Blood-pressure reduction with LCZ696, a novel dual-acting inhibitor of the angiotensin II receptor and neprilysin: a randomised, double-blind, placebo-controlled, active comparator study

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Summary
Background LCZ696 is a first-in-class inhibitor of the angiotensin II receptor and neprilysin. We aimed to establish whether the dual actions of LCZ696 lead to further lowering of blood pressure, compared with the angiotensin-receptor blocker valsartan.

Methods 1328 patients aged 18–75 years with mild-to-moderate hypertension were randomly assigned (double-blind) to 8 weeks’ treatment in one of eight groups: 100 mg (n=156 patients), 200 mg (n=169), or 400 mg (n=172) LCZ696; 80 mg (n=163), 160 mg (n=166), or 320 mg (n=164) valsartan; 200 mg AHU377 (n=165); or placebo (n=173). The primary endpoint was the mean difference across the three single-dose pairwise comparisons of LCZ696 versus valsartan (100 mg vs 80 mg, 200 mg vs 160 mg, and 400 mg vs 320 mg) in mean sitting diastolic blood pressure during the 8-week treatment period. Analysis was by intention to treat. This trial is registered with ClinicalTrials.gov, number NCT00549770.

Findings 1215 patients completed the 8-week treatment period. The average reduction in mean sitting diastolic blood pressure across the doses of LCZ696 versus the appropriate comparator dose of valsartan showed significantly greater reductions with LCZ696 (mean reduction: −2·17 mm Hg, 95% CI −3·28 to −1·06; p<0·0001). The reduction in mean sitting diastolic blood pressure was significantly different for 200 mg LCZ696 versus 160 mg valsartan (−2·97 mm Hg, 95% CI −4·88 to −1·07, p=0·0023) and for 400 mg LCZ696 versus 320 mg valsartan (−2·70 mm Hg, −4·61 to −0·80, p=0·0055). LCZ696 was well tolerated and no cases of angio-oedema were reported; only three serious adverse events occurred during the 8-week treatment period, of which none was judged to be related to the study drug, and no patients died.

Interpretation Compared with valsartan, dual-acting LCZ696 provides complementary and fully additive reduction of blood pressure, which suggests that the drug holds promise for treatment of hypertension and cardiovascular disease.

Funding Novartis.

Introduction Natriuretic peptides have potent natriuretic and vasodilator properties, inhibit the activity of the renin–angiotensin–aldosterone system, reduce sympathetic drive, and have antiproliferative and antihypertrophic effects. Increased concentration of natriuretic peptides from inhibition of neprilysin (neutral endopeptidase 24·11) represents a therapeutic approach with the potential to confer cardiac, vascular, and renal protection. Neprilysin inhibition alone does not cause clinically meaningful reduction in blood pressure, possibly because of neprilysin-dependent breakdown of polypeptide vasoconstrictors such as angiotensin II. However, clinical benefits of neprilysin inhibition could be increased by concomitant inhibition of the renin–angiotensin–aldosterone system. Vasopeptidase inhibitors simultaneously inhibit two key enzymes that participate in regulation of cardiovascular function: neprilysin and angiotensin-converting enzyme (ACE). Vasopeptidase inhibitors reduce vasoconstriction and increase vasodilation, thereby decreasing vascular tone and lowering blood pressure. Omapatrilat, the most extensively studied vasopeptidase inhibitor, has shown greater lowering of blood pressure and vasculoventilative effects than have other therapeutic classes, including ACE inhibitors and calcium-channel blockers. However, omapatrilat treatment was associated with angio-oedema, probably due to concomitant inhibition of three enzymes (ACE, aminopeptidase P, and neprilysin) that participate in the breakdown of bradykinin, the putative mediator of angio-oedema induced by ACE inhibitors. Because angiotensin-receptor blockers have a lower risk of angio-oedema than do ACE inhibitors—probably because of their neutral effect on metallopeptidases participating in bradykinin breakdown—drugs that concurrently inhibit neprilysin and block angiotensin II receptors could offer the cardioprotective benefits of vasopeptidase inhibitors without increased risk of angio-oedema.
LCZ696 is a dual-acting angiotensin II-receptor and neprilysin inhibitor (ARNI) in a single molecule: angiotensin-receptor blockade via its valsartan molecular moiety, and neprilysin inhibition via its AHU377 molecular moiety. The molecular structure of LCZ696—trisodium \( \text{[1S,3R]-1-biphenyl-4-ylmethyl-3-ethoxycarbonyl-1-butylcarbamoyl} \| \text{propionate-[S]-3' \,-methyl-2' - [pentanoyl(2' -(tetrazol-5-ylate)bibiphenyl-4' -ylmethyl)} \| \text{amino]butyrate) hemipentahydrate—was established by X-ray crystallographic techniques.\(^1\) We report results of a proof-of-concept trial for concomitant inhibition of neprilysin and the angiotensin II type 1 receptor for the treatment of cardiovascular disorders with LCZ696. We investigated whether the dual actions lead to complementary effects, as assessed by lowering of blood pressure.

