Circulation

ORIGINAL RESEARCH ARTICLE

Sacubitril/Valsartan in Pediatric Heart Failure (PANORAMA-HF): A Randomized, Multicenter, Double-Blind Trial

Robert Shaddy, MD; Michael Burch, MD; Paul F. Kantor, MBBCh; Susan Solar-Yohay, MSc; Tania Garito, MD; Sijia Zhang, PhD; Michele Kocun, MSN; Chad Mao, MD; Antoinette Cilliers, MD; Xu Wang, MD; Charles Canter, MD; Joseph Rossano, MD; Gonzalo Wallis, MD; Jondavid Menteer, MD; Linda Daou, MD; Jacek Kusa, MD; Kursat Tokel, MD; Daniel Dilber, MD; Zhuoming Xu, MD; Tingting Xiao, MD; Nancy Halnon, MD; Kevin P. Daly, MD; Matthew J. Bock, MD; Warren Zuckerman, MD; Tajinder P. Singh, MD; Manisha Chakrabarti, MD; Aviva Levitas, MD; Michele Senni, MD; Giorgia Grutter, MD; Gi Beom Kim, MD; Jinyoung Song, MD; Hyoung Doo Lee, MD; Ching Kit Chen, MMed Paed; Joan Sanchez-de-Toledo, MD; Yuk Law, MD; Suthep Wanitkun, MD; Yanqin Cui, MD; Rui Anjos, MD; Timur Mese, MD; Damien Bonnet, MD; on behalf of the PANORAMA-HF Investigators

BACKGROUND: Sacubitril/valsartan, an angiotensin receptor-neprilysin inhibitor (ARNI), is an established treatment for heart failure (HF) with reduced left ventricular ejection fraction. It has not been rigorously compared with angiotensin-converting enzyme inhibitors in children. PANORAMA-HF (Prospective Trial to Assess the Angiotensin Receptor Blocker Neprilysin Inhibitor LCZ696 Versus Angiotensin-Converting Enzyme Inhibitor for the Medical Treatment of Pediatric HF) is a randomized, double-blind trial that evaluated the pharmacokinetics and pharmacodynamics (PK/PD), safety, and efficacy of sacubitril/valsartan versus enalapril in children 1 month to <18 years of age with HF attributable to systemic left ventricular systolic dysfunction (LVSD).

METHODS: Children with HF attributable to LVSD were randomized to sacubitril/valsartan versus enalapril to assess the efficacy and safety of sacubitril/valsartan at 52 weeks of follow-up. The primary end point of the study was to determine whether sacubitril/valsartan was superior to enalapril for the treatment of pediatric patients with HF attributable to systemic LVSD, assessed using a primary global rank end point consisting of ranking patients from worst to best on the basis of clinical events such as death, listing for urgent heart transplant, mechanical life support requirement, worsening HF, New York Heart Association (NYHA)/Ross class, Patient Global Impression of Severity (PGIS), and Pediatric Quality of Life Inventory physical functioning domain. The change from baseline to 52 weeks in NT-proBNP (N-terminal pro–B-type natriuretic peptide) was an exploratory end point.

RESULTS: A total of 375 children (mean age, 8.1±5.6 years; 52% female) were randomized to sacubitril/valsartan (N=187) or enalapril (N=188). At week 52, no significant difference was observed between the 2 treatment arms in the global rank end point (Mann-Whitney probability, 0.52 [95% CI, 0.47–0.58]; Mann-Whitney odds, 0.91 [95% CI, 0.72–1.14]; *P*=0.42). At week 52, clinically meaningful reductions were observed in both treatment arms in NYHA/Ross, PGIS, Patient Global Impression of Change, and NT-proBNP, without significant differences between groups. Adverse events were similar between treatment arms (incidence: sacubitril/valsartan, 88.8%; enalapril, 87.8%), and the safety profile of sacubitril/valsartan was acceptable in children.

Correspondence to: Robert Shaddy, MD, Children's Hospital Los Angeles, 4650 Sunset Blvd, Los Angeles, CA 90027. Email shaddy@usc.edu

Supplemental Material, the podcast, and transcript are available with this article at https://www.ahajournals.org/doi/suppl/10.1161/CIRCULATIONAHA.123.066605.

Continuing medical education (CME) credit is available for this article. Go to http://cme.ahajournals.org to take the quiz.

For Sources of Funding and Disclosures, see page 1765.

Circulation is available at www.ahajournals.org/journal/circ

CONCLUSIONS: In this study, sacubitril/valsartan did not show superiority over enalapril in the treatment of children with HF attributable to systemic LVSD using the prespecified global rank end point. However, both treatment arms showed clinically meaningful improvements over 52 weeks.

REGISTRATION: URL: https://www.clinicaltrials.gov; Unique identifier: NCT02678312.

Key Words: enalapril ■ heart failure ■ valsartan ■ ventricular dysfunction, left

ORIGINAL RESEARCH ARTICLE

Clinical Perspective

What Is New?

