The Angiotensin Receptor Neprilysin Inhibitor LCZ696 in Heart Failure with Preserved Ejection Fraction

The Prospective comparison of ARNI with ARB on Management Of heart failUre with preserved ejectioN fraction (PARAMOUNT) Trial

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Disclosures

- Drs. Solomon, Zile, Pieske, Voors, Shah, Packer and McMurray have received research support and have consulted for Novartis.
- Drs. Shi, Bransford, Lefkowitz and Gong are employees of Novartis.
- Dr. Kraigher-Krainer and Ms. Takeuchi have no conflicts to report.

Background

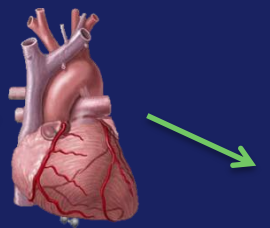
- Heart failure with preserved ejection fraction (HFpEF) accounts for up to half of heart failure cases, and is associated with substantial morbidity and mortality.
- Pharmacologic therapies that have been tested in clinical trials include beta-blockers, calcium-channel blockers, angiotensin converting enzyme (ACE) inhibitors, and angiotensin receptor blockers; to date no therapies have been shown to improve clinical outcomes in this condition.
- Several pathophysiologic mechanisms have been implicated in this disorder, including abnormalities of diastolic function and impaired natriuretic response to acute volume expansion.

LCZ696 – A First-in-Class Angiotensin Receptor Neprilysin Inhibitor

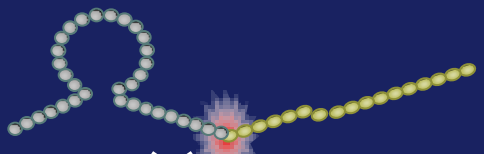
Natriuretic Peptide System

Heart Failure

Renin Angiotensin System

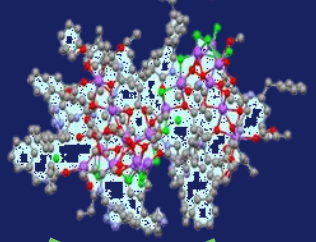


pro-BNP



BNP

NT-pro BNP



LCZ696

Angiotensinogen (liver secretion)

Angiotensin I

Angiotensin II

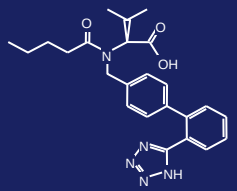
Neprilysin

Inactive fragments

AHU377

↓

LBQ657



Valsartan

AT_1 receptor

Vasodilation
- ↓ blood pressure
- ↓ sympathetic tone
- ↓aldosterone levels
- ↓ fibrosis
- ↓ hypertrophy

Natriuresis/Diuresis

Vasoconstriction
- ↑ blood pressure
- ↑ sympathetic tone
- ↑ aldosterone
- ↑ fibrosis
- ↑ hypertrophy

Objectives and Hypothesis

- The PARAMOUNT trial was designed to test the safety and efficacy of LCZ696 in patients with HFpEF.
- We hypothesized that LCZ696 would reduce NT-proBNP to a greater extent than the ARB valsartan at 12 weeks, and would be associated with favorable changes in cardiac structure and function at 36 weeks

Inclusion and Exclusion Criteria

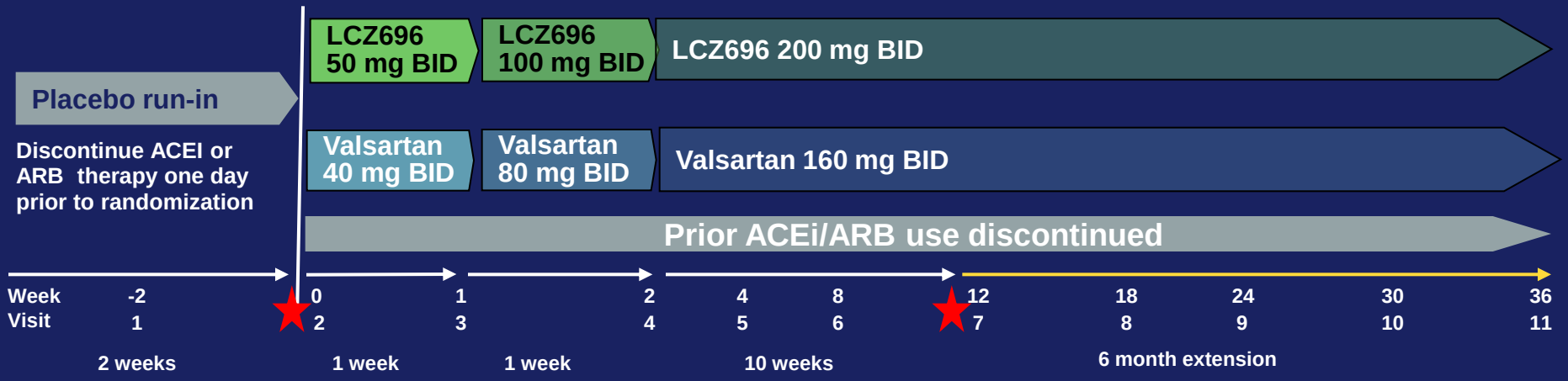
Key Inclusion Criteria

- Age ≥ 40 years
- Documented stable chronic heart failure (NYHA II-IV) with signs and symptoms of heart failure (Dyspnea on exertion/ Orthopnea/ Paroxysmal nocturnal dyspnea/ Peripheral edema)
- LVEF ≥ 45%
- Plasma NT-proBNP > 400 pg/ml at screening (Visit 1)
- On diuretic therapy prior to Visit 1, controlled systolic BP (<140 mm Hg, or BP <160 mm Hg if on 3 meds)
- eGFR ≥ 30 ml/min/1.73 m2 (MDRD)
- Patients with a potassium ≤5.2 mmol/l at Visit 1