**Methods**

**Patients**

Patients were recruited from 134 sites (clinics and academic institutions) in 18 countries (Argentina, Canada, Denmark, Finland, France, Germany, Hungary, Italy, Latvia, Lithuania, Netherlands, Poland, Russia, Slovakia, Spain, Sweden, Taiwan, and USA) between Sept 28, 2007, and March 4, 2008, and they were treated between Oct 12, 2007, and July 7, 2008. Eligible patients were aged 18–75 years and had uncomplicated mild-to-moderate essential hypertension (mean sitting diastolic blood pressure of 90–109 mm Hg after antihypertensive washout, or 95–109 mm Hg for untreated patients). Major exclusion criteria were: severe hypertension (mean sitting systolic blood pressure ≥180 mm Hg); history of angio-oedema or allergy to an angiotensin-receptor blocker or neprilysin inhibitor; type 1 or 2 diabetes; secondary hypertension; history or presence of a serious structural or functional cardiac disorder; hepatic or renal disease; clinically important anaemia; or abnormal serum sodium or potassium concentrations. Further, use of certain medications was prohibited: antihypertensives other than those specified by the study protocol; antiarrhythmics; tricyclic antidepressants and monoamine oxidase inhibitors; systemic corticosteroids; non-steroidal anti-inflammatory drugs; sympathomimetic drugs (chronic use); α blockers; cholestyramine and colestipol resins; and phosphodiesterase inhibitors taken within 48 h of scheduled visits.

The study protocol was approved by the independent ethics committee or institutional review board for every treatment centre, and the study was done in accordance with the ethical principles of the Declaration of Helsinki. All patients provided written informed consent before randomisation.

**Randomisation and masking**

For the first 2 weeks of the study (washout period), patients and investigators were unmasked, and for the following 2 weeks (placebo run-in period), patients only were masked. After the 4-week introductory period, a validated, automated, interactive voice-response system was used to randomly assign patients (double-blind), stratified by treatment centre, in equal numbers to eight weeks of treatment in one of eight groups: 100 mg LCZ696, 200 mg LCZ696, 400 mg LCZ696 (1 week on 200 mg followed by 7 weeks on 400 mg), 80 mg valsartan, 160 mg valsartan, 320 mg valsartan (1 week on 160 mg followed by 7 weeks on 320 mg), 200 mg AHU377, or placebo. Randomisation sequences were computer-generated by a provider of the interactive voice-response system; randomisation numbers were linked with the different treatment groups, which in turn were linked to numbers of treatment packs.

Patients’ assignment was kept strictly confidential from participants, individuals giving interventions, and individuals assessing outcomes until the time of unmasking. The interactive voice-response system was used to notify the sponsor if a patient was unmasked. The identity of treatments was concealed by use of identical packing, labelling, and administration schedules. After 8 weeks’ treatment, patients were randomised again in a 1:1 ratio (double-blind) to continue receiving their assigned treatment or switch to placebo for 1 week (withdrawal period). Data analysis was done once all patients had completed the study; masking continued until all data were entered into the clinical database, verified, and locked.

