4331

Safety and efficacy of sacubitril/valsartan by dose level in patients hospitalized with acute heart failure: Observations from PIONEER-HF

D.A. Morrow[1], E.J. Velazquez[2], A.D. Devore[3], C.I. Duffy[4], Y. Gurmu[1], K. McCague[4], R. Rocha[4], E. Braunwald[1]

[1]Brigham and Women's Hospital, Cardiovascular Medicine, Boston, United States of America; [2]Yale University, Department of Internal Medicine, New Haven, United States of America; [3]Duke Clinical Research Institute, Durham, United States of America; [4]Novartis Pharmaceuticals, East Hanover, United States of America

Funding Acknowledgement: Novartis Pharmaceuticals

Background: In hemodynamically stabilized patients with acute decompensated heart failure (ADHF) enrolled in the PIONEER-HF trial, compared with enalapril, sacubitril/valsartan started in-hospital and continued for 8 weeks was well tolerated, achieved a greater reduction in NT-proBNP, and reduced cardiovascular death or rehospitalization for HF. Nearly 1/2 of patients achieved the target dose of blinded study drug. We performed an exploratory analysis of the safety and efficacy of sacubitril/valsartan according to the dose level dispensed at 4 weeks in PIONEER-HF

Methods: PIONEER-HF was a randomized, double-blind, active-controlled trial of sacubitril/valsartan vs. enalapril in 881 hospitalized ADHF pts following hemodynamic stabilization. Blinded study medication was administered for 8-weeks, with initial dosing selected based on the systolic blood pressure (SBP) at randomization (starting dose 24/26 or 49/51 mg twice daily vs 2.5 or 5 mg twice daily) and titrated toward a target of sacubitril/valsartan 97 mg/103 mg twice daily, or enalapril 10 mg twice daily with an algorithm using SBP along w/ the investigator's assessment of tolerability.

Results: At the week 4 visit, 199 patients (45.2%) in the sacubitril/valsartan group and 210 (47.6%) in the enalapril group were dispensed the target dose. Baseline characteristics were similar in the 2 treatment groups within each dose level. The prespecified adverse events of special interest were similar between sacubitril/valsartan and enalapril irrespective of dose level (Table) with no significant heterogeneity. In addition, there was no heterogeneity across dose levels in the favorable effect of sacubitril/valsartan on the change in NTproBNP by week 8 (Table, p-interaction=0.54) or the serious composite endpoint (p-interaction=0.71).

Conclusion: In hemodynamically stabilized patients with ADHF, the safety and efficacy of sacubitril/valsartan appears generally consistent among patients at various dose levels.

Dose Level at Week 4 Visit	Dose level 1		Dose Level 2		Dose Level 3	
Dose Details						
Study rx	Enalapril	Sacubitril/Val	Enalapril	Sacubitril/Val	Enalapril	Sacubitril/Val
Dose (2x/d)	2.5mg	24mg/26mg	5mg	49mg/51mg	10mg	97mg/103mg
N	66 (15.0)	70 (15.9)	82 (18.6)	93 (21.1)	210 (47.6)	199 (45.2)
Safety						
Symptomatic Hypotension	27.3	20.0	19.5	15.1	5.2	10.1
HR [95% CI]	0.73 [0.40, 1.35]		0.77 [0.40, 1.48]		1.92 [0.94, 3.90]	
Hyperkalemia	13.6	18.6	12.2	16.1	7.1	6.0
HR [95% CI]	1.36 [0.62, 2.97]		1.32 [0.63, 2.78]		0.84 [0.41, 1.76]	
Worsened renal function	33.3	24.3	22.0	14.0	11.9	12.6
HR [95% CI]	0.73 [0.43, 1.25]		0.64 [0.33, 1.22]		1.06 [0.63, 1.77]	
Efficacy						
NTproBNP ratio 8wk/Baseline	0.69	0.40	0.61	0.47	0.57	0.40
Ratio S/V vs E	0.58 [0.41, 0.83]		0.77 [0.58, 1.01]		0.70 [0.56, 0.87]	
Serious composite	19.8	10.0	11.0	7.5	11.0	3.5
HR [95% CI]	0.48 [0.19, 1.21]		0.66 [0.25, 1.77]		0.31 [0.13, 0.72]	

Event rates are reported as % at 8 wk. Serious Composite = death, HF re-hosp, LVAD, listed for transplant.

Efficacy and Safety by Dose-Tier