Western Europe subgroup.' The ERG rationale that Western Europe is the most representative of the English population could also be argued for the Caucasian subgroup with the latter subgroup being twice the size of the Western Europe subgroup. A large proportion of patients in the Western Europe subgroup ([redacted] See Question A1 in Novartis response to ERG clarification questions) belong to the Caucasian/White subgroup. The average age in the Caucasian/White subgroup for sacubitril/valsartan is [redacted] years and enalapril [redacted] years (See CSR - Table 14.1-3.1.3 [5]) therefore is comparable to the Western Europe subgroup (for sacubitril/valsartan is [redacted] years and enalapril [redacted] years respectively). Face validation of the point estimate HR for the primary endpoint in PARADIGM-HF for the Western Europe subgroup and the Caucasian/White subgroup generates counterintuitive results (0.89 versus 0.80 respectively). The race subgroup analysis also show no p-value for interaction so if the same logic was applied (which we do not support) the Committee should take into account the fact that, the Caucasian subgroup shows a significant benefit for sacubitril/valsartan (CV death HR 0.80 95% CI, 0.70, 0.93). Caution should always be applied when interpreting subgroup analyses in clinical trials. When the full trial population is split into smaller subgroups which are not powered to detect statistically significant differences in treatment effect, the likelihood of chance findings means it is improbable that the observed point estimate HR between two groups will be the same, even if the true treatment effect is not different between them [19, 20].		

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1.4 Quality of life (QoL) in cost-effectiveness model

A linear mixed regression model based on EQ-5D trial data from PARADIGM-HF was applied in the cost-effectiveness model to predict utility scores. The utility model included a small but highly significant treatment effect in favour of sacubitril/valsartan after controlling for the effects of hospitalisations and adverse events. The baseline utility score was based on patient-level data from PARADIGM-HF.

The ERG expressed concerned regarding the validity of the QoL analysis presented in the submission which the Committee agreed with, specifically:

- The ERG could not be certain whether there was a baseline statistically significant difference in patients' EQ-5D scores between the 2 treatment groups of sacubitril/valsartan and enalapril. It suggested the statistical test performed by the company (two-sample t-test), that found there was no statistically significant difference, might not be appropriate.
- 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 QoL across the treatment groups. The ERG suggested that, assuming patients in a healthier state would have better outcomes, the potential imbalance in disease severity might have favoured the sacubitril/valsartan group.

Table 2 below presents the differences between the Novartis and ERG QoL modelling approach – both models are largely identical with the exception of the sacubitril/valsartan treatment effect, baseline EQ-5D and calculation in model.

Table 2: Comparison of Novartis and ERG QoL model features

Features of QoL model	Novartis approach	ERG simplified approach
Assuming treatment benefit of 0.011 with sacubitril/valsartan	Included based on highly significant and persistent improvement with S/V over time for EQ-5D regression models – as well as statistically significant similarity of EQ-5D means at baseline	Excluded based on concern around QoL at baseline
Baseline EQ-5D	0.78 (based on PARADIGM-HF)	0.72 (based on Berg et al.)
Time effect	-0.008	Same as Novartis model

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Novartis proposes that the Committee should accept the utility gain of 0.011 for sacubitril/valsartan as this is an evidence-based outcome and would be a more accurate reflection of the treatment effect, and therefore the cost-effectiveness, of sacubitril/valsartan. This would lead to a most plausible ICER of £25,607 vs the ERG's ICER of £29,478 when applying all other ERG assumptions.

- The key concern is that the EQ-5D analysis did not adjust for baseline difference. However, this is incorrect as the EQ-5D analysis was based on a repeated measures ANCOVA model which controls for any (random) differences or imbalance in baseline EQ-5D and has not affected the results of either the trial or the model.
- Additionally, the EQ-5D benefit is supported by other symptom and QoL measures in the trial including KCCQ and NYHA shift some consistent QoL benefit and symptom reduction with sacubitril/valsartan.