**Procedures**

Figure 1 shows the study periods and timings of study visits. Demographic indicators and clinical characteristics of patients were recorded at entry into the study. Pharmacokinetic studies in healthy volunteers have shown that the three pairwise comparison doses of LCZ696 and valsartan assessed in this trial (100 mg vs 80 mg, 200 mg vs 160 mg, and 400 mg vs 320 mg) provide similar systemic exposure to valsartan, according to area under the curve (AUC) data.\(^2\) Plasma concentrations of valsartan, AHU377, and LBQ657 (active moiety of AHU377) were taken from Gu and colleagues\(^3\) dose-escalation study in healthy volunteers. Thus, we were able to compare every LCZ696 dose with the valsartan dose that provides similar blockade of the angiotensin II receptor, and thereby establish the contribution of concomitant neprilysin inhibition from additional lowering of blood pressure with LCZ696. Furthermore, 400 mg LCZ696 and 200 mg AHU377 provide similar concentrations of neprilysin inhibition.\(^4\) Patients received blister packs of study drugs and were instructed to take one row of drugs (five tablets and two capsules) every day about 30 min before breakfast. Doses were withheld on days of study visits until after study assessments were completed. Study visits were scheduled for 0700–1000 h to coincide with trough concentrations of study drugs. At every visit (study start, and weeks 2, 4, 5, 8, 12, and 13), automated arterial blood-pressure was
assessed in every patient’s dominant arm (highest blood pressure at study entry) with a validated blood-pressure monitor in accordance with British Hypertension Society guidelines. Office-measured sitting diastolic and systolic blood pressure were taken four times with an automatic blood-pressure monitor (Omron, Bannockburn, IL, USA; model HEM705CP used in US and Canadian sites, HEM705INT used in Central and South American sites, HEM705IT used in European sites, and T9P used in Asian sites). We recorded the last three readings and calculated the mean sitting diastolic and systolic blood pressures. For all sites with experience in monitoring of ambulatory blood pressure, 24-h monitoring was done at baseline (week 4) and after 8 weeks’ treatment (week 12), and was expected to include about 40% of patients.

At baseline and after 8 weeks’ treatment in per-protocol subsets of patients, we assessed neprilysin and renin–angiotensin–aldosterone system biomarker concentrations: plasma atrial natriuretic peptide, cyclic guanosine monophosphate, plasma renin, and plasma aldosterone. Plasma atrial natriuretic peptide and plasma cyclic guanosine monophosphate were assessed to confirm neprilysin activity. Additional biomarkers assessed were high-sensitivity C-reactive protein, and urinary albumin-to-creatinine ratio. For these assessments, blood samples were taken at trough concentrations of study drugs.
The primary outcome was the lowering of mean sitting diastolic blood pressure during the 8-week treatment period (endpoint at week 12), which was calculated as the mean of the difference in blood pressure between the three pairwise comparisons of LCZ696 and valsartan doses (100 mg LCZ696 vs 80 mg valsartan, 200 mg LCZ696 vs 160 mg valsartan, and 400 mg LCZ696 vs 320 mg valsartan). Secondary outcomes were: lowering of mean sitting systolic blood pressure across the three pairwise comparisons (calculated as for the primary outcome); single-dose pairwise comparisons for lowering of mean sitting diastolic and systolic blood pressures during the 8-week treatment period; change in mean sitting diastolic and systolic blood pressures during week 13 (withdrawal period); and single-dose pairwise comparisons of change in sitting pulse pressure during the 8-week treatment period to analyse dose response.

As further secondary outcomes, we assessed the percentage of patients in every group who had a successful response after 8 weeks’ treatment for mean sitting diastolic blood pressure (<90 mm Hg or a reduction by ≥10 mm Hg from baseline) and mean sitting systolic blood pressure (<140 mm Hg or a reduction by ≥20 mm Hg from baseline). We also made single-dose pairwise comparisons of control rates after 8 weeks’ treatment in mean sitting diastolic blood pressure (<90 mm Hg), mean sitting systolic blood pressure (<140 mm Hg), and overall blood pressure (<140/90 mm Hg). In a substudy to monitor ambulatory blood pressure for each of the single-dose pairwise comparisons, we assessed changes for the 8-week treatment period in 24-h, daytime (>0600 h to ≤2200 h), and night-time (>2200 h to ≤0600 h) mean ambulatory diastolic and systolic blood pressures; and pulse pressure (difference between mean ambulatory systolic and diastolic blood pressures).

