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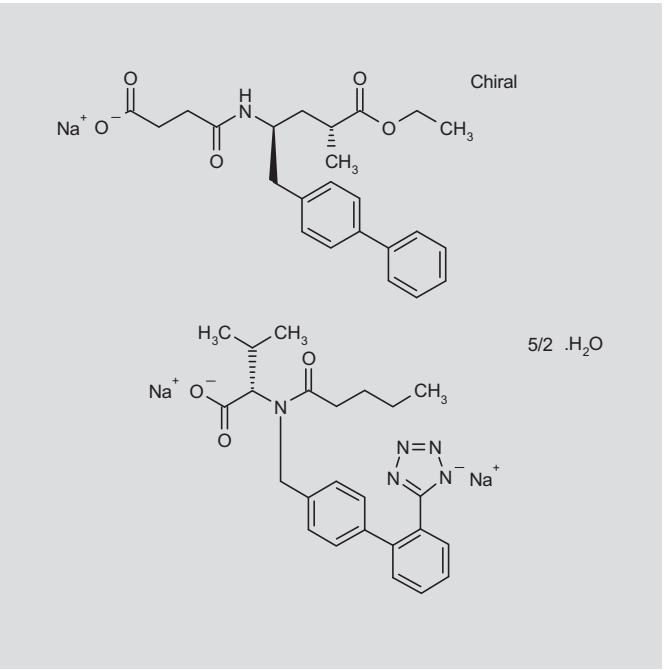
MONOGRAPH

LCZ-696

Angiotensin AT_1 Receptor Antagonist/Neprilysin Inhibitor
Treatment of Heart Failure
Treatment of Hypertension

Complex of 3-[*N*-[1(*S*)-(biphenyl-4-ylmethyl)-4-ethoxy-3(*R*)-methyl-4-oxobutyl]carbamoyl]propionic acid and *N*-pentanoyl-*N*-[2'-(1*H*-tetrazol-5-yl)biphenyl-4-ylmethyl]-L-valine trisodium salt hemipentahydrate

InChI: 1S/C24H29N5O3.C24H29NO5.3Na.H2O/c1-4-5-10-21(30)29(22(16(2)3)24(31)32)15-17-11-13-18(14-12-17)19-8-6-7-9-20(19)23-25-27-28-26-23;1-3-30-24(29)17(2)15-21(25-22(26)13-14-23(27)28)16-18-9-11-20(12-10-18)19-7-5-4-6-8-19;;;;/h6-9,11-14,16,22H,4-5,10,15H2,1-3H3,(H2,25,26,27,28,31,32);4-12,17,21H,3,13-16H2,1-2H3,(H,25,26)(H,27,28);;;;1H2/q;;3*+1;/p-3/t22-;17-,21+;;;;/m01..../s1



$C_{48}H_{57}N_6Na_3O_9$

Mol wt: 930.9703

EN: 469906

SUMMARY

LCZ-696 is an investigational, dual-acting molecule consisting of the angiotensin II (Ang II) type 1 (AT_1) receptor blocker (ARB) valsartan and the neprilysin (neutral endopeptidase, NEP) inhibitor AHU-377. The rationale for the development of LCZ-696 is based on the concept of additive effects for the ARB valsartan and the NEP inhibitor AHU-377 for the treatment of hypertension and heart failure (HF). Valsartan, by blocking the AT_1 receptor, interferes with the vasoconstrictive and cardiovascular remodeling of Ang II and has been shown to be effective for the treatment of hypertension and HF. The other component of LCZ-696, AHU-377, is an NEP inhibitor that interferes with the catabolism of natriuretic peptides (NPs), leading to increased blood levels of NPs and promoting salt and water diuresis. This combined action of LCZ-696 can be very effective for the treatment of hypertension and HF. So far, clinical trials have shown that LCZ-696 is effective and safe for the treatment of hypertension. Large clinical trials for the treatment of HF are under way and results will be reported soon. Based on the current information, approval of LCZ-696 will be a useful addition to our armamentarium for the treatment of hypertension and HF.

PREPARATION AND FORMULATION

LCZ-696 is a novel drug candidate consisting of a supramolecular complex of the angiotensin II (Ang II) type 1 (AT_1) receptor blocker (ARB) valsartan[+] and the selective neprilysin (neutral endopeptidase, NEP) inhibitor AHU-377[+] trisodium salt hemipentahydrate as a single molecular entity in a 1:1 molar ratio (1, 2).

