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Dual angiotensin receptor and neprilysin inhibition as an alternative to angiotensin-converting enzyme inhibition in patients with chronic systolic heart failure: rationale for and design of the Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure trial (PARADIGM-HF)

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Aims Although the focus of therapeutic intervention has been on neurohormonal pathways thought to be harmful in heart failure (HF), such as the renin–angiotensin–aldosterone system (RAAS), potentially beneficial counter-regulatory systems are also active in HF. These promote vaso-dilatation and natriuresis, inhibit abnormal growth, suppress the RAAS and sympathetic nervous system, and augment parasympathetic activity. The best understood of these mediators are the natriuretic peptides which are metabolized by the enzyme neprilysin. LCZ696 belongs to a new class of drugs, the angiotensin receptor neprilysin inhibitors (ARNIs), which both block the RAAS and augment natriuretic peptides.

Methods Patients with chronic HF, NYHA class II–IV symptoms, an elevated plasma BNP or NT-proBNP level, and an LVEF of ≤40% were enrolled in the Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure trial (PARADIGM-HF). Patients entered a single-blind enalapril run-in period (titrated to 10 mg b.i.d.), followed by an LCZ696 run-in period (100 mg titrated to 200 mg b.i.d.). A total of 8436 patients tolerating both periods were randomized 1:1 to either enalapril 10 mg b.i.d. or LCZ696 200 mg b.i.d. The primary outcome is the composite of cardiovascular death or HF hospitalization, although the trial is powered to detect a 15% relative risk reduction in cardiovascular death.

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† See Appendix 1 for a complete list of the PARADIGM-HF Committees and Investigators.

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Introduction

Neurohormonal pathways are thought to be fundamentally important in the pathophysiology of heart failure. The belief that sustained activation of certain neurohumoral pathways such as the renin–angiotensin–aldosterone system (RAAS) and sympathetic nervous system (SNS) is detrimental in heart failure underpins the basis of therapy. The crucial importance of the RAAS is supported by the beneficial effects of ACE inhibitors, ARBs, and mineralocorticoid receptor antagonists. Likewise, the benefits of beta-blockers argue for a key role of the SNS. Although the focus of therapeutic intervention has been on blocking these pathways thought to be harmful in heart failure, potentially beneficial counter-regulatory systems are also activated in heart failure. These pathways variously promote vasodilation and natriuresis, inhibit abnormal growth, suppress the RAAS and SNS, inhibit the release and actions of vasoressin, and augment the parasympathetic nervous system. The best understood mediators exerting these actions are the natriuretic peptides. The first of these to be described, A-type natriuretic peptide (ANP), is secreted in response to atrial distension, activates the ANPR-A receptor, increasing intracellular cyclic guanylate monophosphate (cGMP), and is cleared by the ANPR-C receptor and by the action of the enzyme neutral endopeptidase (NEP), also known as nepri lysin. B-type natriuretic peptide, secreted predominantly by the ventricles in response to increased wall stress, exerts similar actions and is cleared in the same way.

Augmentation of natriuretic peptides has been considered as a therapeutic strategy in heart failure for over two decades. Because oral delivery of these peptides is ineffective and long-term parenteral delivery is problematic, blockade of natriuretic peptide breakdown, by inhibition of nepri lysin, has been developed as an alternative approach to increasing natriuretic peptides. Oral nepri lysin inhibitors, used in combination with ACE inhibitors, had favourable short-term effects on haemodynamic measurements and exercise time in patients with heart failure, but were not developed further. Subsequently, a molecule that was both a nepri lysin and an ACE inhibitor, omapatrilat, was studied in both hypertension and heart failure, but its development was terminated because of an unacceptable incidence of angioedema. This adverse effect was thought to occur because both ACE and nepri lysin break down bradykinin, which directly or indirectly can cause angioedema, and because omapatrilat may also inhibit a third enzyme metabolizing bradykinin, aminopeptidase P. Angiotensin receptor nepri lysin inhibitors (ARNIs) are a new class of drug developed both to block the RAAS and augment natriuretic peptides. By so doing, ARNIs have the potential to modulate favourably the neurohormonal imbalance that characterizes heart failure. Because RAAS blockade is achieved by antagonism of the angiotensin II type 1 receptor, and not by inhibition of ACE (or aminopeptidase P), it is hypothesized that the risk of angioedema will not be increased. LCZ696 is the first ARNI to be tested in patients, and here we describe the design of the Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure trial (PARADIGM-HF).
Screening (Visit 1)
At the screening visit, patient eligibility was assessed according to the inclusion/exclusion criteria (including the criteria in Table 3). Any local measurement of LVEF within the eligibility range made within the past 6 months was acceptable provided there was no subsequent LVEF measurement above it. Eligibility BNP (and NT-proBNP), serum potassium, and estimated glomerular filtration rate (eGFR) were measured in a central laboratory.