Safety assessments done throughout the 13-week study were blood-pressure measurements, standard haematology and biochemistry tests (including serum creatinine and electrolyte concentrations), electrocardiograms, physical examinations, and documentation of adverse events during the 8-week treatment period and the 1-week withdrawal period. Patients were withdrawn from the study if they had a mean sitting diastolic blood pressure of 110 mm Hg or higher, or a mean sitting systolic blood pressure of 180 mm Hg or higher at any study visit during weeks 0–13.

### Table 1: Demographic indicators and clinical characteristics at study entry†

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</table>

Data are mean (SD) or number of patients (%). *Data supplied for 170 patients on placebo, 164 on 200 mg AHU377, 154 on 100 mg LCZ696, 168 on 200 mg LCZ696, 172 on 400 mg LCZ696, 162 on 80 mg valsartan, 166 on 160 mg valsartan, and 162 on 320 mg valsartan; data were missing for remaining patients. †Data were recorded at study entry (week 0) apart from blood pressure measurements, which were recorded at baseline (week 4) just before patients were given the first dose of study drug.
Statistical analysis

With the assumption of a 10% dropout rate and a common within-group SD of 8 mm Hg in change in diastolic blood pressure from baseline, we expected that a sample size of 1320 patients would provide more than 99% power to detect a mean pairwise difference in mean sitting diastolic blood pressure of 3 mm Hg, from baseline to after 8 weeks’ treatment, between the three doses of LCZ696 and the three doses of valsartan.

Analysis was by intention to treat, and included all randomised patients who had baseline data and at least one efficacy measurement taken during the 8-week core treatment period. The safety population included all randomised patients who received at least one dose of study drug during the 8-week treatment period. Data for the primary efficacy variable were analysed with an ANCOVA model, with treatment and centre as fixed factors, and mean sitting diastolic blood pressure at baseline as the covariate. To assess the superiority of LCZ696 versus valsartan for reduction of mean sitting diastolic blood pressure (primary endpoint) and mean sitting systolic blood pressure (secondary endpoint), we regarded one-sided p values lower than 0·025 to be significant.

The same ANCOVA model was used for all single-dose pairwise comparisons for: reduction in mean sitting diastolic and systolic blood pressures; change in sitting pulse pressure; and the substudy to monitor ambulatory blood pressure. For these comparisons, we regarded all two-sided p values lower than 0·05 to be significant. The dose responses of LCZ696 in reductions of mean sitting diastolic and systolic blood pressures were analysed with the MCP-Mod method. Between treatment groups, we compared the proportions of patients achieving a response to treatment at week 8 or blood-pressure control (mean sitting diastolic blood pressure, mean sitting systolic blood pressure, and overall blood pressure), or both, by use of a logistic model with treatment and centre as factors; we regarded two-sided p values of less than 0·05 to be significant. Neurohormone and biomarker data were skewed and so were analysed after they were logarithmically transformed; these results were back-transformed (antilog) and reported as geometric means (95% CI), and changes in geometric means from baseline (95% CI) were calculated from the ratio of geometric means. Occurrences of adverse events and serious adverse events, and change in laboratory markers (haematology, urinalysis, blood chemistry) and vital signs were also recorded.

This trial is registered with ClinicalTrials.gov, number NCT00549770.

Results

1328 patients were randomly assigned to treatment (figure 1). Table 1 shows the demographic indicators and clinical characteristics of patients at baseline. Most patients were white (n=1160 patients, 87%) and male (n=760, 57%). The mean age was 53 years (SD 10·2), with most patients younger than 65 years (n=1141, 86%), and the average duration of hypertension was 6·8 years (SD 7·2). At baseline, overall mean sitting diastolic blood pressure was 99·7 mm Hg (SD 4·0) and mean sitting systolic blood pressure was 155·7 mm Hg (11·7).

1215 (91%) patients completed the 8-week treatment period and 113 (9%) withdrew or were withdrawn from the study (figure 1). Frequency of discontinuation ranged from 4% (7/156) to 7% (11/169) in the three LCZ696 groups, and was lower for all LCZ696 groups than for...
Analysis of the mean of the three pairwise differences for change in mean sitting diastolic and systolic blood pressures during the 8-week treatment period showed that LCZ696 provided significantly superior reductions from baseline in mean sitting diastolic and systolic blood pressures than did valsartan. The least-squares mean reduction between the mean change with the three LCZ696 doses and that with the three valsartan doses was \(-2.17\) mm Hg (95% CI \(-3.28\) to \(-1.06\); p<0.0001) for mean sitting diastolic blood pressure and \(-4.20\) mm Hg (\(-5.94\) to \(-2.46\); p<0.0001) for mean sitting systolic blood pressure.