- International heart failure (HF) guidelines recommend sacubitril/valsartan as first-line treatment of HF with reduced ejection fraction in adults; its benefits as a first-line treatment for pediatric patients with HF have not been studied.
- PANORAMA-HF (Prospective Trial to Assess the Angiotensin Receptor Blocker Neprilysin Inhibitor LCZ696 Versus Angiotensin-Converting Enzyme Inhibitor for the Medical Treatment of Pediatric HF), the largest randomized, double-blind pediatric HF study, evaluated safety and efficacy of sacubitril/valsartan versus enalapril in children (1 month to <18 years of age) with HF attributable to systemic left ventricular systolic dysfunction over 52 weeks using a novel global rank primary end point.
- Sacubitril/valsartan was well tolerated but did not show superiority over enalapril in the treatment of pediatric HF with systemic left ventricular systolic dysfunction.

What Are the Clinical Implications?

- Clinically meaningful improvements in severity of signs and symptoms, functional class, and NT-proBNP (N-terminal pro–B-type natriuretic peptide) levels were observed in pediatric patients with HF attributable to left ventricular systolic dysfunction in both treatment arms without significant differences between treatment groups.
- Preliminary 12-week findings from PANORAMA-HF led to US Food and Drug Administration approval of sacubitril/valsartan in ≥1-year-old pediatric patients with HF attributable to systemic left ventricular systolic dysfunction.

Nonstandard Abbreviations and Acronyms

ACEI	angiotensin-converting enzyme inhibitor
AE	adverse event
ARNI	angiotensin receptor-neprilysin inhibitor
HF	heart failure
HFrEF	heart failure with reduced ejection fraction
LVSD	left ventricular systolic dysfunction
NT-proBNP	N-terminal pro–B-type natriuretic peptide
NYHA	New York Heart Association
PANORAMA-HF	Prospective Trial to Assess the Angiotensin Receptor Blocker Neprilysin Inhibitor LCZ696 Versus Angiotensin-Converting Enzyme Inhibitor for the Medical Treatment of Pediatric HF
PARADIGM-HF	Prospective Comparison of ARNI With ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure
PedsQL	Pediatric Quality of Life Inventory
PGIC	Patient Global Impression of Change
PGIS	Patient Global Impression of Severity

Pediatric heart failure (HF), a common sequela of cardiomyopathy and congenital heart disease, is associated with substantial morbidity and mortality, frequent hospitalizations, and a poor quality of life.[1,2] Because of the heterogeneity in pathogeneses, and the lower prevalence of pediatric HF compared with adult HF, there have been few well-powered randomized trials to help build therapeutic guidelines. Hence, pediatric HF treatment recommendations usually rely on the extrapolation of study results in adults with HF.[3–5]

Sacubitril/valsartan, an angiotensin receptor-neprilysin inhibitor (ARNI), has demonstrated significant, clinically important mortality and morbidity benefits in adult patients with chronic HF and reduced left ventricular ejection fraction compared with enalapril.[6] It is approved by the US Food and Drug Administration to reduce the risk of cardiovascular death and hospitalization in adult patients with chronic HF and for the treatment of symptomatic HF with systemic left ventricular systolic dysfunction (LVSD) in pediatric patients ≥1 year of age.[7] The preliminary 12-week findings of PANORAMA-HF (Prospective Trial to Assess the Angiotensin Receptor

Blocker Neprilysin Inhibitor LCZ696 Versus Angiotensin-Converting Enzyme Inhibitor for the Medical Treatment of Pediatric HF), including the reduction from baseline in NT-proBNP (N-terminal pro–B-type natriuretic peptide) in the sacubitril/valsartan arm compared with enalapril (44% versus 33%, respectively; $P>0.05$), led to the Food and Drug Administration approval of sacubitril/valsartan in pediatric patients ≥1 year of age.[7]

The 2021 European Society of Cardiology HF guidelines and the 2022 American Heart Association/American College of Cardiology/Heart Failure Society of America guidelines recommended an ARNI rather than an angiotensin-converting enzyme inhibitor (ACEI) or an angiotensin receptor blocker for adult patients with HF with reduced ejection fraction (HFrEF) and New York Heart Association (NYHA) functional class II through IV or NYHA functional class II or III, respectively,[8,9] and the 2024 American College of Cardiology Expert Consensus recommended an ARNI specifically for adults with HFrEF and NYHA functional class II through IV.[10] However, the benefits of ARNIs compared with ACEIs have not been studied in children.

PANORAMA-HF was designed to assess whether pediatric patients (1 month to <18 years of age) with HFrEF would derive greater clinical treatment benefit with sacubitril/valsartan compared with enalapril. This is the largest randomized, double-blind pediatric HF study conducted.

METHODS

Data Sharing

Novartis is committed to sharing access to patient-level data and supporting clinical documents from eligible studies with qualified external researchers. These requests are reviewed and approved by an independent review panel on the basis of scientific merit. All data provided are anonymized to respect the privacy of patients who have participated in the trial in line with applicable laws and regulations. This trial data availability is according to the criteria and process described at www.clinicalstudydatarequest.com.

Study Design

The design of PANORAMA-HF has been published previously.[11] In brief, PANORAMA-HF is a phase 2/3, multicenter study conducted in 30 countries and 105 sites across Europe, the Americas, Asia, and Africa. The study comprises 2 parts: part 1, an open-label, single-dose, pharmacokinetic/pharmacodynamic study, the results of which were used to determine dosing for this study; and part 2, a 52-week randomized, double-blind, parallel-group, clinical efficacy study. Here, we present findings from part 2.