Enalapril active run-in period (Visit 2)
At Visit 2, most eligible patients started 2 weeks of single-blind treatment with enalapril 10 mg b.i.d. A lower dose of enalapril (5 mg b.i.d.) was allowed for patients currently treated with an ARB and for those taking a low dose of ACE inhibitor (see Table 1) if the investigator was concerned that switching directly to enalapril 10 mg b.i.d. might not be tolerated (e.g. because of hypotension, renal dysfunction, and/or hyperkalaemia). These patients were up-titrated to enalapril 10 mg b.i.d. after 1–2 weeks. Patients tolerating enalapril 10 mg b.i.d. as defined by the criteria in Table 3 were eligible for Visit 3.

LCZ696 active run-in period (Visits 3 and 4)
At Visit 3, patients started single-blind treatment with LCZ696 100 mg b.i.d. After 1–2 weeks, the dose was up-titrated to 200 mg b.i.d., for a further 2–4 weeks.

Other heart failure medication (except for an ACE inhibitor or ARB) was continued during the run-in periods.

Randomization to double-blind treatment (Visit 5)
Patients tolerating both enalapril 10 mg b.i.d. and LCZ696 200 mg b.i.d., as defined by the criteria in Table 3, were randomized in a 1:1 ratio to double-blind treatment with either enalapril 10 mg b.i.d. or LCZ696 200 mg b.i.d. Study visits occur every 2–8 weeks during the first 4 months of the double-blind period and every 4 months thereafter (with additional unscheduled visits, at the discretion of the investigator).

There were two short washout periods during the run-in periods to minimize the potential risk of angioedema due to overlapping ACE inhibition and NEP inhibition at Visit 3 and Visit 5: (i) enalapril was stopped a day prior to starting LCZ696 at Visit 3 and (ii) LCZ696 was stopped a day prior to starting randomized study drug at Visit 5.

Monitoring of safety and tolerability during double-blind period
Patients are assessed at each study visit for hyperkalaemia, symptomatic hypotension, increase in serum creatinine, angioedema, and other adverse events (AEs) and serious AEs. Patients who can no longer tolerate the target dose of study drug can be down-titrated to the lower dose at the investigator's discretion (after considering whether any other relevant non-disease-modifying...
Table 2 Key exclusion criteria