Change in mean sitting diastolic and systolic blood pressures from single-dose pairwise comparisons (figure 2) showed significantly superior reductions with 200 mg LCZ696 versus 160 mg valsartan (\(-2.97\) mm Hg, 95% CI \(-4.88\) to \(-1.07\) for mean sitting diastolic blood pressure; \(-5.28\) mm Hg, \(-8.28\) to \(-2.28\) for mean sitting systolic blood pressure), and 400 mg LCZ696 versus 320 mg valsartan (\(-2.70\) mm Hg, \(-4.61\) to \(-0.80\) for mean sitting diastolic blood pressure; \(-6.01\) mm Hg, \(-9.01\) to \(-3.02\) for mean sitting systolic blood pressure). 100 mg LCZ696 reduced mean sitting diastolic and systolic blood pressures more than 80 mg valsartan did, but the difference was not significant. Pairwise comparisons also showed superior reductions with 200 mg AHU377 than with placebo (\(-2.99\) mm Hg, \(-4.89\) to \(-1.09\), p=0.0021 for mean sitting diastolic blood pressure; \(-4.20\) mm Hg, \(-7.18\) to \(-1.23\), p=0.0057 for mean sitting systolic blood pressure).

Substantial decreases in mean sitting diastolic and systolic blood pressures were recorded for the first week of treatment in all active treatment groups, with further reductions as the study proceeded (figure 3); most of the antihypertensive effect from LCZ696 had occurred by the fourth week of treatment. Results from the dose-response analysis for mean sitting diastolic and systolic blood pressures during 8 weeks’ treatment showed a non-linear dose response for the three doses of LCZ696 compared with placebo.

Consistent with the results for change from baseline in mean sitting diastolic blood pressure, most frequent treatment responses according to mean sitting diastolic blood pressure were in patients on 200 mg LCZ696 (117/168, 70%) and 400 mg LCZ696 (126/170, 74%). Response rates were significantly higher in patients on 200 mg LCZ696 versus 160 mg valsartan (91/163, 56%, p=0.0095), and on 400 mg LCZ696 versus 320 mg valsartan (103/163, 63%, p=0.0261). Response rates in patients on 200 mg AHU377 (89/164, 54%) were significantly lower than in those on 200 mg LCZ696 (p=0.0041) or 400 mg LCZ696 (p=0.0002). Similar response rates were obtained for mean sitting systolic blood pressure.

The highest control rates after 8 weeks’ treatment occurred in patients on 400 mg LCZ696 and were numerically greater than for those on 320 mg valsartan: 66% (112/170) of patients versus 56% (92/163) for mean sitting diastolic blood pressure; 63% (107/170) versus...
Figure 4: Change in 24-h (A), daytime (B), and night-time (C) ambulatory blood pressure during the 8-week treatment period
NA=not applicable.
The clinical characteristics and demographic indicators of the 427 patients who underwent monitoring of ambulatory blood pressure were similar to those of the overall study population (n=48 on 100 mg LCZ696, n=61 on 200 mg LCZ696, n=53 on 400 mg LCZ696, n=55 on 80 mg valsartan, n=49 on 160 mg valsartan, n=54 on 320 mg valsartan, n=50 on 200 mg AHU377, and n=57 on placebo). The general effects of blood-pressure lowering with LCZ696 were maintained over the full 24-h dosing interval (data not shown). For the 8-week treatment period, differences in 24-h mean ambulatory diastolic blood pressure between LCZ696 and corresponding valsartan doses were small and not significant (figure 4A). By contrast, significant differences in 24-h mean ambulatory systolic blood pressure were recorded for 200 mg LCZ696 versus 160 mg valsartan (−3.23, 95% CI −5.70 to −0.75), and 400 mg LCZ696 versus 320 mg valsartan (−5.14, −7.70 to −2.59), which was consistent with assessments of sitting systolic blood pressure.