Key Exclusion Criteria

- Patients with a prior LVEF reading <45%, at ANY time
- Patients who require treatment with both an ACE inhibitor and an ARB
- Isolated right heart failure due to pulmonary disease
- Dyspnea and/or edema from non-cardiac causes, such as lung disease, anemia, or severe obesity
- Presence of valvular heart disease, hypertrophic cardiomyopathy, infiltrative cardiomyopathy, restrictive cardiomyopathy, or pericardial disease
- Coronary disease requiring revascularization during the study

PARAMOUNT: Study Design



Primary objective	NT pro-BNP reduction from baseline at 12 weeks
Secondary objectives	▪ Echocardiographic measures of diastolic function, left atrial size, LV size and function, PASP ▪ HF symptoms, Clinical composite assessment and Quality of life (KCCQ) ▪ Safety and tolerability

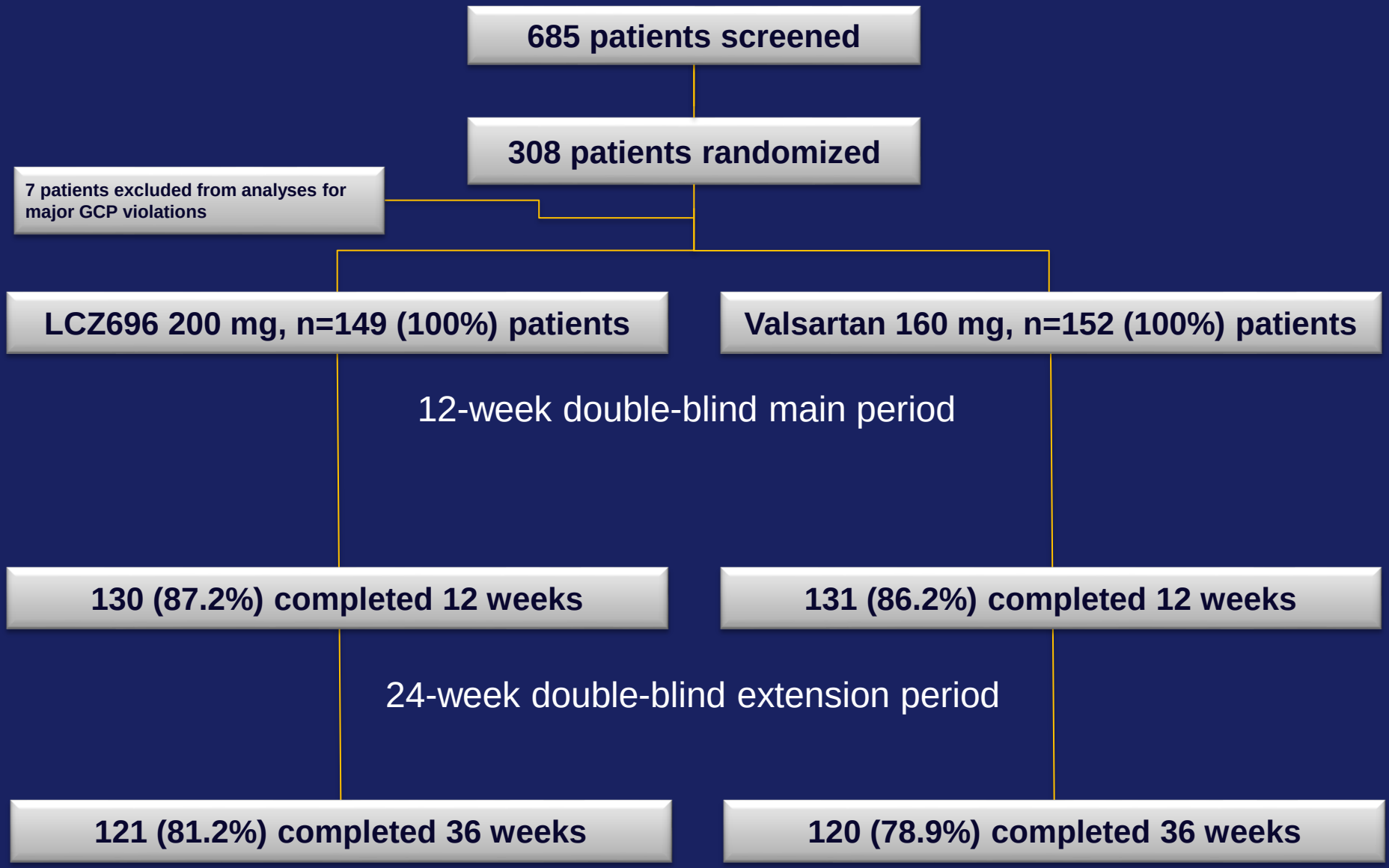
★ Baseline randomization visit and visit at end of 12 weeks of core study