1. History of hypersensitivity or allergy to any of the study drugs, drugs of similar chemical classes, ACE inhibitors (ACEIs), ARBs, or neprilysin inhibitors, as well as known or suspected contraindications to the study drugs.
2. Previous history of intolerance to recommended target doses of ACEIs or ARBs.
3. Known history of angioedema.
4. Requirement for treatment with both ACEIs and ARBs.
5. Current acute decompensated heart failure (exacerbation of chronic heart failure manifested by signs and symptoms that may require intravenous therapy).
6. Symptomatic hypotension and/or a systolic blood pressure <100 mmHg at Visit 1 (screening) or <95 mmHg at Visit 3 or at Visit 5 (randomization).
7. Estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m² at Visit 1 (screening), Visit 3 (end of enalapril run-in), or Visit 5 (end of LCZ696 run-in and randomization) or >35% decline in eGFR between Visit 1 and Visit 3 or between Visit 1 and Visit 5.
8. Serum potassium >5.2 mmol/L at Visit 1 (screening) or >5.4 mmol/L at Visit 3 or Visit 5 (randomization).
9. Acute coronary syndrome, stroke, transient ischaemic attack, cardiac, carotid, or other major cardiovascular surgery, PCI, or carotid angioplasty within the 3 months prior to Visit 1.
10. Coronary or carotid artery disease likely to require surgical or percutaneous intervention within the 6 months after Visit 1.
11. Implantation of a CRT device within 3 months prior Visit 1 or intent to implant a CRT.
12. History of heart transplant or on a transplant list or with LV assistance device.
14. Diagnosis of peripartum- or chemotherapy-induced cardiomyopathy within the 12 months prior to Visit 1.
15. Documented untreated ventricular arrhythmia with syncopeal episodes within the 3 months prior to Visit 1.
16. Symptomatic bradycardia or second- or third-degree atrioventricular block without a pacemaker.
17. Presence of haemodynamically significant mitral and/or aortic valve disease, except mitral regurgitation secondary to LV dilatation.
18. Presence of other haemodynamically significant obstructive lesions of the LV outflow tract, including aortic and subaortic stenosis.
19. Any surgical or medical condition which might significantly alter the absorption, distribution, metabolism, or excretion of study drugs, including, but not limited to, any of the following:
   - History of active inflammatory bowel disease during the 12 months before Visit 1.
   - Active duodenal or gastric ulcers during the 3 months prior to Visit 1.
   - Evidence of hepatic disease as determined by any one of the following: aspartate aminotransferase or alanine aminotransferase values exceeding 2 × upper limit of normal at Visit 1, history of hepatic encephalopathy, history of oesophageal varices, or history of porto-caval shunt.
   - Current treatment with cholestyramine or colestipol resins.
20. Presence of any other disease with a life expectancy of <5 years.

Collection and adjudication of potential angioedema events

Potential angioedema cases are identified in two ways: (i) proactive reporting of any events that resemble angioedema by site investigators; and (ii) routine safety monitoring by the sponsor for signs or symptoms suggestive of potential angioedema. All identified cases are submitted to an independent angioedema adjudication committee for a final decision.

Study objectives

Primary objectives

The purpose of this study is to evaluate the effect of LCZ696 200 mg b.i.d. compared with enalapril 10 mg b.i.d., in addition to conventional heart failure treatment, in delaying time to first occurrence of either cardiovascular (CV) death or heart failure hospitalization.

Secondary objectives

Secondary endpoints were to test whether LCZ696, compared with enalapril, is superior: (i) in improving the Kansas City Cardiomyopathy Questionnaire (KCCQ) clinical summary score for heart failure symptoms and physical limitations at 8 months; (ii) in delaying the time to all-cause mortality; (iii) in delaying time to new onset atrial fibrillation; and (iv) in delaying the time to first occurrence of either: (a) a 50% decline in eGFR relative to baseline (i.e. Visit 5); (b) >30 mL/min/1.73 m² decline in eGFR relative to baseline to a value <60 mL/min/1.73 m²; or (c) reaching end-stage renal disease.

Exploratory objectives

These are listed in Table 4.

Study management and committees

PARADIGM-HF is conducted by Novartis AG under the guidance and leadership of the Executive Committee. The National Leaders of participating countries are listed in Appendix 1.

An independent, external Data Monitoring Committee (DMC) (listed in Appendix 1) has been appointed to oversee the safety of the patients and review the results of the interim analyses. An Endpoint Adjudication Committee (listed in Appendix 1) is responsible for classifying all deaths and for determining whether pre-
specified endpoint criteria are met for the non-fatal events. Another committee is adjudicating suspected cases of angioedema in this and other trials using LCZ696 (listed in Appendix 1).

