Supplemental Online Content

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This supplemental material has been provided by the authors to give readers additional information about their work.

Online only Supplementary Appendix

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Supplement to: Pieske B, et al. Effect of sacubitril/valsartan versus standard medical therapies on plasma NT-proBNP concentration and sub-maximal exercise capacity in patients with heart failure and preserved ejection fraction: The PARALLAX randomized clinical trial

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eTable 1: Key eligibility criteria

Key inclusion criteria

• ≥ 45 years of age, any sex
• LVEF > 40% by echocardiography performed within 6 months prior to screening or during screening
• Symptom(s) of HF (NYHA class II-IV) requiring treatment with diuretics (including loop, or thiazide diuretics, or MRAs) for at least 30 days prior to screening
• Structural heart disease demonstrated by echocardiographic evidence of LAE or LVH: (any local measurement made during the screening or within the 6 months prior to screening):
  ○ LAE defined by at least one of the following: LA width (diameter) ≥ 3.8 cm or LA length ≥5.0 cm or LA area ≥ 20 cm^2 or LA volume ≥ 55 mL or LA volume index ≥29 mL/m^2
  ○ LVH defined by septal thickness or posterior wall thickness ≥ 1.1 cm
• Receiving evidence-based therapy for relevant comorbidities as determined by the individual clinical profile of the patient (e.g. age and number and type of comorbidities) with stable doses for the previous four weeks prior to randomization
• NT-proBNP >220 pg/mL for patients with sinus rhythm or >600 pg/mL for patients with AF on the screening ECG
• KCCQ clinical summary score <75 at Visit 1
• Patients on ACEI or ARB therapy must have had a history of hypertension

Key exclusion criteria
• Any prior echocardiographic measurement of LVEF ≤40%, under stable conditions • Acute decompensated HF within 30 days prior to screening • Acute coronary syndrome (including myocardial infarction), cardiac surgery, other major cardiovascular surgery, or urgent percutaneous coronary intervention within 3 months prior to screening • Any clinical event within the 6 months prior to screening that could have reduced the LVEF, unless an echo measurement was performed after the event confirming the LVEF to be >40% • Current (within 30 days from Visit 1) use of renin inhibitor(s), dual RAS blockade, or sacubitril/valsartan • Walk distance primarily limited by non-cardiac conditions at Visit 1 • Probable alternative diagnoses that could account for the HF symptoms, specifically severe pulmonary disease; anemia (Hb <10 g/dL in males, <9.5 g/dL in females); BMI >40kg/m^2 • Hemodynamically relevant valvular disease; clinically significant congenital heart disease; pericardial constriction; genetic or infiltrative cardiomyopathy • Prior history of any dilated cardiomyopathy, including peripartum cardiomyopathy, chemotherapy-induced cardiomyopathy, or viral myocarditis • Patients with HbA1c >7.5%, not treated for diabetes • SBP <110 mmHg or ≥180 mmHg at screening or SBP >150 to <180 mmHg at screening unless the patient is receiving three or more antihypertensive drugs • Serum potassium >5.2 mmol/L (or equivalent plasma potassium value) at screening • eGFR <30 mL/min/1.73 m^2 at screening • History of angioedema or history of hypersensitivity to sacubitril/valsartan

ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; eGFR, estimated glomerular filtration rate; Hb, hemoglobin; HbA1c, glycated hemoglobin; HF, heart failure; KCCQ, Kansas City Cardiomyopathy Questionnaire; LA, left atrium; LAE, left atrial enlargement; LVEF, left ventricular ejection fraction; LVH, left ventricular hypertrophy; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro B-type natriuretic peptide; NYHA, New York Heart Association; SBP, systolic blood pressure; RAS, renin-angiotensin system