Differences in least-squares mean reductions between LCZ696 and valsartan were small for daytime mean ambulatory diastolic blood pressure and large for daytime mean ambulatory systolic blood pressure, but none of the differences was significant (figure 4B). Significant differences were recorded in night-time mean ambulatory diastolic blood pressure for 200 mg LCZ696 versus 160 mg valsartan (−3.55, 95% CI −6.66 to −0.45), and in night-time mean ambulatory systolic blood pressure for 200 mg LCZ696 versus 160 mg valsartan (−6.03, −10.41 to −1.65), and for 400 mg LCZ696 versus 320 mg valsartan (−4.53, −9.01 to −0.05; figure 4C).

Decreases in sitting pulse pressure were significantly different with 200 mg LCZ696 versus 160 mg valsartan (−2.25, 95% CI −4.45 to −0.06), and 400 mg LCZ696 versus 320 mg valsartan (−4.53, −9.01 to −0.05; figure 5A). Similarly, decreases in ambulatory pulse pressure were significantly different with 200 mg LCZ696 versus 160 mg valsartan (−2.48, −4.80 to −0.17), and 400 mg LCZ696 versus 320 mg valsartan (−3.95, −6.28 to −1.62; figure 5B). Changes in sitting and ambulatory pulse pressure were dose-related in patients receiving valsartan, but not in patients receiving valsartan (data not shown).

At the end of the 1-week withdrawal period, changes in mean sitting diastolic and systolic blood pressures were similar between patients who switched from either LCZ696 or valsartan to placebo, with no evidence of a clinically relevant rebound effect in any treatment groups.
Blood pressure increased but remained below baseline values in all treatment groups (figure 3).

Table 3 shows neurohormonal and biomarker assessments from the 8-week treatment period. Plasma atrial natriuretic peptide concentrations increased with all three doses of LCZ696 and with AHU377, and the changes was significantly different from placebo in all but the 100 mg LCZ696 group. Significant differences were recorded between the pairwise LCZ696 and valsartan doses, and between 200 mg AHU377 and all three valsartan doses.

Results were similar for plasma cyclic guanosine monophosphate, the second messenger for neprilysin activity, with significant differences for all LCZ696 and AHU377 groups compared with placebo. However, changes in plasma atrial natriuretic peptide and cyclic guanosine monophosphate were not related to LCZ696 changes in plasma atrial natriuretic peptide and cyclic guanosine monophosphate were not related to LCZ696.
change was not significant in the AHU377 group compared with placebo (p=0·96). The pairwise LCZ696 and valsartan doses did not result in significantly different concentrations. Plasma aldosterone concentration did not differ between any treatment groups.

To establish the predictive value of these neurohormonal measurements, we assessed the correlation with blood-pressure response. Both absolute concentrations at baseline and changes in concentrations from baseline poorly correlated with reductions in blood pressure for LCZ696 or valsartan (|r|≤0·203 for all correlations; webappendix pp 2–4). Notably, although slight, the strongest recorded correlation was between baseline plasma renin concentration and change in mean sitting diastolic blood pressure in the AHU377 group (r=–0·4008, p=0·0064); but the correlation for mean sitting systolic blood pressure was not significant (r=–0·2384, p=0·1147).

Assessment of high sensitivity C-reactive protein showed no differences in concentrations between any treatment groups (table 3). Overall for all treatment groups, mean urinary albumin-to-creatinine ratio was in the normoalbuminuric range at baseline (week 4), and decreased in all LCZ696 and valsartan groups during treatment. Changes were significantly different from that of the placebo group, in which the ratio increased; the ratio did not change significantly for the AHU377 group compared with that of placebo (p=0·06). No significant differences were recorded between the pairwise LCZ696 and valsartan doses.

Generally, adverse events that occurred during the 8-week treatment period were infrequent, mild, and transient, and did not show dose dependence. Occurrences were similar for the eight treatment groups, with slightly increased frequency in the 400 mg LCZ696 and placebo groups (table 4). Overall, the most frequently reported adverse event was headache (42/1328, 3%), occurring most frequently in the placebo group. Diarrhoea was reported more frequently in the 400 mg LCZ696 than in the other treatment groups, but was only slightly increased compared with the placebo group. Dizziness was infrequent, and hypotension or syncope occurred in five patients (one each in the placebo, 400 mg LCZ696, and 200 mg AHU377 groups, and two in the 200 mg LCZ696 group).