Clinicaltrials.gov NCT00887588

Statistical Analysis

- A sample size of 290 patients ensured at least 80% power to detect a 25% reduction in NT pro-BNP vs comparator
- Primary endpoint (NT-proBNP) was evaluated as the ratio of the 12 week to baseline log-transformed NT-proBNP, and data are presented as geometric means
- We performed a last observation carried forward analysis, as well as a completers only analysis and multiple imputation for missing values as sensitivity analyses.
- All analyses of primary and secondary endpoints were adjusted for baseline values, and for the stratification strata (region and prior ACE/ARB use).

Patient Flow



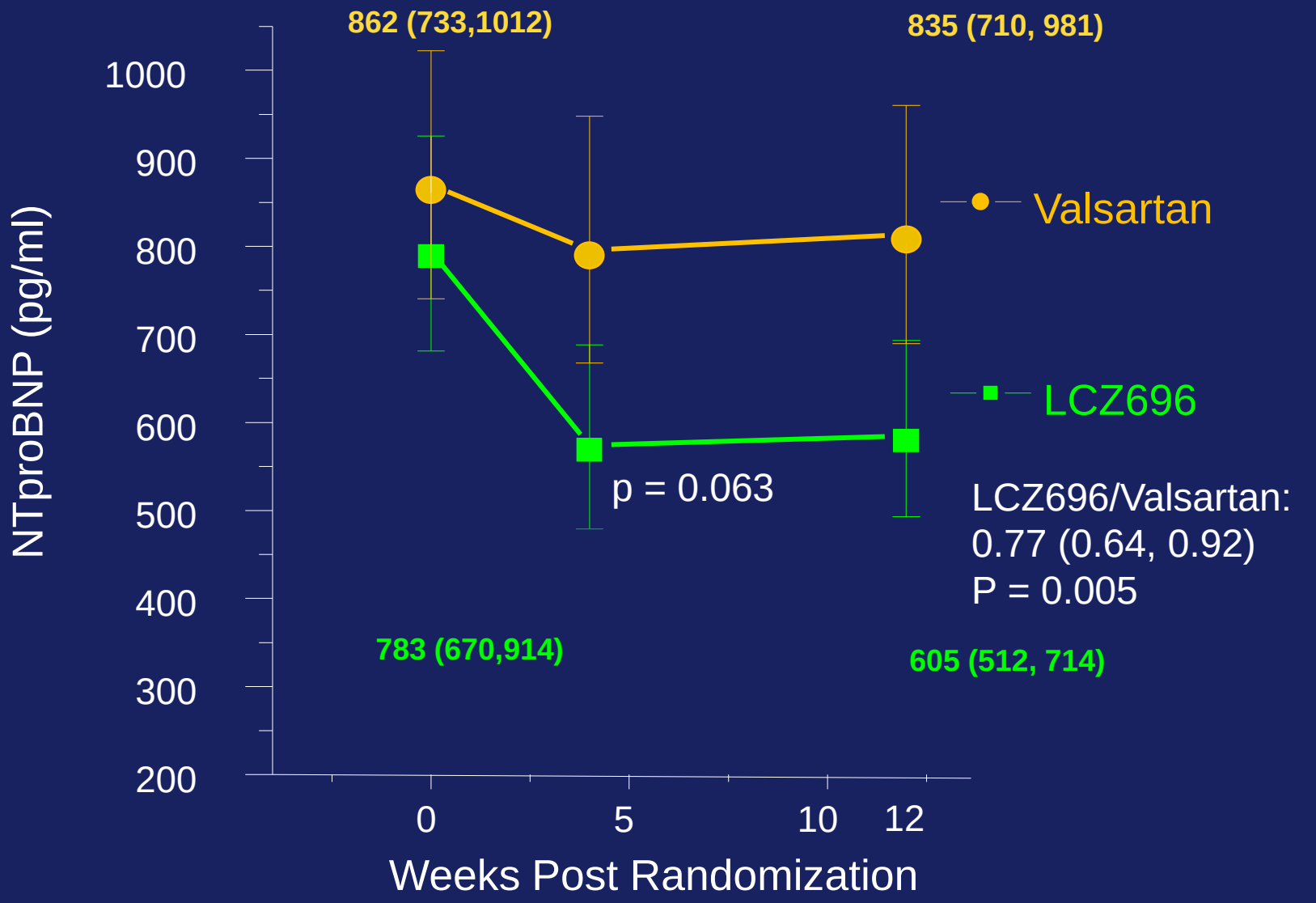
Baseline Characteristics

Baseline Characteristic	LCZ696	Valsartan
	N=149	N=152
Mean age	70.9 (9.4)	71.2 (8.9)
Female gender (n, %)	57%	56%
NYHA class		
Class II (%)	81%	78%
Class III (%)	19%	21%
History of prior heart failure hospitalization (n, %)	40%	45%
Atrial Fibrillation at Screening (n, %)	27%	30%
History of Hypertension (n, %)	95%	92%
History of Diabetes (n, %)	41%	35%
eGFR < 60 (%)	38%	45%
SBP/DBP median (interquartile range)	136 (130,145) / 80 (74, 85)	136 (126, 145) / 78 (70, 84)
NT-ProBNP geometric mean (95% CI)	794 (681, 925)	870 (740, 1022)