eTable 2: Secondary endpoint changes at Week 24 by stratum

	ACEI stratum		ARB stratum		No RASi stratum	
	Sacubitril/valsartan	**Enalapril**	**Sacubitril/valsartan**	**Valsartan**	**Sacubitril/valsartan**	**Placebo**
Change from baseline in KCCQ clinical summary score at Week 24[a,b]						
n	510	506	546	557	151	147
Adjusted mean change from baseline (95% CI)	11.2 (9.7, 12.8)	10.8 (9.3, 12.4)	14.2 (12.7, 15.7)	12.6 (11.1, 14.1)	9.6 (6.5, 12.7)	12.5 (9.4, 15.7)
Adjusted mean difference (95% CI)	0.4 (-1.8, 2.6)		1.6 (-0.6, 3.7)		-2.9 (-7.4, 1.5)	
≥5 points improvement, n (%)	348 (68.2%)	325 (64.2%)	383 (70.2%)	373 (67.0)	89 (58.9)	97 (66.0)
Adjusted odds ratio[c] (95% CI)	1.29 (0.83, 2.02)		1.15 (0.74, 1.76)		0.62 (0.28, 1.38)	
≥5 points deterioration, n (%)	77 (15.1)	88 (17.4)	71 (13.0)	90 (16.2)	39 (25.8)	24 (16.3)
Adjusted odds ratio[c] (95% CI)	0.83 (0.49, 1.38)		0.73 (0.44, 1.21)		2.01 (0.84, 4.82)	
Change from baseline in NYHA class at Week 24[a,b*]						
n	518	511	557	567	153	151
Improved, n (%)	98 (18.9%)	118 (23.1%)	146 (26.2%)	138(24.3%)	46 (30.1%)	39(25.8%)
Worsened, n (%)	21(4.1%)	18 (3.5%)	19 (3.4%)	28(4.9%)	11(7.2%)	7(4.6%)
Adjusted odds ratio to be in favorable NYHA class (95% CI)	0.7 (0.5, 1.0)		1.2 (0.9, 1.5)		1.2 (0.7, 1.9)	

All comparisons are sacubitril/valsartan vs. background medication based individualized comparator

[a]The MMRM model includes stratum (ACEI, ARB, No RASi), region, treatment (sacubitril/valsartan and background medication based individualized comparator), visit, and treatment-by-visit as fixed-effect factors; baseline values, baseline SBP, stratum-by-baseline value, stratum-by-baseline SBP, and visit-by-baseline value interactions as covariates.

[b]An adjusted mean difference > 0 favors sacubitril/valsartan.

[c]An adjusted odds ratio > 1 favors sacubitril/valsartan.

n = number of patients with NYHA improved/worsened from baseline at the visit.

ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; CI, confidence interval; KCCQ CSS, Kansas City Cardiomyopathy Questionnaire clinical summary score; NYHA, New York Heart Association; RASi, renin-angiotensin system inhibitor; SBP, systolic blood pressure

eTable 3: Incidence of death, key serious AEs and AEs (safety set[a])