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The company did not provide additional evidence regarding the implementation of patients' health-related QoL in the economic model.

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Company's comment summary	Description of proposed amendment	ERG's response

Hospitalisation decrement	-0.21	Same as Novartis model
Hypotension decrement	-0.06	Same as Novartis model
Cough decrement	-0.07	Same as Novartis model
Calculation of EQ-5D in model	EQ-5D predicted at all time points using the model of HRQoL	Estimated decline in EQ-5D, effects of AEs/ hospitalisation are applied to a baseline value (which may be defined/edited by the user)

The selection of the EQ-5D at baseline from PARADIGM-HF data follows the NICE reference case, which states that EQ-5D should be sourced from the clinical trial, and if not available data can be sourced from the literature [21]. However due to the run-in period in PARADIGM-HF, we accept the exploration of a lower baseline EQ-5D from the literature to understand the potential impact on the ICER (which was minimal).

However, the removal of the sacubitril/valsartan EQ-5D treatment effect from the QoL model was based on a scientifically and methodologically incorrect conclusion that there may have been a statistically significant difference in patients' EQ-5D scores at baseline which may have biased the EQ-5D outcomes in favour of sacubitril/valsartan. The below sections provide argumentation against the assumption of differential baseline scores for both EQ-5D and KCCQ measures from PARADIGM-HF.

EQ-5D

It is important to note that testing for baseline differences between the intervention and control group in randomised controlled trials is typically not appropriate [22] as differences at baseline across both groups are by definition due to chance given randomisation. Furthermore, the EQ-5D analysis was based on a repeated measures ANCOVA model which includes treatment, region, visit, and treatment-by-visit interaction as fixed effect factors and baseline value as a covariate with a common unstructured covariance for each treatment group. Therefore, any (random) differences or imbalance in baseline EQ-5D have been controlled for and have not affected the results of either the trial or the model.

Company's comment summary	Description of proposed amendment	ERG's response
With regards to the ERG's specific concern around the appropriateness of the t-test used to assess similarity of means at baseline, 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 [(23)]. Both the means and standard deviations from the two samples are almost identical. This supports the argument that the t-test is an appropriate statistical test to assess similarity of mean EQ-5D at baseline. Therefore, the ERG's concerns regarding a potential difference in baseline EQ-5D biasing the trial results in favour of sacubitril/valsartan are unfounded and not based on evidence. As such, we argue that the highly statistically significant EQ-5D treatment effect associated with sacubitril/valsartan is valid (and not a product of bias) and should be included in the base case model analysis. The QoL benefit of sacubitril/valsartan compared to enalapril demonstrated with EQ-5D is further supported by NYHA shift and KCCQ outcomes showing benefit of sacubitril/valsartan in terms of symptoms and QoL. More people in sacubitril/valsartan arm were reporting improvement in symptoms as evidenced by KCCQ and NYHA [(18)]. ***KCCQ*** The ERG expressed concern that a statistically significant difference in KCCQ scores at baseline could be considered clinically meaningful and that this could potentially bias the trial and model outcomes, as well as imply a difference of EQ-5D at baseline in the same PARADIGM-HF population. A study by Spertus et al.[(24)] states that a minimal difference of 5 points over time depicts a clinically meaningful difference in HF. Even though this is not across treatments, this is transferable to this example. The difference between sacubitril/valsartan and KCCQ at baseline is statistically significant, however not clinically meaningful as it is 1.26 points, substantially below the 5 point mark. Further to the above argument regarding the clinically meaningful difference in KCCQ scores, the ERG did not acknowledge that the KCCQ analysis in PARADIGM-HF was in fact adjusted for at baseline (in contrast to their assumption that KCCQ was not controlled for at baseline in p.161 of ERG report, [(5)]). The KCCQ analysis was based on a repeated measures ANCOVA model which includes treatment, region, visit, and treatment-by-visit interaction as fixed effect factors and baseline value as a covariate with a common unstructured covariance for each treatment group. Therefore, any (random) differences in baseline KCCQ have been controlled for and have not affected the results of either the trial or the model.		