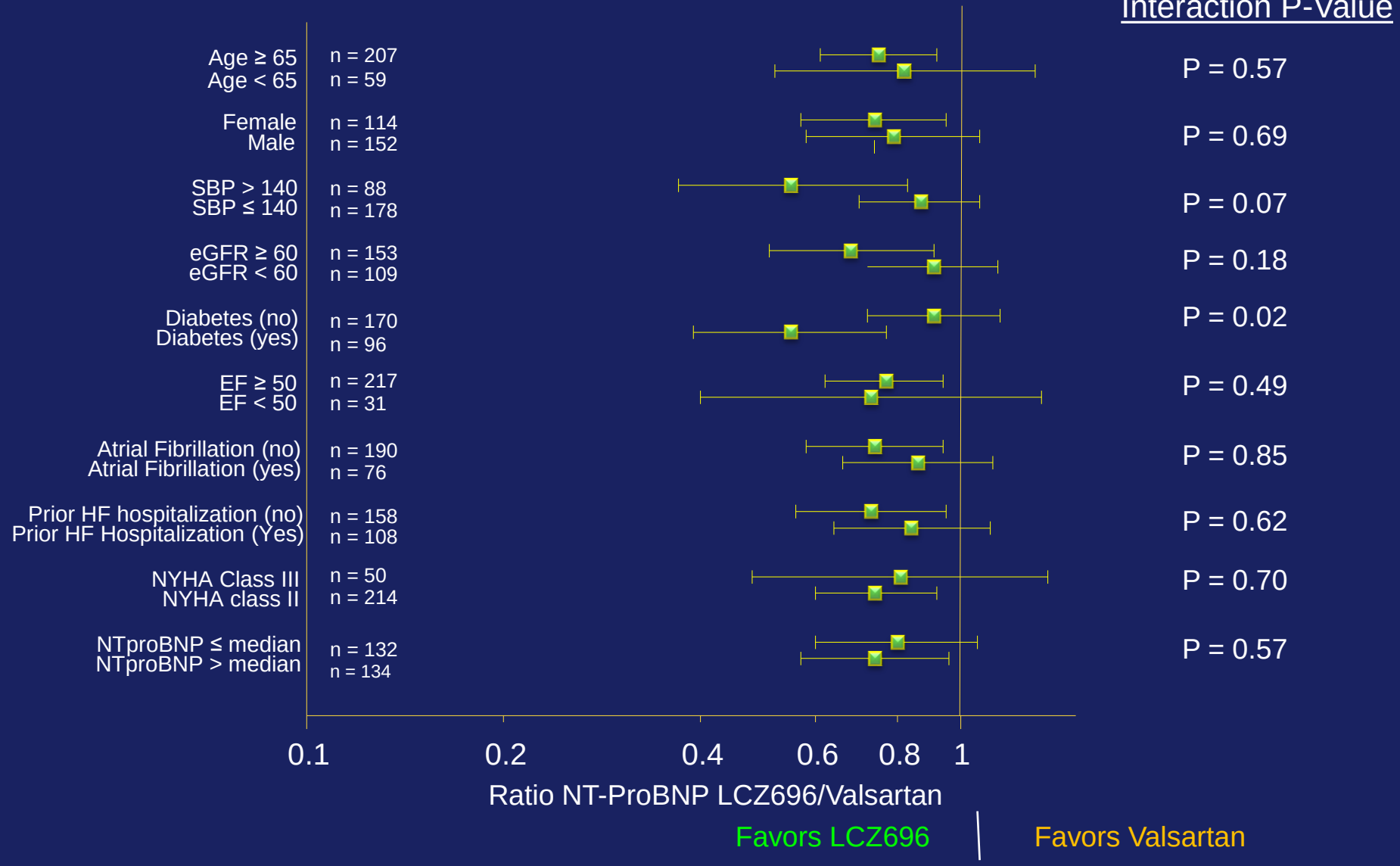
Baseline Characteristics (2)

Baseline Medications	LCZ696	Valsartan
ACE Inhibitors (n, %)	56%	53%
ARBs (n, %)	38%	41%
ACE inhibitors or ARBs (n, %)	93%	93%
Diuretics (n, %)	100%	100%
Beta-Blockers (n, %)	79%	80%
Aldosterone Antagonists (n, %)	19%	23%
Baseline Echocardiographic Measures		
Left Ventricular Ejection Fraction (%)	58 (7.3)	58 (8.1)
Left Ventricular Ejection Fraction ≥ 50%	76%	82%
Lateral Mitral Relaxation Velocity (E') (cm/s)	7.8 (2.7)	7.3 (2.9)
Mitral Inflow to Mitral Relaxation Velocity Ratio (E/E')	12.4 (8.1)	13.0 (7.0)
Left Atrial Dimension (cm)	3.7 (0.45)	3.7 (0.54)
Left Atrial Volume (ml)	65.6 (22.7)	67.4 (28.4)
Left Ventricular mass (g)	145 (40.5)	150 (43.8)