	Sacubitril/valsartan N=1280	Background-medication based individualized comparator N=1284
Death, n (%)	23 (1.8%)	17 (1.3%)
Serious adverse events, n (%)		
At least one serious AE	186 (14.5%)	191 (14.9%)
At least one suspected study drug related serious AE	11 (0.9%)	10 (0.8%)
Adverse events, n (%)		
At least one AE	1087 (84.9%)	1030 (80.2%)
At least one suspected study drug related AE	390 (30.5%)	290 (22.6%)
At least one AE leading to permanent discontinuation of study treatment	116 (9.0%)	87 (6.8%)
At least one AE leading to dose adjustment or temporarily interruption of study treatment	248 (19.4%)	186 (14.5%)
Key adverse events, n (%)		
Hypotension	180 (14.1%)	70 (5.5%)
Hypotension with SBP <100 mmHg	75 (5.9%)	21 (1.6%)
Urine albumin/creatinine ratio increased	157 (12.3%)	97 (7.6%)
Hyperkalemia	149 (11.6%)	140 (10.9%)
Renal impairment	149 (11.6%)	110 (8.6%)
Hematuria	145 (11.3%)	105 (8.2%)
Glomerular filtration rate decreased	137 (10.7%)	150 (11.7%)
Proteinuria	121 (9.5%)	84 (6.5%)
Dizziness	70 (5.5%)	63 (4.9%)
Urinary protein/creatinine ratio increased	66 (5.2%)	65 (5.1%)
Cardiac failure	54 (4.2%)	69 (5.4%)
Hypertension	42 (3.3%)	81 (6.3%)
Angioedema[b]	4 (0.3%)	3 (0.2%)
Serum creatinine increase, n/N (%)		
>50% increase	88/1270 (6.9%)	92/1271 (7.2%)
>0.5 mg/dL	100/1270 (7.9%)	113/1271 (8.9%)
>2.0 mg/dL,	87/1271 (6.9%)	73/1271 (5.7%)
>2.5 mg/dL	20/1271 (1.6%)	21/1271 (1.7%)
>3.0 mg/dL	4/1271 (0.3%)	3/1271 (0.2%)
eGFR decrease(mL/min/1.73m^2), n/N (%)		
>25% decrease	304/1270 (23.9%)	295/1271 (23.2%)
>40% decrease	69/1270 (5.4%)	76/1271 (6.0%)
>50% decrease	19/1270 (1.5%)	33/1271 (2.6%)
>30 mL/min/1.73m^2 decrease	45/1270 (3.5%)	61/1271 (4.8%)
>60 mL/min/1.73m^2 decrease	4/1270 (0.3%)	5/1271 (0.4%)
Serum potassium, n/N (%)		

≥5.5 mmol/L	230/1271 (18.1%)	203/1270 (16.0%)
>6.0 mmol/L	32/1271 (2.5%)	27/1271 (2.1%)
>6.5 mmol/L	9/1271 (0.7%)	7/1271 (0.6%)
Key serious AEs, n (%)		
Cardiac disorders	70 (5.5%)	94 (7.3%)
Cardiac failure	21 (1.6%)	31 (2.4%)
Atrial fibrillation	13 (1.0%)	17 (1.3%)
Angina pectoris	8 (0.6%)	8 (0.6%)
Angina unstable	6 (0.5%)	7 (0.6%)
Infections and infestations	39 (3.0%)	32 (2.5%)
Renal and urinary disorders	10 (0.8%)	12 (0.9%)

[a]The safety set includes all randomized patients who received at least one dose of study drug. Patients were analyzed according to the treatment actually received
[b]Includes patients with adjudication confirmed angioedema events
A patient with multiple adverse events within one category is counted only once in the category
MedDRA version 22.1 was used for reporting of AEs
AE, adverse event; eGFR, estimated glomerular filtration rate; SBP, systolic blood pressure