Overall, adverse events resulting in treatment discontinuation occurred in 1% (17/1328) of patients, with the highest occurrence in the AHU377 and placebo groups. Only three patients had serious adverse events during the 8-week treatment period, one each in patients on: 100 mg LCZ696 (road accident, upper limb fracture), 400 mg LCZ696 (back pain, dyspnoea), and 80 mg valsartan (endometrial cancer). No serious adverse events were suspected to be related to study drug. No cases of angio-oedema were reported, and there were no deaths.

Adverse events during the 1-week withdrawal period were infrequent, ranging from 1% (1/80) to 6% (4/68); no differences in occurrences of adverse events were recorded between patients assigned to placebo or continuing treatment during this period. We did not identify any consistent differences in the occurrence of adverse events.

### Table 4: Adverse events during the 8-week treatment period

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Any adverse event</th>
<th>Adverse events reported in ≥2% of patients in any treatment group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo (n=173)</td>
<td>49 (28%)</td>
<td>Diarrhoea 3 (2%), Back pain 2 (1%), Bronchitis 4 (2%), Cough 2 (1%), Dizziness 2 (1%), Dyspepsia 0, Headache 13 (8%), Influenza 3 (2%), Nasopharyngitis 3 (2%), Pharyngolaryngeal pain 0, Pruritus 0, Pharyngitis 4 (2%), Sinusitis 2 (1%), Upper-respiratory-tract infection 0, Vomiting 0, Discontinuations due to adverse events 4 (2%)</td>
</tr>
<tr>
<td>200 mg AHU377</td>
<td>45 (27%)</td>
<td></td>
</tr>
<tr>
<td>100 mg LCZ696</td>
<td>36 (23%)</td>
<td></td>
</tr>
<tr>
<td>200 mg LCZ696</td>
<td>40 (24%)</td>
<td></td>
</tr>
<tr>
<td>400 mg LCZ696</td>
<td>50 (29%)</td>
<td></td>
</tr>
<tr>
<td>80 mg valsartan</td>
<td>36 (22%)</td>
<td></td>
</tr>
<tr>
<td>160 mg valsartan</td>
<td>34 (20%)</td>
<td></td>
</tr>
<tr>
<td>320 mg valsartan</td>
<td>38 (23%)</td>
<td></td>
</tr>
</tbody>
</table>

Data are number of patients (%).
between patients who continued to receive active treatment and those who were randomly assigned from active treatment to placebo. Two patients, both on 80 mg valsartan, had a serious adverse event (one had myocardial infarction, and the other had bronchitis and asthma).

During the full study, changes in laboratory values (haematology and biochemistry) were generally small, and the investigators at the study sites judged that most changes were unrelated to treatment (data not shown). Heart rate decreased by 1–2 beats per min in all treatment groups. Changes in orthostatic blood pressure were not consistent across treatment groups (range 4–7%, with the lowest value in the 400 mg LCZ696 group), and no significant changes in bodyweight were recorded in any group during the study. Electrocardiogram and physical examination findings were clinically unremarkable.

**Discussion**

Results from this trial show the efficacy and safety of an ARNI for the treatment of cardiovascular disorders. In patients with mild-to-moderate hypertension, treatment with LCZ696 provided significant reductions in blood pressure compared with valsartan. This shows that dual inhibition of the angiotensin II receptor and neprilysin have complementary effects, and suggests that kinin effects from ACE inhibitors are not needed for these beneficial effects. LCZ696 was safe and well tolerated at all doses. There were no episodes of angio-oedema, possibly because neprilysin is a minor enzyme in the metabolic pathway for bradykinin degradation. Additionally, angiotensin-receptor blockers have not been associated with an excess occurrence of angio-oedema. Notably, this trial has shown that monotherapy with a neprilysin inhibitor has an effect, albeit slight, on blood pressure.

200 mg LCZ696 versus 160 mg valsartan, and 400 mg LCZ696 versus 320 mg valsartan, caused significantly increased lowering of sitting blood pressure (difference: −3 and −3 mm Hg in placebo-subtracted mean sitting diastolic blood pressure; −5 and −6 mm Hg in placebo-subtracted mean sitting systolic blood pressure), sitting and ambulatory pulse pressure, and 24-h ambulatory systolic blood pressure. Compared with 200 mg AHU377 and 320 mg valsartan, 400 mg LCZ696 showed full additivity for reduction of mean sitting diastolic blood pressure, and more than full additivity for reduction of mean sitting systolic blood pressure, underscoring the complementary effects of the dual mechanisms of action.