### Statistical considerations

The estimated annual event rate for the primary endpoint in the control (enalapril) arm of PARADIGM-HF was based on the Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity (CHARM)-Added trial where the annual event rate for the primary endpoint in the candesartan group was 15.8%.[25] Because patients are treated with a higher dose of ACE inhibitor (or LCZ696 equivalent) in PARADIGM-HF and a greater proportion were expected to receive a beta-blocker and a mineralocorticoid antagonist, a more conservative expected annual event rate of 14.5% was chosen for sample size calculation. The annual CV mortality rate of 7% was estimated from the CHARM-Added trial in a similar manner. We also anticipated that the requirement for an elevated BNP or NT-proBNP level at enrolment would ensure an adequate event rate. The sample size is based upon the CV mortality (although the trial will continue until the required number of patients have the same composite was 16.6% in the placebo group and 14.1% in the candesartan group).[25] Because patients are treated with a higher dose of ACE inhibitor (or LCZ696 equivalent) in PARADIGM-HF and a greater proportion were expected to receive a beta-blocker and a mineralocorticoid antagonist, a more conservative expected annual event rate of 14.5% was chosen for sample size calculation. The annual CV mortality rate of 7% was estimated from the CHARM-Added trial in a similar manner. We also anticipated that the requirement for an elevated BNP or NT-proBNP level at enrolment would ensure an adequate event rate. The sample size is based upon the CV mortality (although the trial will continue until the required number of patients have

<table>
<thead>
<tr>
<th>Trial</th>
<th>n</th>
<th>Target dose (mg)</th>
<th>Mean/median daily dose (mg)</th>
</tr>
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<td>CONSSENSUS (1987)</td>
<td>127</td>
<td>20 b.i.d.</td>
<td>18.39</td>
</tr>
<tr>
<td>SOLVD-T (1991)</td>
<td>1285</td>
<td>10 b.i.d.</td>
<td>16.65</td>
</tr>
<tr>
<td>SOLVD-P (1992)</td>
<td>2111</td>
<td>10 b.i.d.</td>
<td>16.78</td>
</tr>
<tr>
<td>V-HeFT II (1991)</td>
<td>403</td>
<td>10 b.i.d.</td>
<td>15.71</td>
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<tr>
<td>NETWORK (1998)</td>
<td>516</td>
<td>10 b.i.d.</td>
<td>17.93</td>
</tr>
<tr>
<td>Nanas et al. (2000)</td>
<td>122 low</td>
<td>10 b.i.d.</td>
<td>17.93</td>
</tr>
<tr>
<td></td>
<td>126 high</td>
<td>30 b.i.d.</td>
<td>19.33</td>
</tr>
<tr>
<td>OVERTURE (2002)</td>
<td>2884</td>
<td>10 b.i.d.</td>
<td>17.77</td>
</tr>
<tr>
<td>CARMEN (2004)</td>
<td>190 E only</td>
<td>10 b.i.d.</td>
<td>16.84</td>
</tr>
<tr>
<td></td>
<td>191 E + C</td>
<td>10 b.i.d.</td>
<td>14.93</td>
</tr>
<tr>
<td>CIBIS-3 (2005)</td>
<td>505 B first</td>
<td>10 b.i.d.</td>
<td>15.85</td>
</tr>
<tr>
<td></td>
<td>505 E first</td>
<td>10 b.i.d.</td>
<td>17.25</td>
</tr>
</tbody>
</table>
experience a primary event. This means that PARADIGM-HF should have >97% power to detect a relative risk reduction of 15% in this composite.

A final statistical analysis plan will be developed prior to the end of the study and treatment unblinding.