eTable 4: Incidence of key adverse events by stratum

	ACEI stratum		ARB stratum		No RASi stratum	
	Sacubitril/ valsartan (N=532)	Enalapril (N=533)	Sacubitril/ valsartan (N=586)	Valsartan (N-588)	Sacubitril/ valsartan (N=162)	Placebo (N=163)
Serious adverse events, n (%)						
Death	14 (2.6%)	5 (0.9%)	6 (1.0%)	10 (1.7%)	3 (1.9%)	2 (1.2%)
At least one serious AE	80 (15%)	77 (14.5%)	78 (13.3%)	87 (14.8%)	28 (17.3%)	27 (16.6%)
At least one suspected study drug related serious AE	4 (0.8%)	2 (0.4%)	3 (0.5%)	7 (1.2%)	4 (2.5%)	1 (0.6%)
Cardiac failure	10 (1.9%)	12 (2.3%)	8 (1.4%)	13 (2.2%)	3 (1.9%)	6 (3.7%)
Atrial fibrillation	7 (1.3%)	6 (1.1%)	3 (0.5%)	9 (1.5%)	3 (1.9%)	2 (1.2%)
Angina pectoris	3 (0.6)	3 (0.6)	3 (0.5)	5 (0.9)	2 (1.2)	0
Adverse events, n (%)						
At least one AE	439 (82.5%)	420 (78.8%)	499 (85.2%)	478 (81.3%)	149 (92.0%)	132 (81.0%)
At least one suspected study drug related AE	158 (29.7%)	126 (23.6%)	163 (27.8%)	137 (23.3%)	69 (42.6%)	27 (16.6%)
At least one AE leading to permanent discontinuation of study treatment	48 (9.0%)	41 (7.7%)	47 (8.0%)	43 (7.3%)	26 (16.1%)	9 (5.5%)
AE leading to dose adjustment or temporary discontinuation of study treatment	102 (19.2%)	72 (13.5%)	97 (16.6%)	92 (15.7%)	49 (30.3%)	22 (13.5%)
Most common treatment emergent AEs, n (%)						
Hypotension	69 (13.0%)	31 (5.8%)	74 (12.6%)	32 (5.4%)	37 (22.8%)	7 (4.3%)
UACR increased	65 (12.2%)	45 (8.4%)	81 (13.8%)	46 (7.8%)	11 (6.8%)	6 (3.7%)
Hyperkalemia	64 (12.0%)	64 (12.0%)	62 (10.6%)	64 (10.9%)	23 (14.2%)	12 (7.4%)
Renal impairment	61 (11.5%)	50 (9.4%)	61 (10.4%)	49 (8.3%)	27 (16.7%)	11 (6.8%)
Hematuria	65 (12.2%)	42 (7.9%)	69 (11.8%)	49 (8.3%)	11 (6.8%)	14 (8.6%)
Proteinuria	49 (9.2%)	38 (7.1%)	62 (10.6%)	38 (6.5%)	10 (6.2%)	8 (4.9%)
Dizziness	22 (4.1%)	22 (4.1%)	36 (6.1%)	30 (5.1%)	12 (7.4%)	11 (6.8%)
UPCR increased	27 (5.1%)	24 (4.5%)	29 (5.0%)	35 (6.0%)	10 (6.2%)	6 (3.7%)
Cardiac failure	21 (4.0%)	25 (4.7%)	22 (3.8%)	31 (5.3%)	11 (6.8%)	13 (8.0%)