Company's comment summary	Description of proposed amendment	ERG's response
1.5 Summary of cost-effectiveness model issues Please note Novartis was able to replicate the ERG's ICER (£19,843) with all the following modifications incorporated (Table 86 in ERG report): • Mean age at baseline of 75 years • Change in baseline utility to reflect Berg et al utility (0.72) • Change in QoL modelling approach • Change in pharmaceutical costs to reflect drug target dose • Change in pharmaceutical costs to reflect the cost of ramipril However, Novartis was not able to exactly replicate the ERG's ICER with all changes incorporated (£29,478) nor the ICER compared with base case for the Western Europe subgroup (£20,550) in Table 86 of the ERG report, even when precisely following the instructions detailed in the 'Addendum to the ERG report' (received on the 10th November 2015). Following these instructions, Novartis generated a final ERG ICER of £26,061 per QALY and an ICER versus base case for the Western Europe subgroup of £19,948. Novartis noted that the modifications associated with the Western Europe subgroup overrode previous ERG assumptions (i.e. any changes to baseline characteristics), which could explain these discrepancies. However, even when Novartis re-incorporated these previous assumptions around baseline characteristics, the ERG's ICER still could not be exactly replicated.	Novartis proposes that the ERG updates the Addendum to the ERG report to be able to replicate all ICERs in Table 86 and that this is reflected in the final guidance. Additionally, Novartis proposes that the Committee use PARADIGM-HF data from the overall trial population and accept the utility gain of 0.011 for sacubitril/valsartan (as discussed above in Sections 2.3 and 2.4) to generate the most plausible ICER for sacubitril/valsartan. Implementing the above changes and keeping the remaining ERG ICER assumptions (as per Table 86 of the ERG report) would lead to a most plausible ICER of £19,530 (vs the ERG's ICER of £29,478).	The ERG confirms that the Western European baseline characteristics were overridden by changes to selected characteristics, e.g. mean age and utility score, as noted by the company. However, the override was not applied to the Western European mean values in the "Regression Values" sheet of the electronic model. The ERG considers that no further action is needed as the company could replicate approximately, albeit not exactly, the ERG's results. However, the ERG is happy to provide a detailed explanation of its changes to the company's model should the company wish to evaluate this further. The company did not provide additional evidence supporting the proposed changes.
2 Are the provisional recommendations sound and a suitable basis for guidance to the NHS? In Section 4.19 of the ACD it is stated that 'the Committee was aware that sacubitril/valsartan has been granted a promising innovative medicine (PIM) designation by the Medicines and Healthcare Products Regulatory Agency. The ACD does not mention that sacubitril/valsartan received a positive opinion for the Early Access to Medicine Scheme (EAMS) by the MHRA.	Novartis proposes the following change to the wording to Section 4.19 In addition, the Committee was aware that sacubitril/valsartan has been granted a promising innovative medicine designation and received a positive opinion for the Early Access to Medicine Scheme by the Medicines and Healthcare Products Regulatory Agency. Additionally, Novartis proposes that Section 5.1 states that drugs	No additional evidence; this is a consideration for the NICE Appraisal Committee.

Company's comment summary	Description of proposed amendment	ERG's response
	introduced through EAMS are expected to be introduced prior to the 90 day limit set out in the regulations. CCGs and Trusts will be expected to implement the NICE TA within a 30 day period (https://www.england.nhs.uk/wp-content/uploads/2015/10/eams-letter-oct15.pdf).	
3 Consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity? Novartis does not foresee any significant equality issues above associated with the use of sacubitril/valsartan in people with HFrEF, other than the issues we have highlighted throughout the document that are as a result of the restrictions proposed by NICE.	N/A	N/A

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