LCZ-696 is a white to off-white powder formulated as film-coated tablets of 100, 200 and 400 mg for oral administration (3, 4). These tablets are ovaloid, biconvex, level edged and covered with a brown film coat. In addition to the active drug substance, the tablets contain microcrystalline cellulose, talc, hydroxypropyl cellulose, colloidal silicon dioxide, crosprovidone and magnesium stearate (vegetable origin) as excipients. The film-coated tablets must be stored in closed bottles or blisters at a temperature not to exceed 25 °C. Each dose of LCZ-696 contains an equimolar ratio (1:1) of AHU-377 and valsartan and delivers 48.6% in weight of anhydrous salt-free AHU-377, and 51.4% in weight of anhydrous salt-free valsartan (4).

[+]The syntheses of each individual chemical component of LCZ-696, valsartan and AHU-377 are reported in Thomson Reuters Integrity[SM].

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BACKGROUND

LCZ-696 is a new dual-acting molecule consisting of the angiotensin II (Ang II) receptor AT_1 blocker (ARB) valsartan and the neprilysin (neutral endopeptidase, NEP) inhibitor AHU-377. The rationale for the development of LCZ-696 lies in the concept of an additive effect for the ARB valsartan and the NEP inhibitor AHU-377 for the treatment of hypertension and heart failure (HF). Valsartan, by selectively blocking the AT_1 receptor, interferes with the vasoconstrictive and cardiovascular remodeling effects of Ang II and has been shown to be beneficial for the treatment of hypertension and HF (5-8). The other component of LCZ-696, AHU-377, is an NEP inhibitor that prevents the catabolism of natriuretic peptides (NPs) (3, 9). The NPs are endogenous hormones that are released from the heart in response to myocardial stretching and overloading effects (10-12).

Since the discovery of atrial natriuretic factor by de Bold et al. (13), three mammalian NPs have been identified and synthesized, i.e., the atrial natriuretic peptide (ANP), the B-type natriuretic peptide (BNP) and the C-type natriuretic peptide (CNP), all sharing structural similarities (10-14). These NPs exert their effects through binding to their receptors atrial natriuretic peptide receptor type A (NPR-A) and B (NPR-B) (15), resulting in the generation of cyclic guanosine monophosphate (cGMP). cGMP mediates natriuresis and inhibition of renin and aldosterone, and induces vasorelaxant, antifibrotic and antihypertrophic effects (12, 16). ANP and BNP bind to NPR-A, whereas CNP binds to NPR-B (15, 17). ANP and BNP are released from the heart due to myocardial stretch from volume overload and result in alleviation of symptoms of congestion through reduction of pressure and volume overload from vasodilation, diuresis and natriuresis (12, 17, 18). CNP is primarily of vascular endothelial and renal cell origin and has a paracrine action (19). The natriuretic peptides, although they are all potent diuretic and natriuretic substances, have a short-lived action due to their rapid metabolism by NEP.

Therefore, the use of a substance that blocks the action of NEP, like LCZ-696, will interfere with their rapid metabolism, extend their life, increase their blood levels and consequently increase their effectiveness in the treatment of HF and hypertension (20, 21).

PRECLINICAL PHARMACOLOGY

Oral administration of LCZ-696 to double transgenic rats (dTGRs), an animal model of Ang II-dependent hypertension (22), demonstrated a dose-dependent and long-lasting antihypertensive effect (4). The results of this study are presented in Table I.

In another study, the NEP inhibitory effects of LCZ-696 were studied in six groups of conscious Sprague–Dawley rats. Rat ANP was given i.v. at 450 ng/kg/min to achieve steady state and the six groups of rats were randomized to group 1 (untreated control), group 2 (empty minicapsule) and groups 3-6 receiving the active drug (2, 6, 20 and 60 mg/kg, respectively). The ANP infusion was continued for an additional 8 hours and blood samples were collected at prespecified time points (4). Before ANP infusion, ANP levels were low (0.9-1.4 ng/mL) and were similar in all six groups. After 30 minutes of infusion of exogenous ANP, blood levels rose rapidly to 10 ng/mL, and this level was maintained constant for the duration of the experiment in the untreated and vehicle-treated rats. In those rats treated with LCZ-696, the levels of ANP rose rapidly and dose-dependently (within 15 minutes), remained elevated for the 8 hours of ANP infusion, and then returned slowly to baseline levels 24 hours later.