**Study duration, interim analyses, and early termination**

As PARADIGM-HF is an event-driven trial, all randomized patients will remain in the trial until 2410 patients have experienced a CV death or heart failure hospitalization, unless the DMC recommends that the study be stopped earlier for efficacy or safety reasons. The total length of the trial will depend on the duration of the patient recruitment period and the time taken to accrue the pre-specified number of patients with a primary event. Currently, three interim efficacy analyses are planned when approximately one-third, one-half, and two-thirds of the primary events have occurred. The one-sided significance level of $\alpha$ to be used for the final analysis will be adjusted for the interim efficacy analyses to control the overall type I error at 2.5% (one-sided). A futility analysis will also be performed at each of these interim analyses, permitting early termination of the trial for lack of efficacy.

**Safety considerations**

In view of the limited exposure of patients with heart failure to LCZ696 before the start of PARADIGM-HF, the DMC performed a safety assessment after the first 100, 300, and 600 patients completed the run-in period and the number of patients exposed to study drug was also limited to 600 until the DMC had evaluated safety in the first 200 patients to complete 4 weeks of double-blind therapy. Thus, this study employed a seamless design, incorporating ‘Phase II’ into a ‘Phase III’ outcomes trial, as considered further in the Discussion. Further interim safety assessments are planned twice a year.

**Current status**

The protocol was approved by the Ethics Committee/Institutional Review Board affiliated to each investigative site. Patients started enrolling in PARADIGM-HF on 8 December 2009. As of 17 January 2013, the study was fully enrolled, with 8436 validly randomized patients at 985 centres in 47 countries distributed across all major geographical regions.

The study is being conducted in accordance with Good Clinical Practice, Declaration of Helsinki 2002. The trial has been registered on Clinicaltrials.gov, NCT01035255.

**Discussion**

A strategy of dual RAAS blockade and natriuretic peptide augmentation is theoretically attractive in heart failure and was tried previously with the dual neprilysin/ACE inhibitor omapatrilat in the Omapatrilat Versus Enalapril Randomized Trial of Utility in Reducing Events trial (OVERTURE). Although omapatrilat did not reduce the primary endpoint of death or hospitalization for heart failure requiring intravenous treatment, compared with enalapril 10 mg b.i.d., it was superior to enalapril in relation to the secondary endpoint of CV death or CV hospitalization. Furthermore, when the effect of omapatrilat on the primary endpoint was evaluated, retrospectively, using the same definition of hospitalization for heart failure as had been used in the Studies of Left Ventricular Dysfunction Treatment-trial (SOLVD-Treatment), where the use of intravenous therapy was not required for positive adjudication, omapatrilat was superior to enalapril. Furthermore, administration of a single, large, dose of omapatrilat once daily may have on the one hand caused excessive post-dose hypotension and on the other not provided complete 24 h RAAS blockade or 24 h neprilysin inhibition. Ultimately, however, because omapatrilat caused an unacceptable incidence of angioedema in patients with hypertension, its development was halted.

LCZ696 is a first-in-class ARNI. After ingestion, LCZ696 delivers systemic exposure to AHU377, a neprilysin inhibitor pro-drug, and valsartan, an ARB. AHU377 is then rapidly metabolized by non-specific esterases to the active neprilysin inhibitor LBQ657. LCZ696 causes dose-dependent increases in ANP, plasma and urinary cGMP, plasma renin activity, and angiotensin II, effects consistent with activation of the NPR-A receptor and blockade of the angiotensin II type 1 receptor. In healthy volunteers and patients with heart failure, a total daily dose of 400 mg of LCZ696 gives systemic exposure to valsartan similar to Diovan® 320 mg daily.

Several features of the design of PARADIGM-HF are worthy of discussion.

The patients included in PARADIGM-HF are similar to those enrolled in SOLVD-Treatment, i.e. in NYHA class II–IV and with an LVEF $\leq 35\%$ (in most cases). However, PARADIGM-HF also had natriuretic peptide entry criteria. We used a BNP entry threshold of $\geq 150$ pg/mL (or NT-proBNP $\geq 600$ pg/mL) at Visit 1 or a BNP $\geq 100$ pg/mL (or NT-proBNP $\geq 400$ pg/mL) if the patient was hospitalized for heart failure within the last 12 months. This is because BNP and NT-proBNP are powerful predictors of CV events in patients with heart failure and are, therefore, useful in helping select a higher risk population.