The study protocol and all amendments were approved by the independent ethics committee or institutional review board of all participating centers. Because the traditional end points of trials including adults with HF (eg, death and heart failure hospitalization) could not be used in this pediatric trial because of the anticipated low enrollment numbers, a global rank end point based on 5 categories of clinical events was used (Table 1). All patients or their legally acceptable representatives provided written informed consent. Assent was provided by the patients if possible in terms of their age and developmental ability. The study was conducted in accordance with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use E6 Guidelines for Good Clinical Practice and the Declaration of Helsinki. An independent clinical end point committee adjudicated events reported by the investigators, confirming them as positively adjudicated clinical events where protocol-prespecified criteria were met appropriately.

Patients

Inpatient or outpatient pediatric patients (1 month to <18 years of age) with HF, biventricular cardiac physiology, and systemic LVSD were included in the study. Patients were required to have left ventricular ejection fraction ≤45% or fractional shortening ≤22.5%. Patients were excluded if they had single-ventricle physiology, a systemic morphologic right ventricle, restrictive cardiomyopathy, or hypertrophic cardiomyopathy.[11]

Eligible patients were initially sequentially stratified at randomization into groups by age (group 1: 6 to <18 years; group 2: 1 to <6 years; and group 3: 1 month to <1 year) and functional classification (NYHA/Ross classification group I/II or III/IV). Because of the sequential age-related recruitment of participants into the study, with older participants being recruited first, in addition to the inherent challenges in recruiting infants into the study, recruitment of very young patients with HF proved to be more challenging than anticipated. Therefore, patients were stratified for the analysis by modified age groups in accordance with International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use E11-recommended age ranges (see the Supplemental Material for additional details). Group 1 remained unchanged, but groups 2 and 3 were modified to groups 2a (2 to <6 years of age) and 3a (1 month to <2 years of age), respectively.[12] This modification of the age groups enabled a more robust analysis of the safety and efficacy data for children <2 years of age. Race and ethnicity categorization is described in the Supplemental Material.

Randomization and Masking

Patients were randomized (1:1) to receive either sacubitril/valsartan or enalapril. Details of the randomization process have been published previously and are described in the Supplemental Material.[11]

Dosing

Based on data from part 1, pharmacokinetic and pharmacodynamic analysis confirmed that the target dose of sacubitril/valsartan was 3.1 mg/kg twice daily for groups 1 and 2, and 2.3 mg/kg twice daily for group 3. The dose levels are explained in the Supplemental Material.

Outcomes

The primary objective of the study was to determine whether sacubitril/valsartan was superior to enalapril for the treatment

Table 1. Primary Global Rank End Point Algorithm Using Ranked Analysis

Category	Subcategory	Description	Ranking algorithm
1	Death; UNOS status 1A listing for heart transplant or equivalent; VAD/ECMO/mechanical ventilation/intra-aortic balloon pump requirement for life support		
	A	Death UNOS status 1A listing for heart transplant or equivalent VAD/ECMO/mechanical ventilation/intra-aortic balloon pump requirement for life support	Ranked within this category by time to first event. All category 1 events were considered equal. Patients who discontinued from the study without a category 1 event were classified to category 1.
2	Worsening HF; defined by signs and symptoms of worsening HF that require an intensification of HF therapy		
	B	Worsening HF hospitalization with intensive care unit stay	Within category 2, the patients were ranked first by event subcategory, and then by number of events within each subcategory. Further ranking by time to first event in the worst subcategory.
	C	Worsening HF hospitalization without intensive care unit stay	
	D	Worsening HF without hospitalization	
3	Worsened; worse NYHA/Ross or worse PGIS; and further ranking by PedsQL physical functioning domain		
	E	NYHA/Ross or PGIS worsened on the basis of last available assessment compared with baseline	Ranked by combination of NYHA/Ross and PGIS degree of change. Within a group of the same degree of NYHA/Ross and PGIS change, further ranked by PedsQL (physical functioning domain*) change from baseline
4	Unchanged; unchanged NYHA/Ross and unchanged PGIS; and further ranking by PedsQL physical functioning domain		
	F	NYHA/Ross and PGIS unchanged on the basis of last available assessment compared with baseline	Worst baseline combination of NYHA/Ross functional class and PGIS without change was ranked worse than a better baseline NYHA/Ross functional class and PGIS. Within a group of the same baseline NYHA/Ross and PGIS, further ranked by PedsQL (physical functioning domain*) change from baseline
5	Improved; improved NYHA/Ross or improved PGIS (neither can be worse); and further ranking by PedsQL physical functioning domain		
	G	NYHA/Ross or PGIS improved (neither worsened) on the basis of last available assessment compared with baseline	Ranked by a combination of NYHA/Ross and PGIS degree of change. Within a group of the same degree of NYHA/Ross and PGIS change, further ranked by PedsQL (physical functioning domain*) change from baseline.