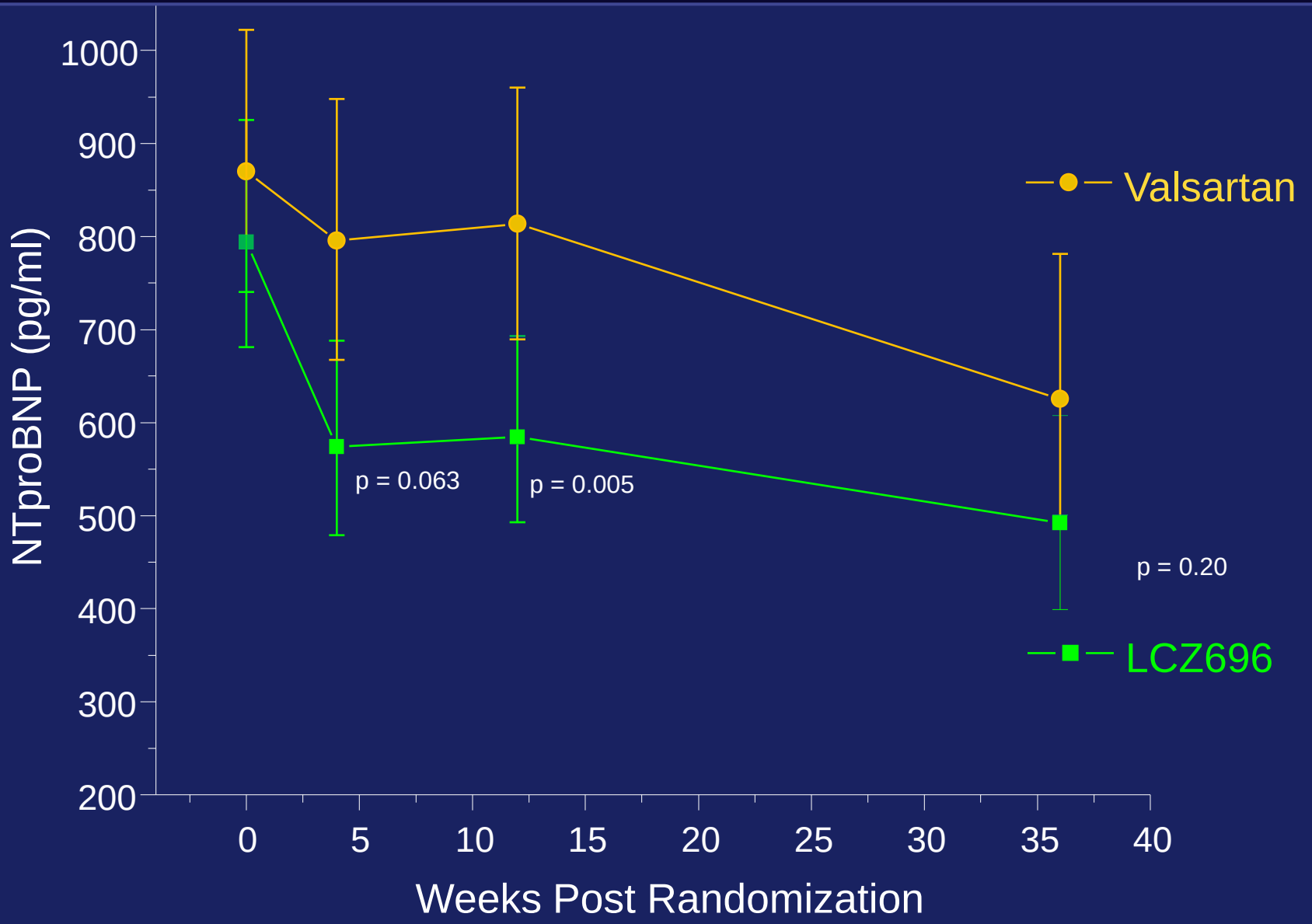
Primary Endpoint: NT-proBNP at 12 Weeks