This was necessary, in the light of recent improvements in outcome in patients with heart failure as a result of new drug and device therapies, to ensure a realistic trial size, and a trial with adequate power to show a modest but still important treatment effect. Note that patients in PARADIGM-HF are required to be treated with a beta-blocker unless contraindicated or not tolerated, and investigators are encouraged to use a mineralocorticoid (aldosterone) receptor antagonist, as indicated.

The choice of active comparator was based upon the SOLVD-Treatment trial which was a pivotal ACE inhibitor mortality/morbidity study in a broad spectrum of patients with HF-REF.
that trial, the target dose of enalapril was 10 mg b.i.d. and the mean daily prescribed dose in patients taking enalapril was 16.6 mg. The same target dose of enalapril was used in at least seven other large heart failure trials (Table 5).30–36 These trials and another large community study of >17500 patients achieved a mean daily dose of enalapril of between 15 and 18 mg.37 Two trials, which had higher target doses (20 mg b.i.d. and 30 mg b.i.d.), achieved only slightly greater average doses, with less than half of patients titrated to target. Therefore, from a regulatory perspective, the ‘gold standard’ comparator for LCZ696 is enalapril 10 mg b.i.d., the most tested ACE inhibitor in HF-REF. Moreover, we anticipate that achievement of a similar average dose to that attained in the SOLVD-Treatment trial will be required, although in two more recent trials where enalapril was used in addition to a beta-blocker (which was rarely used in SOLVD-Treatment), a lower average achieved dose of enalapril was attained.35,36

The choice of dose of LCZ696 was first and foremost based on the need to achieve serum concentrations of valsartan equivalent to those obtained with the Diovan formulation of valsartan 160 mg b.i.d., the dose shown to be effective in Val-HeFT and VALIANT.38,39 Secondly, the dose of LCZ696 also had to achieve adequate inhibition of neprilysin. LCZ696 200 mg b.i.d. achieves systemic exposure similar to valsartan 160 mg b.i.d. and, at that dose, also achieves 90% of its maximum inhibition of neprilysin and leads to sustained increases in plasma cGMP concentrations in healthy volunteers.20,21 In addition, in patients with hypertension, LCZ696 200 mg once daily lowered sitting systolic (difference 5.3 mmHg) and diastolic (difference 3.0 mmHg) blood pressure more than valsartan 160 mg, an incremental blood pressure-lowering effect attributed to neprilysin inhibition.21 Furthermore, in a proof-of-concept study in patients with HF-REF, the Prospective comparison of ARNI with ARB on Management Of heart failUre with preserved ejectioN fraction trial (PARAMOUNT), LCZ696 200 mg b.i.d., compared with valsartan 160 mg b.i.d., led to a sustained reduction over 36 weeks in plasma NT-proBNP concentration (a marker of LV diastolic wall stress and not a substrate for neprilysin) and left atrial (LA) size (as a potential marker of LA and LV end-diastolic pressure).40

The active run-in period of PARADIGM-HF served two main functions. First, both the enalapril and LCZ696 run-in periods maximized attainment of the target doses of each drug which is important as outlined above. The LCZ696 run-in period also provided investigator-unblinded, albeit short-term, safety information on the ARNI, which was important in light of the limited data on tolerability of LCZ696 in patients with heart failure available before PARADIGM-HF commenced—in essence the development programme for LCZ696 in systolic heart failure bypassed the typical ‘Phase II’ development stage. The decision to do this, rather than conduct an initial ‘stand-alone’ Phase II trial, was based on substantial and reassuring safety experience with LCZ696 in hypertension and prior experience with omapatrilat. Furthermore, Phase II studies rarely predict success in Phase III trials in heart failure and simply prolong the time and increase the cost involved in making a definitive determination of the efficacy and safety of a new treatment, which always requires a large mortality/morbidity trial.