Table I. *Peak dose-dependent decrease in mean arterial pressure (MAP) after single daily doses of LCZ-696 in double transgenic rats.*

LCZ-696 (mg/kg)	MAP (mmHg)
Vehicle	−21 ± 6
2	−31 ± 8
6	−52 ± 8
20	−57 ± 4
60	−73 ± 5

PHARMACOKINETICS AND METABOLISM

Following oral administration, LCZ-696 is rapidly absorbed and efficiently converted to valsartan and LBQ-657, the active metabolite of AHU-377 (4). Administration of LCZ-696 to beagle dogs (n = 3) was associated with rapid absorption and conversion to valsartan, with a t_{max} of 1.3 hours, whereas separate administration of valsartan and AHU-377 yielded a t_{max} for valsartan of 4.0 hours. Also, the C_{max} and AUC for valsartan were about three times higher with LCZ-696 than when valsartan and AHU-377 were administered separately. Single-dose administration of LCZ-696 to human volunteers also resulted in rapid absorption of the drug and conversion to valsartan and LBQ-657, with a C_{max} for valsartan and LBQ-657 of 1.7-2.2 and 1.9-3.5 hours, respectively. Mean half-life ($t_{1/2}$) values for valsartan and LBQ-657 ranged from 8.9 to 16.6 and 9.9 to 11.1 hours, respectively. In addition, single daily doses of LCZ-696 of 200-1200 mg resulted in proportional increases in C_{max} and AUC for AHU-377 and LBQ-657. The AUC and C_{max} for valsartan were linear with the dose of LCZ-696, albeit less proportional to the dose. During the multiple dosing period of LCZ-696, peak plasma concentrations for valsartan, AHU-377 and LBQ-657 were 1.6-4.9, 0.6-0.9 and 1.8-2.7 hours, respectively. Comparison of C_{max} and $AUC_{0\text{-last}}$ values for days 1 and 14 did not show significant accumulation for valsartan, AHU-377 or LBQ-657. With respect to bioavailability, single oral doses of LCZ-696 400 mg and valsartan 320 mg resulted in plasma C_{max} for valsartan at 2.0 and 4.0 hours, respectively, after LCZ-696 and valsartan administration (3). The mean terminal $t_{1/2}$ of valsartan was 18 hours and was similar after LCZ-696 and valsartan administration. However, there was a 40% higher exposure of valsartan following LCZ-696 administration compared to valsartan alone.

The pharmacodynamic effects of LCZ-696 were assessed in healthy volunteers. Following multiple-dose administration of LCZ-696, the biomarkers of NEP inhibition, plasma renin concentration (PRC), plasma renin activity (PRA) and Ang II, were all significantly increased (93-634%, 280-1768% and 241-1188%, respectively) (3). All doses of LCZ-696 increased the 24-hour mean levels of cGMP, with the maximum (40%) increase with LCZ-696 200 mg on day 12. Significant increases in cGMP were also noted at 4 and 12 hours after LCZ-696 administration at 600 and 900 mg, and returned to baseline levels 23 hours later.

SAFETY

The safety of LCZ-696 was tested in several animal studies. The morbidity/mortality of LCZ-696 was tested in CD-1 mice. The drug

was administered orally at doses of 0, 50, 200, 400 and 800 mg/kg/day for 2 weeks to five rats sex/group. Increased morbidity/mortality was seen with the 800 mg/kg/day dose, whereas decreased locomotor activity, dehydration, weight loss, muscle tremors and labored respiration were seen with 400 mg/kg/day. Autopsy did not reveal the cause of death. Mucosal inflammation of the stomach was seen with doses ≥ 200 mg/kg/day (4).

In another study, LCZ-696 was administered orally to Wistar–Hanover rats at doses of 0, 50, 200, 600 and 1200 mg/kg for 2 weeks. Increased morbidity/mortality was noted from day 2 to day 10 of treatment in male rats (3 of 20) and female rats (4 of 20) at a dose of 1200 mg/kg/day. Signs of pale appearance, coldness to touch, abdominal distension, labored respiration, rales and decreased locomotor activity were seen with the 600 mg/kg/day dose (4).

In a 13-week study, LCZ-696 was administered to Wistar–Hanover rats as single daily doses of 0, 10, 30 and 100 mg/kg. There was no mortality observed. However, weight loss or reduction in weight gain were seen with the dose of 100 mg/kg/day in males (7-29%) and in females (6-27%) (4).

In another study in cynomolgus monkeys, oral administration of LCZ-696 at doses of 0, 25 and 100 mg/kg/day for 1 week resulted in no drug-related mortality, body weight changes, food consumption, ECG changes or organ pathology (4).