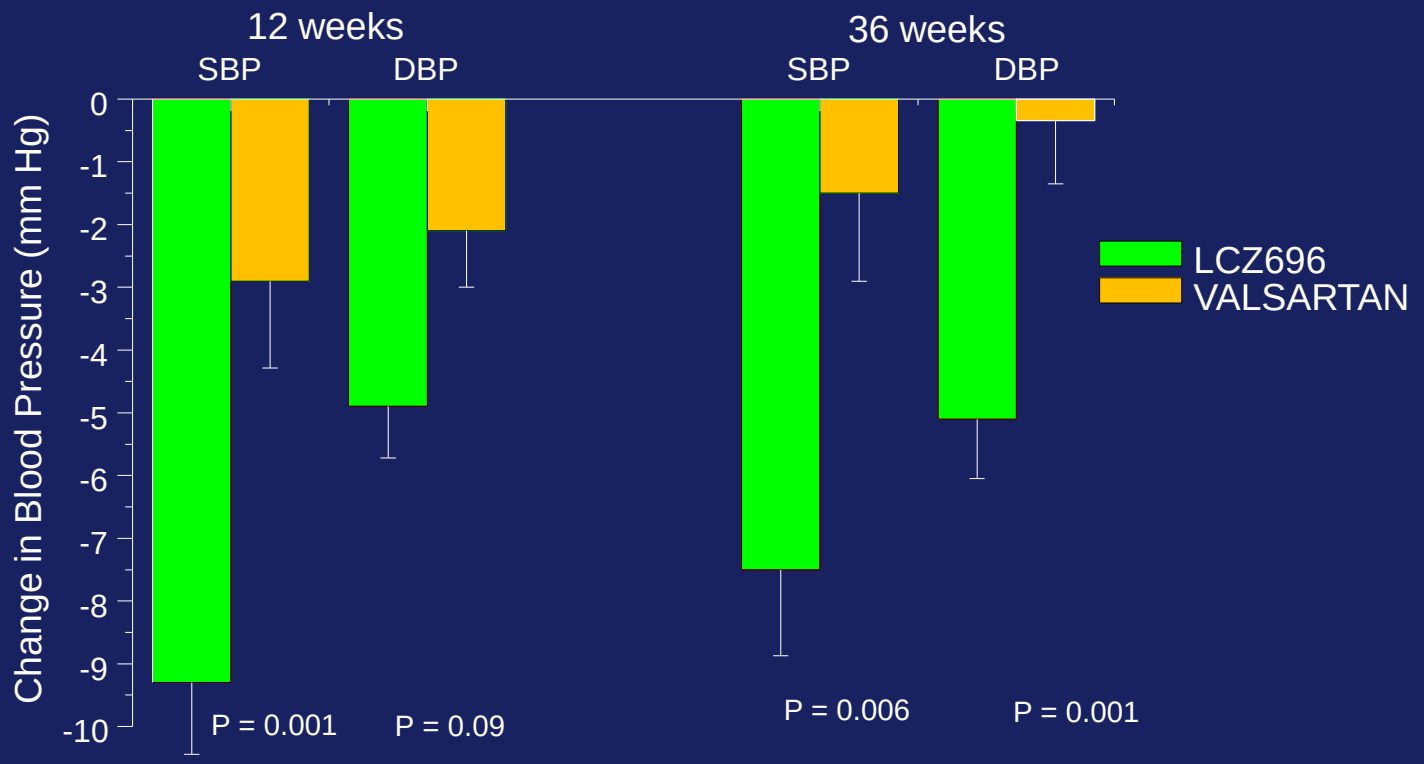
Similar Treatment Effect in All Predefined Subgroups