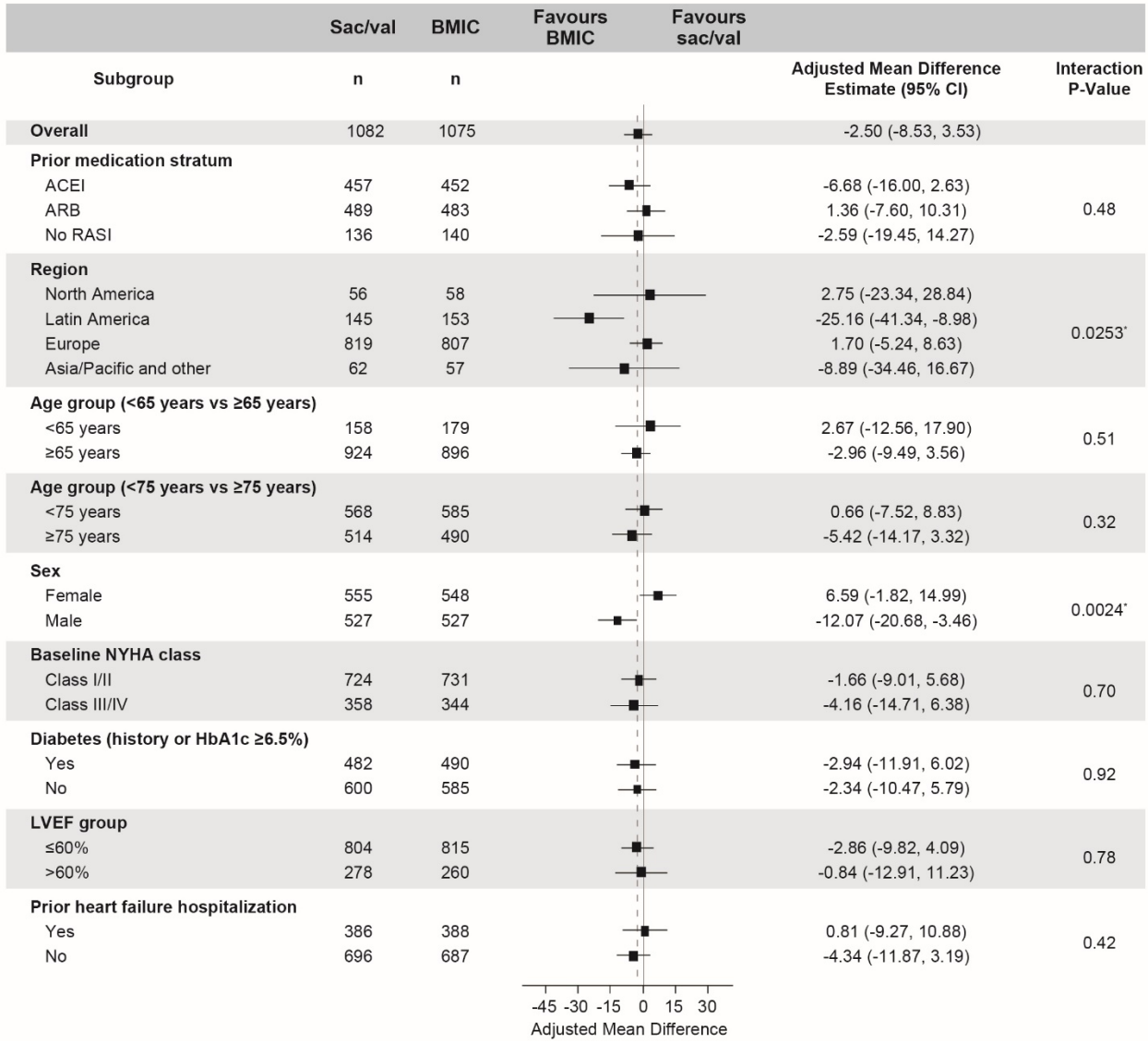
A patient with multiple adverse events within one category is counted only once in the category
MedDRA version 22.1 was used for reporting of AEs
ACEI, angiotensin converting enzyme inhibitor; AE, adverse event; ARB, angiotensin receptor blocker; RASi, renin-angiotensin system inhibitor; UACR, urinary albumin creatinine ratio; UPCR, urinary protein creatinine ratio

eTable 5: Incidence of low SBP, abnormal renal parameters and angioedema at any time post baseline, by stratum