Mutagenicity studies were performed in pregnant New Zealand white rabbits. In this study, LCZ-696 was given as oral doses of 0, 3, 10 and 30 mg/kg/day to 20 rabbits/group from gestation day 7 to day 20. At a dose of 30 mg/kg/day, four does were found dead, one doe was sacrificed after aborting and five were sacrificed due to early delivery. At 10 mg/kg/day, one doe was found dead and one doe was sacrificed after aborting. Decreased locomotor activity was seen in two animals on day 2 prior to being found dead following a dose of 30 mg/kg/day. Also, this dose was associated with late resorptions and a decrease in gravid uterine weight. A low incidence of hydrocephaly was also observed in fetuses at doses of ≥ 10 mg/kg/day, which was associated with maternal toxicity. There were no such findings seen with the dose of 3 mg/kg/day (4).

CLINICAL STUDIES

LCZ-696 is being evaluated for the treatment of hypertension and HF in phase I and II studies.

The pharmacokinetics, pharmacodynamics, safety and tolerability of LCZ-696 were studied in a dose-escalation and a bioavailability study in healthy male and female subjects aged 18-55 years old with a body mass index (BMI) of 18-30 kg/m^2. The female subjects were either post-menopausal or had undergone hysterectomy or ovariectomy. All subjects signed an IRB approved consent form before participation in the studies.

The dose-escalation study examined the single- and multiple-dose pharmacokinetics and pharmacodynamics of ascending oral doses of LCZ-696. This study was a randomized, double-blind, placebo-controlled, parallel-group trial including 8 cohorts of 10 individuals each (3). Four cohorts received a single oral dose of LCZ-696 of 200, 600, 900 and 1200 mg, and four other cohorts received multiple oral doses of 50, 200, 600 and 900 mg. The drug was administered with 240 mL of water between 7:00 and 9:00 A.M. after an overnight fast. Escalation to the next dose was permitted only if the safety and tolerability data from the previous dose were satisfactory.

The bioavailability study was a randomized, open-label, crossover study. Eligible subjects were randomized to a single dose of either LCZ-696 400 mg or valsartan 320 mg given between 7:00 and 9:00 A.M. after an overnight fast of at least 10 hours. Following a 5-day washout period, the subjects were crossed over to the other drug. In this study, mean plasma concentration–time profiles for valsartan were similar following the administration of LCZ-696 400 mg or valsartan 320 mg. Peak plasma concentrations of valsartan occurred 2 hours following LCZ-696 and 4 hours following valsartan administration. Plasma concentrations of valsartan were 40% higher following administration of LCZ-696 400 mg than after administration of valsartan 320 mg (3).

Overall, 10 participants reported AEs following LCZ-696 administration and 8 following valsartan administration. All AEs were clinically mild and did not result in drug discontinuation, with the exception of four subjects, two on LCZ-696 and two on valsartan, who discontinued due to abnormal liver tests. No cough or angioedema was noted in any of these subjects.

Two phase II studies have been reported so far with LCZ-696, one in hypertension and another in HF. The study in patients with hypertension was a multicenter, randomized, double-blind, placebo-controlled study of LCZ-696 and valsartan in subjects with mild to moderate hypertension (9). In this study, 1,328 subjects 18-75 years old were randomized to LCZ-696 100 (n = 156), 200 (n = 169) and 400 mg/day (n = 172), valsartan 80 (n = 163), 160 (n = 166) and 320 mg/day (n = 164), or placebo (n = 173), and were followed for 8 weeks. The effects on BP according to drug dose are listed in Table II. There was a drug dose–response reduction in BP. Also, the placebo-subtracted dose-dependent effects of AHU-77, LCZ-696 and valsartan on systolic blood pressure (SBP) and diastolic blood pressure (DBP) are depicted in Figure 1. All drugs caused significant reductions in both SBP and DBP. However, LCZ-696 was more potent than valsartan in reducing both the SBP and DBP. In addition, the dose-dependent effects of LCZ-696 and valsartan on various biomarkers are listed in Table III. The biomarker changes from baseline were similar for LCZ-696 and valsartan, with the exception of ANP and cGMP, which were significantly greater with LCZ-696 than valsartan. Overall, the drugs were well tolerated and only 1% of subjects discontinued the study. Only three patients had serious AEs, but none were drug-related.