ECMO indicates extracorporeal membrane oxygenation; HF, heart failure; NYHA, New York Heart Association; PedsQL, Pediatric Quality of Life Inventory; PGIS, Patient Global Impression of Severity; UNOS, United Network for Organ Sharing; and VAD, ventricular assist device.

*PedsQL physical functioning was used only for the global rank end point for age group 1.

of pediatric patients with HF attributable to systemic LVSD, assessed using a primary global rank end point through 52 weeks of treatment. The patients were ranked from worst to best on the basis of 5 categories of clinical HF events (Table 1).[11] Using data from a carvedilol trial in pediatric patients with HF, underlying probabilities were assumed for each category.[11,13]

Key secondary efficacy end points included the time to the first occurrence of a category 1 or category 2 event, change from baseline through 52 weeks in NYHA/Ross functional class, and patient-reported outcome and Patient Global Impression of Severity (PGIS) scores (for details, refer to the Supplemental Material). Key exploratory end points included change from baseline in NT-proBNP level and patient-reported outcome scores, including Pediatric Quality of Life Inventory (PedsQL) and Patient Global Impression of Change (PGIC), through 52 weeks. A change of ≥4.5 is considered to be the minimal clinically meaningful difference in the PedsQL score.[14,15]

Safety and tolerability were primarily based on the frequency of adverse events (AEs), serious AEs, and laboratory abnormalities through 52 weeks.

Statistical Analysis

Efficacy end points were analyzed using the full analysis set. The global rank end point was presented as Mann-Whitney probability and as Mann-Whitney odds, which were analyzed using the stratified Wilcoxon rank-sum test (details are provided in the Supplemental Material). The null hypothesis was that the Mann-Whitney odds in all strata were equal to 1. Mann-Whitney probability=0.5 refers to no difference between the 2 treatment arms. Statistical testing for the secondary or exploratory variables was performed at the significance level of 2-sided 0.05. *P* values were not adjusted for multiplicity (details of the analyses are provided in the Supplemental Material). For the components of the global rank end point, each was analyzed separately. Time to first occurrence of the composite of category 1 or 2 events was analyzed using Cox proportional hazard model, stratified by age group and NYHA/Ross class group. On the basis of this model, the estimate and the 95% CI were provided for the adjusted hazard ratio (sacubitril/valsartan over enalapril). The proportional hazards assumption was tested by plotting the estimated log-log survival curves for individuals on the same graph; the 2 plots were approximately parallel in most of the parts.

NYHA/Ross, PGIS, and PGIC were analyzed using proportional cumulative odds model. NT-proBNP and PedsQL score were analyzed by a mixed model for repeated measures and PGIC score by visit proportional cumulative odds model. The randomization stratification (NYHA/Ross class, modified age group) was included in all the models.

The mixed model for repeated measures model includes change from baseline in log-transformed NT-proBNP as response; modified age group, NYHA/Ross class group at randomization, region, treatment, visit, and treatment-by-visit

interaction as fixed-effect factors; and log baseline NT-proBNP and visit-by-log-baseline interaction as covariates. For mixed model for repeated measures, the restricted maximum likelihood estimation approach was used with unstructured covariance structure. No random effects were used. Data were analyzed using SAS 9.4.

Diverse Representation

The authors leading this study are from multiple countries across Europe, the Americas, Asia, and Africa. The authors declare that all efforts were made to avoid any criteria that would exclude patients from different sexes or racial or ethnic backgrounds.

RESULTS

Between November 2016 and January 2021, 420 patients were screened for part 2; of these, 375 eligible patients (mean age, 8.1±5.6 years; 52% female) were randomized to receive either sacubitril/valsartan (N=187) or enalapril (N=188). The proportion of patients on the target dose level 4 at the end of week 52 was 64.7% with sacubitril/valsartan compared with 68.9% with enalapril; there was a similar trend across all 3 age groups. Patient disposition is presented in Figure S1. In the sacubitril/valsartan arm, 18 patients discontinued the study; 24 patients in the enalapril arm discontinued the study.

The baseline demographic and disease characteristics of the patients were comparable between the 2 treatment arms (Table 2). Additional details on demographic and disease characteristics have been published previously.[11] The majority of patients (>80%) were NYHA/Ross class II or higher at baseline. More than 80% of patients had a left ventricular ejection fraction <40% or a fractional shortening <20%. Primary HF pathogenesis was similar across the 3 age groups. Congenital cardiac malformations captured (13.3% of the patients) as part of general medical history are presented in Table S1. Overall, cardiomyopathy was observed in >60% of patients, of which 34.7% was idiopathic cardiomyopathy, 17.6% was attributable to familial or genetic cardiomyopathies, and 11.2% was attributable to left ventricular noncompaction.[12] The correlation between treatment interaction and causes of HF could not be estimated because of small study population size.

No statistically significant differences were observed between the 2 treatment arms in the global rank end point (Mann-Whitney probability, 0.52 [95% CI, 0.47–0.58]; Mann-Whitney odds, 0.91 [95% CI, 0.72–1.14]; *P*=0.42; Table 3). Similar trends were observed across the age groups. Patient allocation for the global rank primary end point (based on positively adjudicated clinical events) is shown in Table 4.