For safety reasons, there are also two short washout periods during the run-in. These washout periods are designed to minimize concomitant neprilysin and ACE inhibition which is likely to increase the risk of angioedema. Although the risk of angioedema is expected to be low, for the reasons outlined earlier,22 a special committee of experts are adjudicating all cases of suspected angioedema in PARADIGM-HF and other studies with LCZ696 (see Appendix 1).

The primary outcome of CV death or heart failure hospitalization was chosen as the one that best reflects the major mortality and morbidity burden of this syndrome and has been used in other recent trials including CHARM-Added, SHIFT, and EMPHASIS-HF.23,40,41 However, uniquely, PARADIGM-HF is powered on the basis of CV mortality giving both adequate power to detect a reduction in CV mortality and >97% power to detect a clinically meaningful reduction in the primary composite outcome. Two of the secondary and exploratory endpoints merit a special mention. Decline in renal function is of interest given that natriuretic peptides and neprilysin inhibition have been reported to increase glomerular filtration and because renal impairment as an adverse effect was less common with omapatrilat than with enalapril in OVERTURE.17,41,42 Similarly, development of diabetes is of interest, given the recent suggestion that low natriuretic peptides levels may be associated with the development of this disease and omapatrilat improved glucose utilization peripherally.45,46

In summary, PARADIGM-HF is addressing, within a major clinical outcome trial, the place of the ARNI LCZ696 as an alternative to the ‘gold-standard’ ACE inhibitor enalapril in patients with chronic systolic heart failure. As the largest clinical trial in heart failure to date, PARADIGM-HF may change our approach to neurohumoral modulation in heart failure.

Funding
PARADIGM-HF is funded by Novartis Pharma AG.

Conflict of interest: All Executive Committee members or their institutions have received consulting fees as well as travel and research support in the planning and conduct of PARADIGM-HF. J.G., M.P.L., A.R.R., and V.C.S. are employees of Novartis.

Appendix 1. Complete list of the PARADIGM-HF Committees and Investigators

Executive Committee: John McMurray (Co-Chair), Milton Packer (Co-Chair), Jean Rouleau, Scott Solomon, Karl Swedberg, Michael Zile.

Data Monitoring Committee: Henry Dargie (Chair), Robert Foley, Gary S. Francis, Michele Komajda, Stuart Pocock.

Angioedema Adjudication Committee: Allen P. Kaplan (Chair), Nancy Brown, Bruce Zuraw.

Endpoint Adjudication Committee: Scott Solomon (Chair), Akshay S. Desai (Co-Chair), Peter Finn, Larry Weintraub, Howard Hartley, Ebrahim Barkoudah, Chau Duong

Investigators: NL = National Leader.
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Belgium

Brazil

Guatemala

Hong Kong
S. Li, H. Tse, B. Yan, G. Yip.

Hungary

Iceland
Karl Andersen (NL), T. Gudnason, A. Sigurdsson, G. Thorjefursson.

India

Israel

Italy

Latvia
Andrejs Erglis (NL), G. Dormidontova, R. Eglite, T. Lvova, G. Rancane, I. Sime.

Lithuania
Zaneta Petruilioniene (NL), D. Luksiene, R. Mazutavicius, R. Miluniene, R. Slapikas.

Malaysia
D. Chew, O. Ismail, T. Ong, A. Wan.

Mexico

The Netherlands

Panama
E. Aviles, G. Frago, B. Gonzalez, R. Nieto.

Peru

Philippines
Poland

Portugal
José Silva-Cardoso (NL), F. Almeida, A. Andrade, N. Braganca, S. Carvalho, J. Ferreira Santos, C. Fonseca, L. Oliveira, F. Padua, R. Soares.

Romania

Russia

South Africa

South Korea

Spain

Sweden

Taiwan

Thailand

Turkey
USA

Venezuela
Ivan Mendoza (NL), M. Alvarez, A. Avendaño, E. Silva, G. Vergara.

References