There are no publications so far regarding the efficacy and safety of LCZ-696 in patients with HF. A small study in 30 patients with HF (ejection fraction: 33.6 ± 4.6%) treated with LCZ-696 was presented at the annual meeting of the American Heart Association in 2010 (23). These patients on optimal background treatment with β-adrenoceptor blockers (90%), aspirin (90%), statins (50%), aldosterone antagonists (33.3%), calcium channel blockers (16.7%), nitrates (33.3%), loop diuretics (63.3%), thiazide diuretics (26.7%) and digoxin (13.3%) were taken off angiotensin-converting enzyme (ACE) inhibitors, and after a short washout period were given LCZ-696 100 mg b.i.d. for an additional 14 days in an open-label study. Of 30 patients enrolled, 27 completed the study. Three patients were

Table II. *Effects of placebo, AHU-377 and various doses of LCZ-696 and valsartan on blood pressure in patients with hypertension.*

	< 0 mmHg	≥ 0 to ≤ 5 mmHg	> 5 to ≤ 10 mmHg	> 10 to ≤ 20 mmHg	> 20 mmHg
Placebo (n = 172)	57 (33%)	24 (14%)	28 (16%)	31 (18%)	32 (19%)
200 mg AHU-377 (n = 164)	37 (23%)	19 (12%)	12 (7%)	52 (32%)	44 (27%)
100 mg LCZ-696 (n = 154)	27 (18%)	24 (16%)	23 (15%)	33 (21%)	47 (31%)
200 mg LCZ-696 (n = 168)	14 (8%)	15 (9%)	24 (14%)	39 (23%)	76 (45%)
400 mg LCZ-696 (n = 170)	17 (10%)	12 (7%)	12 (7%)	42 (25%)	87 (51%)
80 mg valsartan (n = 163)	37 (23%)	15 (9%)	23 (14%)	37 (23%)	51 (31%)
160 mg valsartan (n = 163)	23 (14%)	21 (13%)	20 (12%)	50 (31%)	49 (30%)
320 mg valsartan (n = 163)	27 (17%)	18 (11%)	20 (12%)	45 (28%)	53 (33%)

Data are number of patients and (%) who responded to treatment. Reprinted from: The Lancet, 375 (9722), L.M. Riulope, A. Dukat, M. Böhm, Y. Lacourcière, J. Gong, M.P. Lefkowitz, *Blood pressure reduction with LCZ696, a novel dual-acting inhibitor of the angiotensin II receptor and neprilysin: A randomized, double-blind, placebo-controlled, active comparator study*, 1255-1266, © 2011, with permission from Elsevier.