No significant differences were observed between the 2 treatment arms in the proportion of patients with category 1, positively adjudicated clinical events (more severe

Table 2. Demographic and Baseline Characteristics

Variables	Sacubitril/valsartan (N=187)	Enalapril (N=188)
Age, y	8.0±5.5	8.3±5.7
Female	98 (52.4)	95 (50.5)
Height (age-adjusted percentile) at screening	44.2±35.1	43.6±34.5*
Weight (age-adjusted percentile)	45.2±34.9	46.9±34.9
BMI, kg/m²	18.2±5.4	18.5±6.0*
Region of enrollment		
Americas	61 (32.6)	71 (37.4)†
Asia	68 (36.4)	60 (31.6)†
Europe	58 (31.0)	59 (31.1)†
Race and ethnicity		
White	87 (46.5)	93 (49.5)
Black	23 (12.3)	25 (13.3)
Asian	57 (30.5)	45 (23.9)
American Indian or Alaska Native	3 (1.6)	2 (1.1)
Native Hawaiian or other Pacific Islander	0 (0)	0 (0)
Unknown	8 (4.3)	6 (3.2)
Other	9 (4.8)	17 (9.0)
LVEF % at prerandomization	32.8±7.4‡	31.6±7.9*
NYHA/Ross class		
I	25 (13.4)	34 (18.1)
II	135 (72.2)	125 (66.5)
III	27 (14.4)	27 (14.4)
IV	0 (0)	2 (1.1)
Previous HF hospitalization	130 (69.5)	127 (67.6)
Hospitalization status at prerandomization		
Inpatient	21 (11.2)	16 (8.5)
Outpatient	166 (88.8)	172 (91.5)
Previous HF and cardiovascular medication		
ACEI only	166 (88.8)	166 (88.3)
ARB only	4 (2.1)	4 (2.1)
ACEI and ARB	2 (1.1)	5 (2.7)
Beta-blockers	132 (70.6)	129 (68.6)
Diuretics other than MRAs	152 (81.3)	164 (87.2)
MRAs (including spironolactone)	121 (64.7)	128 (68.1)
Furosemide	113 (60.4)	127 (67.6)
Digoxin	73 (39.0)	65 (34.6)
Antithrombotic agents	94 (50.3)	102 (54.3)
Aspirin	71 (38.0)	83 (44.1)
None	15 (8.0)	13 (6.9)
Blood pressure, mm Hg†		
Systolic	100.7±13.2	100.5±12.3
Diastolic	60.5±10.6§	60.3±10.4*

(*Continued*)

Table 2. Continued

Variables	Sacubitril/valsartan (N=187)	Enalapril (N=188)
Heart rate, bpm	94.3±21.7	95.6±22.3
Previous history of HF	187 (100.0)	188 (100.0)
Primary HF pathogenesis		
Ischemic	9 (4.8)	7 (3.7)
Myocarditis	20 (10.7)	28 (14.9)
Neuromuscular disorder	8 (4.3)	5 (2.7)
Acquired/chemotherapy	8 (4.3)	5 (2.7)
Left ventricular noncompaction	19 (10.2)	19 (10.1)
Mitochondrial disorder	2 (1.1)	0 (0.0)
Cardiomyopathy related	116 (62.0)	122 (64.9)
Congenital cardiac malformation	21 (11.2)	29 (15.4)
Familial or genetic	29 (15.5)	30 (16.0)
Inborn error of metabolism	3 (1.6)	1 (0.5)
Idiopathic	64 (34.2)	62 (33.0)
Other	7 (3.7)	7 (3.7)

Values are mean±SD or n (%). Data collected at randomization unless specified otherwise. ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; HF, heart failure; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; and NYHA, New York Heart Association.

*N=187.

†N=190.

‡N=186.

§N=185.

events, such as death, the requirement of listing for an urgent heart transplant, or the requirement for mechanical circulatory or respiratory support; sacubitril/valsartan arm, n=19 [10.2%]; enalapril arm, n=30 [16.0%]), or category 2, positively adjudicated clinical events (worsening HF with or without intensive care unit or general ward hospitalization; sacubitril/valsartan arm, n=18 [9.6%]; enalapril arm, n=9 [4.8%]). Most patients in both treatment arms were included in categories 3, 4, or 5 (ie, without a clinical event, but classified as worsened, unchanged, or improved on the basis of patient-reported outcomes and clinical functioning as measured by NYHA/Ross classification; see Table 1 for the category definitions).

No significant differences were observed between treatment arms in the time to first positively adjudicated category 1 or 2 events (adjusted hazard ratio, 1.07 [95% CI, 0.66–1.72]; *P*=0.80; Table S2; Figure S2).

At week 52, similar proportions of patients in each treatment arm had a clinically relevant improvement in NYHA/Ross functional class (sacubitril/valsartan, n=58 [37.7%]; enalapril, n=54 [34.0%]). Changes in NYHA/Ross class were comparable between treatment arms at week 52 (odds ratio, 1.1 [95% CI, 0.7–1.7]; nominal 2-sided *P*=0.76).