Change in NT-proBNP over 36 weeks

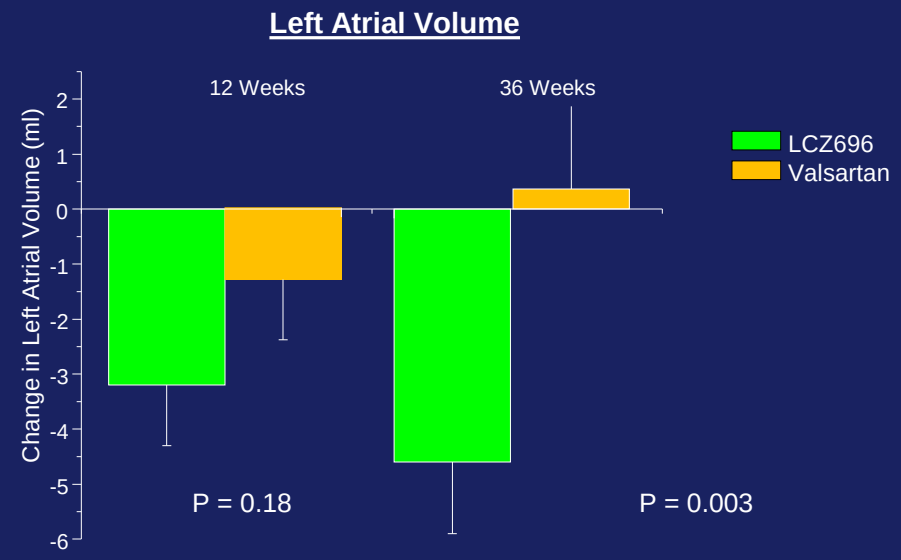


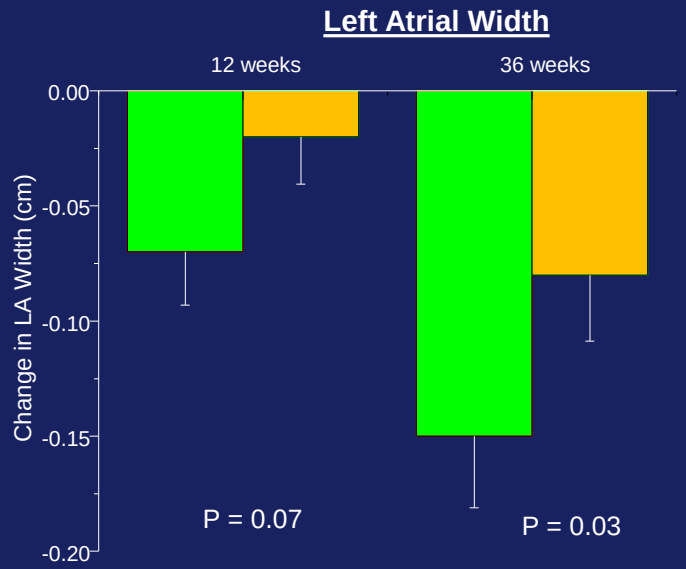
Blood Pressure Reduction

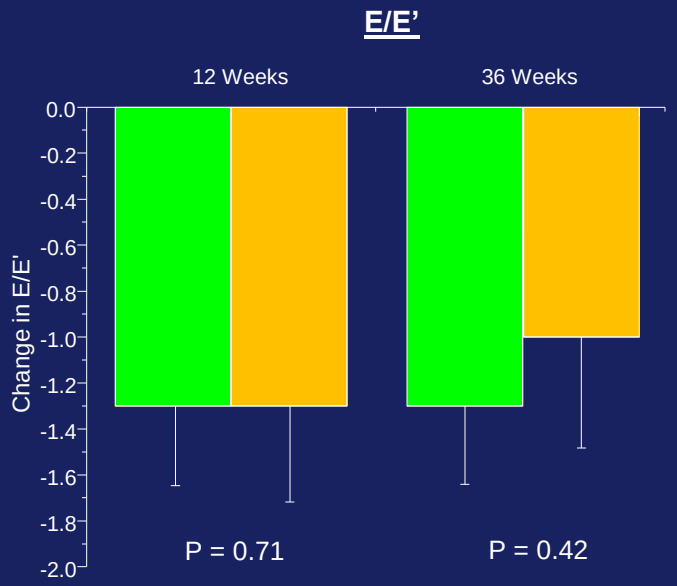


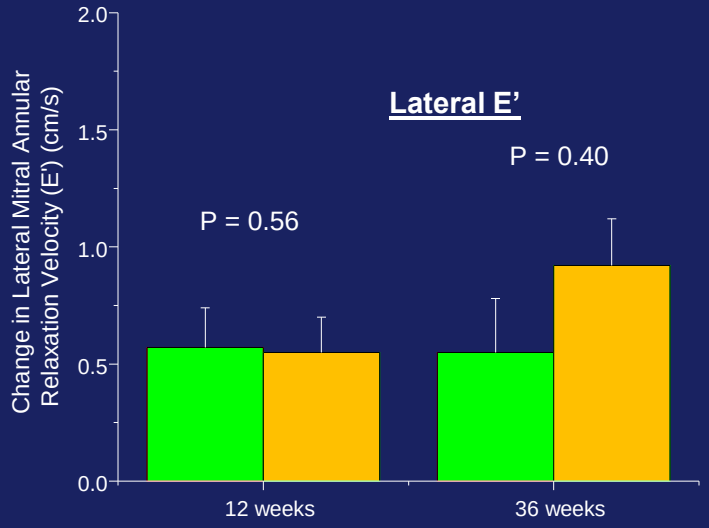
Note: Change in BP correlated poorly with change in NT-proBNP (r = 0.104, p=0.1). After adjustment for change in BP, the reduction in NT-proBNP between groups remained statistically significant (p=0.01).