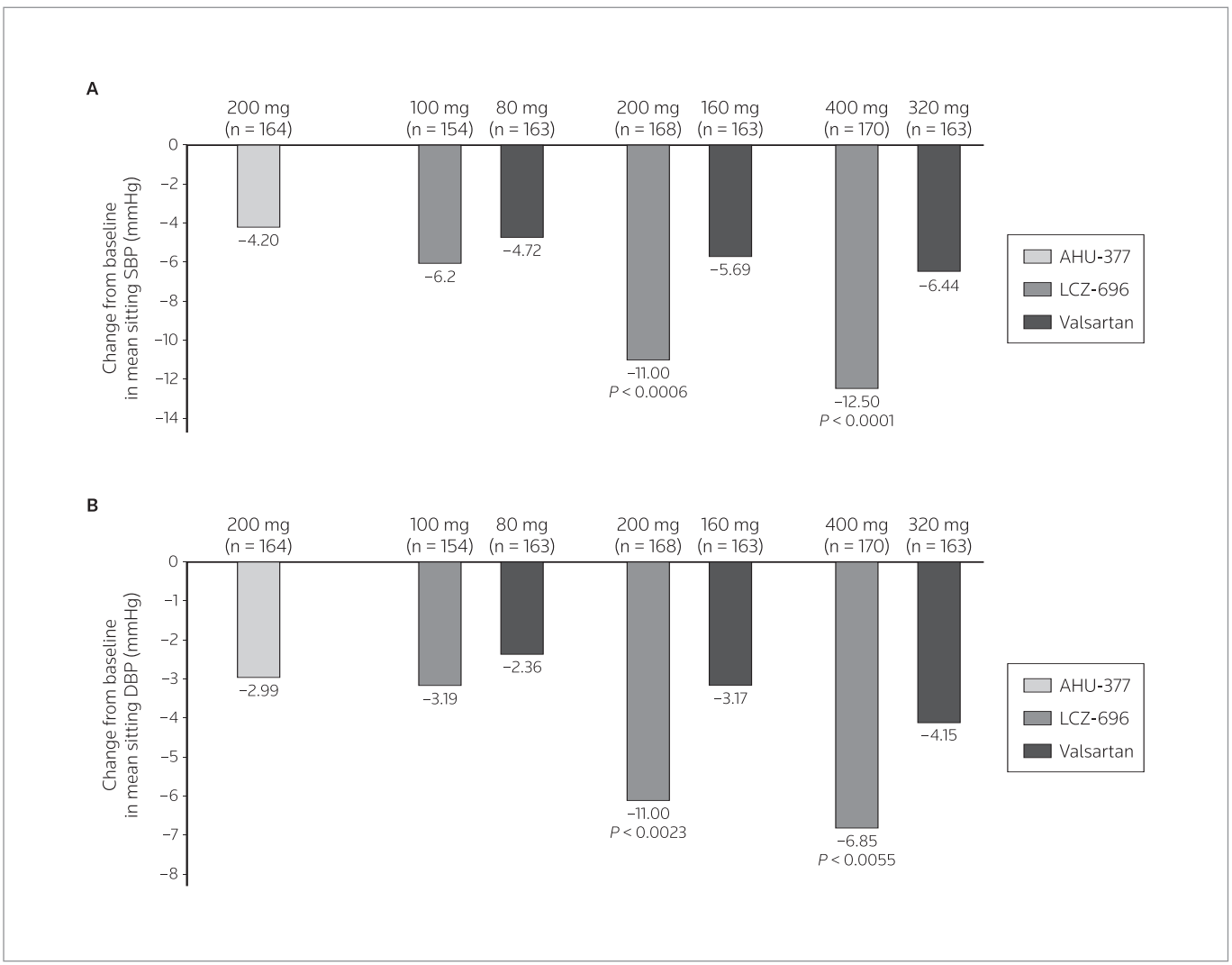

Figure 1. This figure depicts the blood pressure response, systolic and diastolic, to the neutral endopeptiadase inhibitor AHU-377 and two different doses of the dual-acting drug LCZ-696 and valsartan from baseline, placebo subtracted. All drugs caused significant reductions in BP from baseline, with the dual-acting drug being more effective than the single drugs. SBP, systolic blood pressure; DBP, diastolic blood pressure. A = $P < 0.0023$; B = $P < 0.0055$; C = $P < 0.0006$; D = $P < 0.0001$. Adapted and modified from: The Lancet, 375(9722), L.M. Riulope, A. Dukat, M. Böhm, Y. Lacourcière, J. Gong, M.P. Lefkowitz, *Blood pressure reduction with LCZ696, a novel dual-acting inhibitor of the angiotensin II receptor and neprilysin: A randomized, double-blind, placebo-controlled, active comparator study*, 1255-1266, © 2011, with permission from Elsevier.

Table III. *Effects of placebo, AHU-377, LCZ-696 and valsartan on various biomarkers in patients with hypertension.*