Results of neurohormone measurements were consistent with the mechanisms of action with valsartan and LCZ696. Increases in plasma renin concentration were recorded for all valsartan and LCZ696 groups, with the greatest and similar increases in the 400 mg LCZ696 and 320 mg valsartan groups; these results suggest similar blockade of the angiotensin II receptor in both groups, and are consistent with similar valsartan exposure (based on AUC), as reported previously. For LCZ696, the absence of a dose response in change in plasma atrial natriuretic peptide and cyclic guanosine monophosphate is probably indicative of the fact that samples were obtained at trough drug concentrations. However, a previous study made assessments over a 24-h interval and showed dose-dependent effects: 200–400 mg LCZ696 provided near maximum inhibition of neprilysin, whereas 100 mg LCZ696 provided less inhibition. These findings are consistent with our results of significantly greater blood-pressure lowering with 200 mg LCZ696 versus 160 mg valsartan and 400 mg LCZ696 versus 320 mg valsartan, but of no significant difference with 100 mg LCZ696 versus 80 mg valsartan.

In this study, neurohormone concentrations did not predict blood-pressure response to LCZ696. This finding could be related to the drug’s complementary mechanism of action and effects on several neurohormones. Although a slight correlation was recorded in the AHU377 group between plasma renin concentration and change in mean sitting diastolic blood pressure, this could be a chance finding, as suggested by the absence of a correlation with change in mean sitting systolic blood pressure. We are not aware of previous studies of hypertension or heart failure that have attempted to correlate neurohormone concentrations and response to neprilysin inhibitors; however, natriuretic peptide concentrations could be particularly relevant for the treatment of heart failure with neprilysin inhibition. For valsartan, plasma renin concentration was not correlated with blood-pressure response, which is consistent with a study in a similar heterogeneous hypertensive population in which blood-pressure reductions with ramipril were independent of baseline plasma renin activity.

Importantly, our results from monitoring of both sitting and ambulatory blood pressure suggest that LCZ696 preferentially reduces systolic blood pressure compared with diastolic blood pressure, thereby providing obvious improvements in pulse pressure reduction compared with valsartan. This finding could potentially offer improved protection from several signs of cardiovascular disease related to systolic hypertension (increased pulse pressure) and vascular stiffness, such as stroke and diastolic heart failure. Indeed, pulse pressure is an independent predictor of cardiovascular events (including myocardial infarction, congestive heart failure, and cardiovascular death) in hypertensive and general populations.

Our study has several limitations. First, pulse pressure was assessed during the trial, but central blood pressure and arterial stiffness were not, precluding a more thorough assessment of the antihypertensive properties of LCZ696. Second, the absence of angio-oedema in this study is positive, but needs to be confirmed particularly in black patients because angio-oedema was more frequently recorded in black patients by Kostis and colleagues in a trial of treatment with omapatrilat. Few black patients were studied in our trial (about 8%). Future research should address these limitations, and
identify hypertensive patient populations that would most benefit from LCZ696 (including elderly patients and those with diabetes). Furthermore, our results suggest that the dual inhibition of the angiotensin II receptor and nephrilysin could provide clinical benefits in a range of cardiovascular diseases, including hypertension and heart failure; we need to establish the effects of LCZ696 in heart failure, pulmonary hypertension, and related cardiovascular disorders in which vasoconstriction, volume overload, and neurohormonal activation play a part in pathophysiology.

Contributors
LMR, JG, and MPL contributed to the study design. LMR, AD, MB, and YL collected data. LMR, AD, MB, and YL did local assessments and follow-up of patients at study sites. JG and MPL analysed the data, and all authors contributed to data interpretation. LMR, MB, YL, and MPL wrote the report, and AD, MB, and JG contributed to review and revision of the report.

Conflicts of interest
LMR has been an adviser and speaker for Novartis. MB has received speaker’s honoraria from Novartis. YL has received consulting fees from, and is a member of the speakers’ bureau for Novartis, Merck, and Boehringer Ingelheim. JG and MPL are employees of Novartis. AD declares that he has no conflicts of interest.

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