Improvements in NYHA/Ross functional class were observed in both treatment arms during the study (Figure 1). A similar trend was observed in the individual age groups. The proportion of patients with NYHA/Ross class I (no symptoms or limitations) increased from baseline to week 52 in both treatment arms (from 13.4% to 48.5% in the sacubitril/valsartan arm and from 18.1% to 47.5% in the enalapril arm).

Throughout the trial, there was an increase in the proportion of patients with an improved PGIS score in both treatment arms, and this proportion was higher than those who worsened. However, at week 52, there was no difference in the change from baseline in PGIS score between sacubitril/valsartan and enalapril (odds ratio, 1.2 [95% CI, 0.7–1.8]; nominal 2-sided *P*=0.54). For details on the PGIS score, refer to the Supplemental Material.

Improvements from baseline to week 52 in both patient-reported and parent-reported PedsQL scores (reflected in higher scores) were observed in both treatment arms across all age groups and were comparable (Table S3). In the sacubitril/valsartan arm, the change from baseline in the PedsQL total score exceeded the previously published minimal clinically meaningful difference threshold of 4.5 at weeks 36 and 52 for both patient-reported and parent-reported PedsQL; however, this threshold was not crossed in the enalapril arm.[14]

Table 3. Global Rank End Point Primary Rank Scores

Groups	Sacubitril/valsartan, n	Enalapril, n	Total, n	Sacubitril/valsartan-enalapril wins/loses/ties, %			Mann-Whitney probability, estimate (95% CI)	Mann-Whitney odds, estimate (95% CI)	Two-sided *P* value
				Sacubitril/valsartan wins	Enalapril wins	Sacubitril/valsartan equals enalapril			
Overall	187	188	375	50.0	45.1	5.0	0.52 (0.47–0.58)	0.91 (0.72–1.14)	0.42
Age groups									
1: 6 to <18 y	109	111	220	52.2	47.2	0.6	0.53 (0.45–0.60)	0.91 (0.67–1.22)	
2a: 2 to <6 y	47	38	85	44.5	44.2	11.3	0.50 (0.38–0.62)	0.99 (0.61–1.62)	
3a: 1 mo to <2 y	31	39	70	49.3	39.4	11.2	0.55 (0.42–0.68)	0.82 (0.48–1.41)	

Mann-Whitney probability >0.5 favors sacubitril/valsartan, equivalently, Mann-Whitney odds <1. The null hypothesis was that the Mann-Whitney odds in all strata were equal to 1. Mann-Whitney probability=0.5 refers to no difference between the 2 treatment arms. Refer to the Supplemental Material for details on positively adjudicated clinical events adjudication.

Table 4. Global Rank End Point: Patient Allocation

Worst event per patient contributing to the global ranking	Sacubitril/valsartan (N=187), n (%)	Enalapril (N=188), n (%)	Total (n=375), n (%)
Category 1 (death; UNOS status 1A listing for heart transplant or equivalent; VAD/ECMO/mechanical ventilation/intra-aortic balloon pump requirement for life support)	19 (10.2)	30 (16.0)	49 (13.1)
Category 2	18 (9.6)	9 (4.8)	27 (7.2)
Worsening HF hospitalization with intensive care unit stay	11 (5.9)	3 (1.6)	14 (3.7)
Worsening HF hospitalization without intensive care unit stay	5 (2.7)	5 (2.7)	10 (2.7)
Worsening HF without hospitalization	2 (1.1)	1 (0.5)	3 (0.8)
Category 3 to category 5: last observation carried forward			
Category 3 (worsened)	20 (10.7)	15 (8.0)	35 (9.3)
Category 4 (unchanged)	45 (24.1)	57 (30.3)	102 (27.2)
Category 5 (improved)	85 (45.5)	77 (41.0)	162 (43.2)

Patients were classified into categories 1 or 2 on the basis of positively adjudicated clinical events. A patient with multiple events within a category was counted only once within the category, and a patient with multiple events across different categories was placed in their worst category. Patients who discontinued participation in the study during the double-blind epoch without a category 1 event were classified into category 1 with the event date imputed by the last known alive date. ECMO indicates extracorporeal membrane oxygenation; HF, heart failure; UNOS, United Network for Organ Sharing; and VAD, ventricular assist device.

Findings from week 12 from PANORAMA-HF showed a similar reduction in NT-proBNP levels from baseline (44% and 33% in the sacubitril/valsartan arm and enalapril arm, respectively; $P>0.05$) in pediatric patients with HF (1–6 years of age, n=20; 6–18 years of age, n=90).[7]

At baseline, the geometric mean NT-proBNP levels (exponential of the mean values to the log-transformed NT-proBNP) for the sacubitril/valsartan arm and enalapril arm were not statistically different in the sacubitril/valsartan arm than in the enalapril arm (879.3 versus 737.4 pg/mL, respectively). In both treatment arms, there was a large decrease in NT-proBNP from baseline as early as week 4, with further decreases up to week 52.

Whereas NT-proBNP levels decreased more with sacubitril/valsartan than with enalapril at week 4 (adjusted geometric mean ratio, 0.73 [95% CI, 0.61–0.87]; $P=0.001$), the reductions were similar between the treatment arms at week 12 (adjusted geometric mean ratio, 0.91 [95% CI, 0.76–1.10]; $P=0.32$) and week 52 (adjusted geometric mean ratio, 0.91 [95% CI, 0.69–1.20]; $P=0.50$). Results by age groups are shown in Figure 2.