	Placebo	200 mg AHU-377	*P* value*	100 mg LCZ-696	80 mg Valsartan	*P* value†	200 mg LCZ-696	160 mg Valsartan	*P* value†	400 mg LCZ-696	320 mg Valsartan	*P* value†
Plasma atrial natriuretic peptide (pg/mL)												
Number of patients	57	64	—	59	62	—	72	61	—	76	62	—
Baseline	46.8	40.7	—	39.1	43.2	—	42.7	43.3	—	41.7	41.7	—
	(41.4-52.8)	(36.4-45.5)		(35.6-43.0)	(39.0-47.8)		(38.8-46.9)	(38.6-48.5)		(37.6-46.1)	(38.9-47.2)	
Change from	0%	32%	< 0.0001	13%	−9%	0.0008	18%	−11%	< 0.0001	15%	−3%	0.0042
baseline	(−9 to 10)	(21-44)¶		(2-24)	(−17 to 0)		(8-28)‡	(−19 to −3)		(5-24)‡	(−16 to 6)	
Cyclic guanosine monophosphate (nmol/L)												
Number of patients	61	66	—	61	65	—	75	63	—	77	69	—
Baseline	6.7	6.2	—	5.7	5.7	—	5.9	6.1	—	6.2	6.3	—
	(6.1-7.2)	(5.7-6.8)		(5.2-6.2)	(5.2-6.2)		(5.5-6.4)	(5.5-6.6)		(5.9-6.6)	(5.9-6.7)	
Change from	−3%	21%	< 0.0001	10%	−7%	0.0006	10%	−8%	0.0002	9%	−9%	
baseline	(−10 to 5)	(13-30)¶		(2-19)‡	(−14 to 0)		(3-18)‡	(−15 to −1)		(2-17)‡	(−16 to −3)	
Plasma renin (mU/L)												
Number of patients	34	42	—	31	51	—	46	43	—	56	51	—
Baseline	11.8	10.7	—	11.0	9.6	—	10.2	10.6	—	11.6	13.1	—
	(9.1-15.2)	(9.4-12.1)		(9.1-13.2)	(8.4-11.0)		(8.9-11.6)	(9.0-12.5)		(9.6-13.3)	(10.5-16.4)	
Change from	13%	12%	< 0.0001	72%	79%	0.82	94%	77%	0.56	157%	162%	0.89
baseline	(−13 to 47)	(−11 to 42)		(31-126)‡	(44-123)‡		(55-143)§	(41-124)‡		(108-216)¶	(111-226)¶	
Plasma aldosterone (pmol/L)												
Number of patients	50	54	—	43	54	—	58	48	—	67	52	—
Baseline	217.7	233.0	—	237.8	200.8	—	231.1	245.7	—	224.6	263.4	—
	(192.5-246.2)	(206.2-263.2)		(206.3-274.0)	(179.8-224.3)		(206.9-258.2)	(212.4-284.3)		(202.1-249.7)	(234.4-296.0)	
Change from	8%	4%	0.85	14%	10%	0.64	4%	−8%	0.15	8%	2%	0.46
baseline	(−6 to 23)	(−9 to 19)		(−1 to 32)	(−4 to 25)		(−8 to 17)	(−20 to 5)		(−4 to 22)	(−11 to 16)	
High-sensitivity C-reactive protein (mg/L)												
Number of patients	61	69	—	60	65	—	73	60	—	82	69	—
Baseline	2.1	2.1	—	2.5	2.6	—	1.9	2.1	—	1.9	2.1	—
	(1.6-2.7)	(1.6-2.7)		(2.0-3.3)	(2.1-3.2)		(1.5-2.5)	(1.7-2.7)		(1.5-2.4)	(1.7-2.6)	
Change from	17%	6%	0.60	−2%	23%	0.14	14%	−3%	0.28	−8%	18%	0.07
baseline	(0.6-45)	(−14 to 31)		(−22 to 23)	(−1 to 53)		(−7 to 39)	(−23 to 22)		(−24 to 11)	(−5 to 45)	
Urinary albumin-to-creatinine ratio (mg/mmol)												
Number of patients	49	62	—	54	60	—	59	49	—	68	58	—
Baseline	1.2	1.5	—	1.2	1.5	—	1.3	1.5	—	1.2	1.1	—
	(0.9-1.6)	(1.2-2.0)		(0.9-1.6)	(1.1-2.1)		(1.0-1.6)	(1.1-2.2)		(0.9-1.4)	(0.9-1.3)	
Change from	24%	−2%	0.28	−10%	−16%	0.55	−4%	−12%	0.49	−12%	−10%	0.86
baseline	(2-49)	(−18 to 16)		(−25 to 9)‡	(−30 to 0)‡		(−20 to 14)‡	(−27 to 6)‡		(−25 to 4)‡	(−24 to 8)‡	

Data are geometric means at baseline (95% confidence interval [CI]) or percentage changes from baseline (95% CI). All measurements were plasma except for urinary albumin-to-creatinine ratio.—, data unavailable or not applicable. **P* values to compare change from baseline with AHU-377 versus all valsartan doses. †*P* values to compare change from baseline with LCZ-696 versus corresponding valsartan dose. ‡$P < 0.05$ versus placebo. §$P < 0.001$ versus placebo. ¶$P < 0.0001$ versus placebo. Reprinted from: The Lancet, 375 (9722), L.M. Riulope, A. Dukat, M. Böhm, Y. Lacourcière, J. Gong, M.P. Lefkowitz, *Blood pressure reduction with LCZ696, a novel dual-acting inhibitor of the angiotensin II receptor and neprilysin: A randomized, double-blind, placebo-controlled, active comparator study*, 1255-1266, © 2011, with permission from Elsevier.

withdrawn from the study due to $K^+ > 5.5$ mEq/L. The rest of the patients tolerated the drug well and no serious AEs were noted.