Changes in Key Echocardiographic Measures



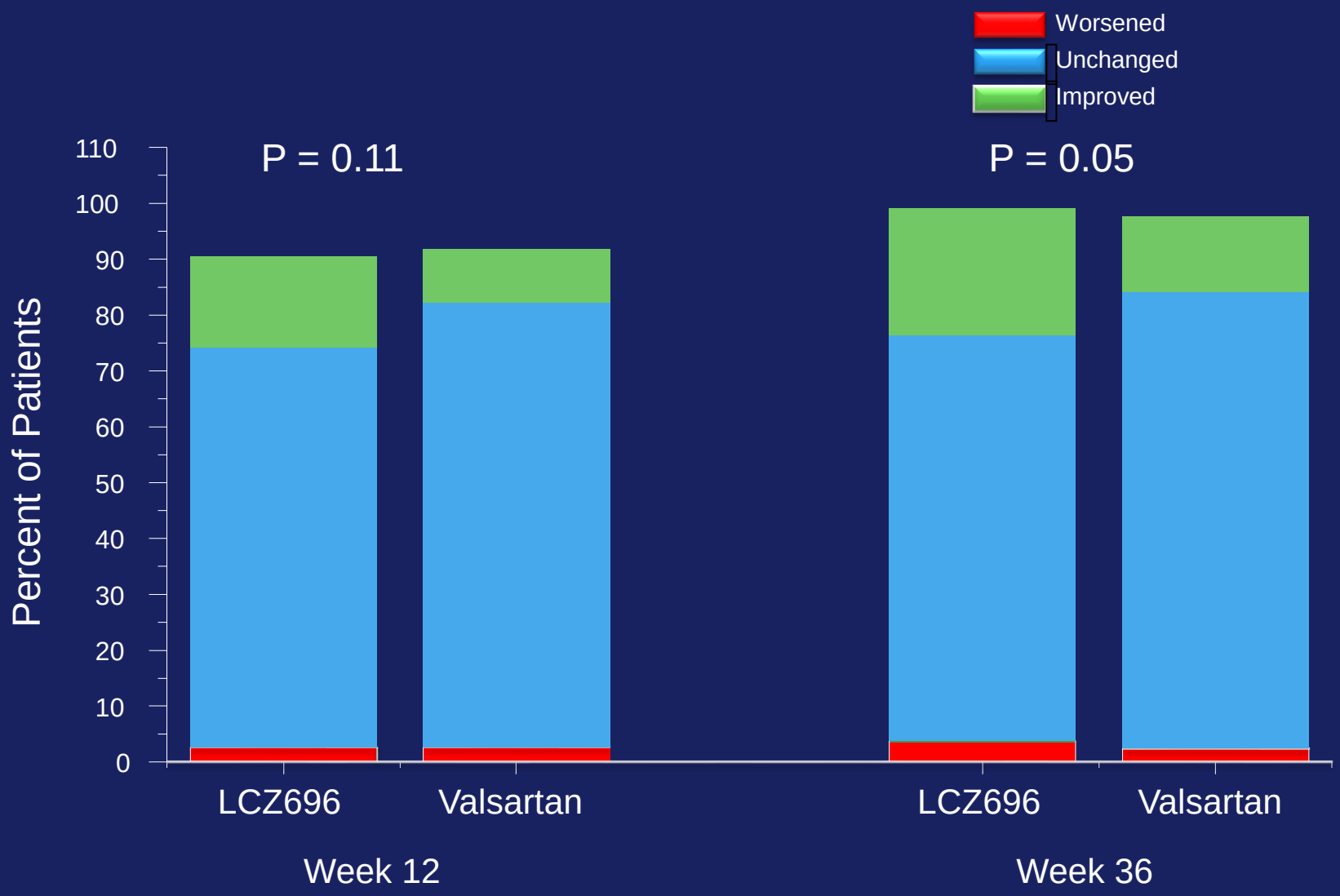






No Significant Changes in LV volumes, Ejection Fraction, or LV mass at 12 or 36 weeks

Change in NYHA Class



Adverse Events and Laboratory Values

	LCZ696 (n=149)	Valsartan (n=152)	p-value
Any Serious Adverse Event (SAE)	22 (15%)	30 (20%)	0.32
Deaths	1 (0.7%)	2 (1.3%)	0.99
All Cardiac	9 (6.0%)	12(7.9%)	0.69
Heart Failure	4 (2.7%)	6 (3.9%)	0.77
Any Adverse Event (AE)	96 (64%)	111 (73%)	0.14
Adverse events of Interest			
Symptomatic Hypotension	28 (19%)	27 (18%)	0.88
Renal Dysfunction	3 (2.0%)	7 (4.6%)	0.34
Hyperkalemia	12 (8.1%)	9 (5.9%)	0.50
Abnormal Laboratory Values			
Potassium > 5.5	24 (16%)	16 (11%)	0.21
Potassium ≥ 6.0	5 (3.4%)	6 (4.2%)	0.97
≥ 50% decrease in eGFR	5 (3.4%)	4 (2.8%)	0.98

Conclusions

- We found that in patients with HFpEF, the angiotensin receptor neprilysin inhibitor LCZ696 reduced NT-proBNP, a marker associated with worse outcomes in HFpEF, to a greater extent than valsartan after 12 weeks of therapy. This reduction became evident at 4 weeks and was sustained to 36 weeks, though the between group difference was no longer significant.
- We further observed a reduction in left atrial size, indicative of reverse left atrial remodeling, and improvement in NYHA class in patients randomized to LCZ696 after 36 weeks, compared with those randomized to valsartan.
- LCZ696 was well tolerated.
- These hypothesis generating findings suggest that LCZ696 may have beneficial effects in patients with HFpEF and that further testing of this compound may be warranted in patients with this condition.

The angiotensin receptor neprilysin inhibitor LCZ696 in heart failure with preserved ejection fraction: a phase 2 double-blind randomised controlled trial

*Scott D Solomon, Michael Zile, Burkert Pieske, Adriaan Voors, Amil Shah, Elisabeth Kraigher-Krainer, Victor Shi, Toni Bransford, Madoka Takeuchi, Jianjian Gong, Martin Lefkowitz, Milton Packer, John J V McMurray, for the Prospective comparison of ARNI with ARB on Management Of heart failUre with preserved ejectioN fraction (PARAMOUNT) Investigators**

Summary

Background Heart failure with preserved ejection fraction is associated with substantial morbidity and mortality, but effective treatments are lacking. We assessed the efficacy and safety of LCZ696, a first-in-class angiotensin receptor neprilysin inhibitor, in patients with this disorder.

Methods PARAMOUNT was a phase 2, randomised, parallel-group, double-blind multicentre trial in patients with New York Heart Association (NYHA) class II–III heart failure, left ventricular ejection fraction 45% or higher, and NT-proBNP greater than 400 pg/mL. Participants were randomly assigned (1:1) by central interactive voice response system to LCZ696 titrated to 200 mg twice daily or valsartan titrated to 160 mg twice daily, and treated for 36 weeks. Investigators and participants were masked to treatment assignment. The primary endpoint was change in NT-proBNP, a marker of left ventricular wall stress, from baseline to 12 weeks; analysis included all patients randomly assigned to treatment groups who had a baseline and at least one postbaseline assessment. This trial is registered at Clinicaltrials.gov, number NCT00887588.

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