A post hoc analysis found that both baseline values and changes from baseline in NT-proBNP were strongly associated with the risk of category 1 or 2 events in pediatric patients with HF (Table S4).[16] Doubling of the baseline NT-proBNP levels was associated with an approximately 1.8-fold increased risk of a category 1 or 2 event. Similarly, doubling of the post-baseline NT-proBNP levels was associated with an ≈2.1-fold increased risk of a category 1 or 2 event, respectively ($P<0.0001$ for post-baseline changes). Conversely, halving of the NT-proBNP levels was associated with a 52.2% decrease in the risk (hazard) of a category 1 or 2 event.

At each visit of the study, a progressive increase in the proportion of patients who felt "much better" or "better" was observed in both treatment arms across all age groups.

At week 52, no significant difference in the PGIC score was observed between treatment arms (Table S5). Total drug exposure to sacubitril/valsartan was 173.7 patient-years; 89.8% of these patients had an exposure of ≥6 months.

Safety

The incidence of serious AEs was comparable between the sacubitril/valsartan arm (36.9%) and the enalapril

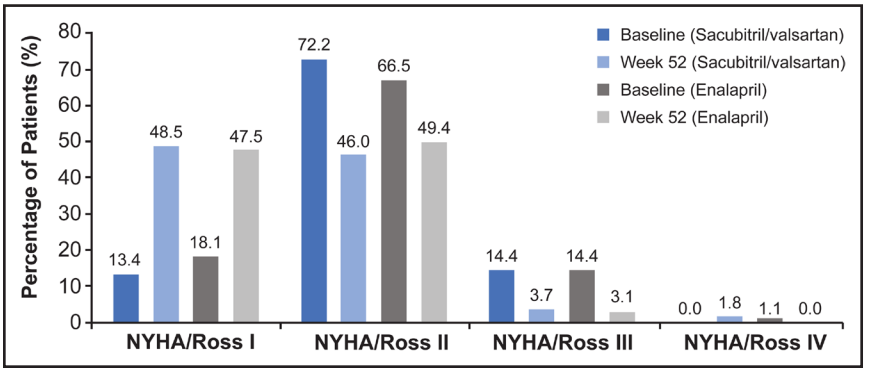

Figure 1. New York Heart Association/Ross classification status at baseline and week 52 (overall).
*Odds ratio, 1.08 [95% CI, 0.7–1.7]; nominal 2-sided $P=0.76$. NYHA indicates New York Heart Association.