	ACEI stratum		ARB stratum		No RASi stratum	
	Sacubitril/valsartan (N=532)	Enalapril (N=533)	Sacubitril/valsartan (N=586)	Valsartan (N-588)	Sacubitril/valsartan (N=162)	Placebo (N=163)
Reductions in SBP, n (%)						
SBP <100 mmHg	78/527 (14.8%)	29/531 (5.5%)	79/583 (13.6%)	46/585 (7.9%)	46/160 (28.8%)	101/161 (6.2%)
SBP <100 mmHg and ≥30 mmHg decrease from baseline	37/527 (7.0%)	15/531 (2.8%)	35/583 (6.0%)	24/585 (4.1%)	22/160 (13.8%)	4/161 (2.5%)
SBP <90 mmHg and >20 mmHg decrease from baseline	13/527 (2.5%)	3/531 (0.6%)	7/583 (1.2%)	6/585 (1.0%)	11/160 (6.9%)	2/161 (1.2%)
Serum creatinine increase, n (%)						
>50% increase	43/527 (8.2%)	41/529 (7.8%)	29/583 (5.0%)	42/583 (7.2%)	16/160 (10.0%)	9/159 (5.7%)
>0.5 mg/dL	45/527 (8.5%)	50/529 (9.5%)	36/583 (6.2%)	53/583 (9.1%)	19/160 (11.9%)	10/159 (6.3%)
>2.0 mg/dL	41/528 (7.8%)	30/529 (5.7%)	31/583 (5.3%)	37/583 (6.4%)	15/160 (9.4%)	6/159 (3.8%)
>2.5 mg/dL	9/528 (1.7%)	7/529 (1.3%)	8/583 (1.4%)	11/583 (1.9%)	3/160 (1.9%)	3/159 (1.9%)
>3.0 mg/dL	2/528 (0.4%)	1/529 (0.2%)	2/583 (0.3%)	2/583 (0.3%)	0 (0.0%)	0 (0.0%)
Serum potassium, n (%)						
≥5.5 mmol/L	106/528 (20.1%)	102/529 (19.3%)	87/583 (14.9%)	84/583 (14.4%)	37/160 (23.1%)	17/159 (10.7%)
>6.0 mmol/L	14/528 (2.7%)	8/529 (1.5%)	12/583 (2.1%)	14/583 (2.4%)	6/160 (3.8%)	5/159 (3.14%)
>6.5 mmol/L	3/528 (0.6%)	2/529 (0.4%)	4/583 (0.7%)	4/583 (0.7%)	2/160 (1.3%)	1/159 (0.63%)
eGFR decrease n (%)						
>25%	138/527 (26.2%)	136/529 (25.7%)	118/583 (20.2%)	138/583 (23.7%)	48/160 (30.0%)	21/159 (13.2%)
>40%	35/527 (6.6%)	33/529 (6.2%)	22/583 (3.8%)	35/583 (6.0%)	12/160 (7.5%)	8/159 (5.0%)
>50%	12/527 (2.3%)	13/529 (2.5%)	6/583 (1.0%)	17/583 (2.9%)	1/160 (0.6%)	3/159 (1.9%)
>30 mL/min/1.73 m^2	28/527 (5.3%)	28/529 (5.3%)	11/583 (1.9%)	30/583 (5.2%)	6/160 (3.8%)	3/159 (1.9%)
>60 mL/min/1.73 m^2	3/527 (0.6%)	1/529 (0.2%)	0/583 (0.0%)	4/583 (0.7%)	1/160 (0.6%)	0/159 (0.0%)
Angioedema[a], n (%)	2 (0.4%)	2 (0.4%)	1 (0.2%)	0 (0.0%)	1 (0.6%)	1 (0.6%)

[a]Patients with adjudication confirmed angioedema events
Data are presented as m/n (%) unless otherwise specified
ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; eGFR, estimated glomerular filtration rate; RASi, renin-angiotensin system inhibitor; SBP, systolic blood pressure

eFigure. Effect of sacubitril/valsartan and background-medication based individualized comparator on 6MWD in various pre-defined subgroups



An adjusted mean difference of >0 favors sacubitril/valsartan.
Interaction p-value is for the subgroup-variable-by-treatment interaction at Week 12.
- The MMRM model includes stratum (ACEI, ARB, No RASi), region, treatment (sacubitril/valsartan, background-medication based individualized comparators), visit, treatment-by-visit interaction, sub-group, sub-group-by-visit interaction, treatment–by-sub-group interaction and treatment–by-sub-group-by-visit interaction as fixed-effect factors; baseline 6MWD, baseline SBP, stratum-by-baseline 6MWD, stratum by baseline SBP, and visit-by-baseline 6MWD interactions as covariates; and models the within patient covariance using an unstructured covariance matrix (a common matrix for the two treatment groups).
6MWD, 6 minute walking distance; AGMR, adjusted geometric mean ratio; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; HbA1c, glycated hemoglobin; BMIC, background-medication based individualized comparator; LVEF, left ventricular ejection fraction; NYHA, New York Heart Failure Association; RASi, renin-angiotensin-system inhibitor; sac/val, sacubitril/valsartan; SBP, systolic blood pressure