In addition to this small, short-term study, two other major multicenter, long-term outcome studies are currently ongoing. One (NCT01035255), sponsored by Novartis, is a phase III study that will include 7,980 patients with HF (ejection fraction < 40%) and follow them for 4 years (24). The patients are randomized to LCZ-696 200 mg b.i.d. or enalapril 10 mg b.i.d., and the trial is expected to be completed by July 2013. The primary outcome of this study is time to occurrence of the composite endpoint of either cardiovascular death or HF hospitalization. The secondary outcomes include: a) summary score of HF symptoms; b) time to all-cause mortality; and c) time to occurrence of renal dysfunction. The other study (NCT00887588), also sponsored by Novartis, is a phase II study that will enroll 290 patients with preserved left ventricular function (ejection fraction ≥ 45%). These patients will be randomized to LCZ-696 50 mg/day, titrated to 100 and 200 mg/day, or valsartan 40 mg/day, titrated to 80 and 160 mg/day, and followed for 36 weeks (25). The estimated completion date is December 2011. The primary outcome is change in log-scale in NT-proBNP and the secondary outcomes include: a) change in echocardiographic parameters; b) change in the overall summary score and individual domain score of the Kansas City cardiomyopathy questionnaire; c) change in clinical composite score (NYHA and global patient assessment score); and d) class indicators of signs and symptoms of HF at each visit.

These trials, when completed, will provide the necessary information for the further development of LCZ-696 for the treatment of congestive HF. This drug has already been shown to be effective and safe for the treatment of hypertension.

DISCUSSION

Hypertension is quite common and is a major risk factor for cardiovascular complications, including HF (26-28). In addition, hypertension is rising worldwide and continues to be poorly controlled (29, 30). Currently, according to the National Health and Nutrition Examination Survey (NHAMES 2005-2008), there are about 76.4 million adults with hypertension in the U.S. (30), and the number of hypertensive subjects worldwide is expected to rise to 1 billion by the year 2025 (29). Despite the enormity of the BP burden and its related complications, BP is not well controlled. Hypertension, like HF, requires the combination of multiple drugs for its control. Uncontrolled hypertension will eventually cause systolic and diastolic dysfunction of the left ventricle, leading to HF (28).

In hypertension, like in HF, there is a pressure–volume interaction that sustains hypertension and worsens HF. Drugs that cause arterial vasodilation and promote salt and water excretion will lower BP and improve the symptoms of HF. Blockers of the renin–angiotensin–aldosterone system (RAAS), such as the ARBs, have been shown to lower BP and improve the symptoms and survival of patients with HF (5-8). In addition, both hypertension and HF stimulate the production and release of NPs through left ventricular and atrial distention from pressure and volume overload, respectively, as a defense mechanism (31-34). The NPs (ANP, BNP, CNP) cause vasodilation and increase the elimination of salt and water through stimulation of their receptors A and B (34). However, they are short-lived because they are rapidly metabolized by the NEPs. Therefore, the blockade of their metabolism by NEP inhibitors, such as AHU-377, will prevent their metabolism, increase their blood levels, and promote vasodilation and natriuresis. These effects will decrease BP and improve the symptoms of HF (33-35). However, since the effects of NEPs on BP reduction are modest (34, 35), their combination with potent inhibitors of RAAS, such as ACE inhibitors or ARBs, will potentiate their antihypertensive and beneficial HF effects (9, 36-38).

Omapatrilat was more effective than enalapril in reducing BP and improving HF symptoms and left ventricular function (36-38). However, it caused a significant increase in cough and angioedema compared to enalapril (36), which led to its withdrawal from the market. The reasons for the increased cough on omapatrilat, a combination of an ACE and an NEP inhibitor, are due to the dual inhibitory effects of these substances on the degradation of bradykinin and substance P. Both ACE and NEP catabolize bradykinin and substance P, both strong cough-inducing substances (39, 40). Therefore, the administration of dual inhibitors of bradykinin and substance P, such as omapatrilat, increased the blood and tissue levels of these substances more than ACE inhibitors alone, and increased the incidence of cough and angioedema.

In contrast to ACE inhibitors, cough and angioedema are rare with the ARBs, since these substances do not interfere with the degradation of bradykinin and substance P (5-8, 41, 42). So far, studies with LCZ-696 in hypertension and HF have demonstrated the compound to be effective, safe and well tolerated, without inducing cough or angioedema (3, 9, 23).

Based on the current information and that to be provided by the ongoing trials in HF, it would be safe to speculate that LCZ-696 will be an important addition to our armamentarium for the treatment of hypertension and HF. However, no definitive predictions can be made at this time for the eventual approval of LCZ-696 for the treatment of hypertension and HF, although the available data so far on the drug's efficacy and safety in the treatment of hypertension are encouraging.

SOURCE

Novartis AG (CH).

DISCLOSURES

The author states no conflicts of interest.

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