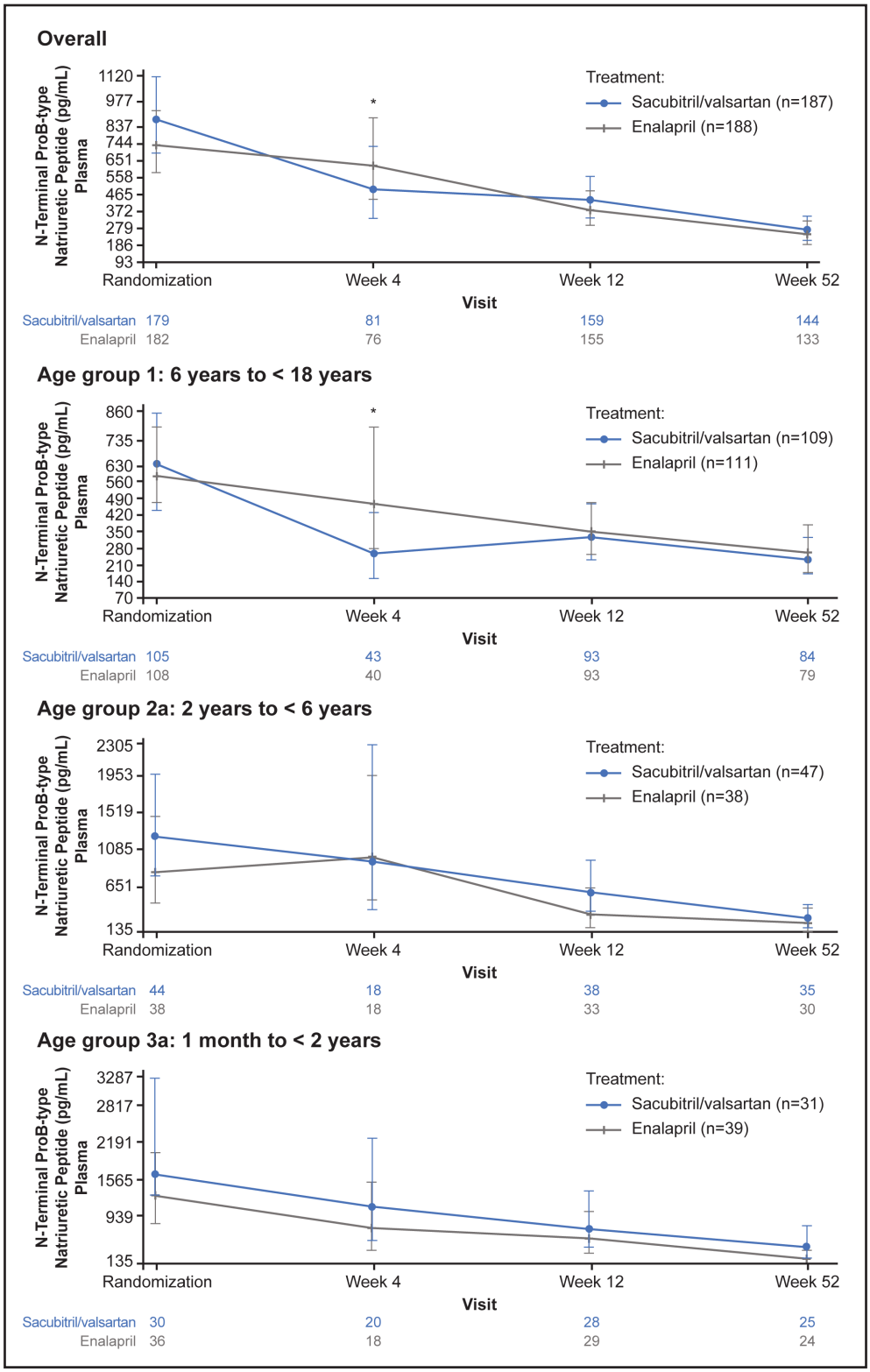

Figure 2. Geometric mean line plots for NT-proBNP levels (overall and by age groups).
Error bars represent 95% CIs. *Significant difference in the NT-proBNP (N-terminal pro–B-type natriuretic peptide) geometric mean data points between 2 treatment arms.

arm (33.0%). Angioedema was reported in one patient in the enalapril arm. Table 5 shows the most clinically relevant serious AEs. The incidence of AEs was 88.8% in the sacubitril/valsartan arm and 87.8% in the enalapril arm (Table S6). The frequency of AEs across the 3 age groups was consistent with the overall population.

Table 5. Most Clinically Relevant Serious Adverse Events (≥1% in Either Treatment Arm, Overall), Regardless of Study Treatment (Part 2 Safety Set)

Most clinically relevant serious adverse event	Sacubitril/valsartan (N=187), n (%)	Enalapril (N=188), n (%)
Hypotension	4 (2.1)	0 (0.0)
Hyperkalemia	0 (0.0)	2 (1.1)
Cough	1 (0.5)	0 (0.0)

Table S6 shows an overall summary of AEs reported during the randomized treatment epoch. Table S7 shows the AEs (≥5%) by preferred term, treatment arm, and age group.

DISCUSSION

PANORAMA-HF assessed the safety and efficacy of sacubitril/valsartan versus enalapril in pediatric patients with HF attributable to systemic LVSD. This study included a relatively homogeneous pediatric HF population with a pathophysiology similar to adults with HFrEF attributable to dilated cardiomyopathy. In PANORAMA-HF, >90% of the patients in both treatment arms were being treated with an ACEI before randomization, as recommended by pediatric HF guidelines.[5] ACEIs[17] (most commonly enalapril) are considered the first-line treatment for pediatric patients with HF according to the European Medicines Agency, and are a class 1 recommendation by the International Society of Heart and Lung Transplantation for the treatment of symptomatic systemic LVSD (Level of Evidence B), although there are limited data about their efficacy in children.[5,17]

The global rank primary end point used in this study was created to address the lack of validated clinical efficacy end points in large cardiovascular outcome trials in pediatric populations and was used to evaluate the efficacy of sacubitril/valsartan versus enalapril.

This end point was developed on the basis of classification of patients into 3 categories: worsened, unchanged, or improved. A comparable clinical composite end point with 3 categories (worsened, unchanged, and improved) was also used in the Pediatric Carvedilol HF study.[13] The global rank end point builds on this composite score by further differentiating the patients between treatment groups[18,19] and ranking the patients from worst to best using important clinical events grouped into categories of severity from death to disease progression (worsening HF) to measures of symptoms and physical functioning.

In PANORAMA-HF, the largest randomized double-blinded pediatric HF clinical trial to date, sacubitril/valsartan did not show superiority over enalapril in the treatment of pediatric HF. This is in contrast to the findings from PARADIGM-HF (Prospective Comparison of ARNI With ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure) in adults, in which sacubitril/valsartan was found to be superior to enalapril in reducing the occurrence of cardiovascular death or HF hospitalization.[5] The discrepant results may be attributable to the fact that PANORAMA-HF was not powered to detect cardiac events as in a large conventional outcome study in adult patients with HF. It was instead powered to detect treatment differences in a Mann-Whitney-Wilcoxon odds of 0.75 with ≈80% power for the primary end point, considering a combination of clinical events, functional status, and patient-reported outcomes. Thus, whereas PARADIGM-HF (n=8442) had an average follow-up time of 27 months after randomization, with a maximum of 51 months after randomization, PANORAMA-HF (n=375) had a fixed duration of 52 weeks, further reducing the probability of cardiac events. Other potential explanations for the difference between PANORAMA-HF and PARADIGM-HF could be the underlying clinical phenotype of HF in children compared with adults and the possibility that children with HF respond differently to sacubitril/valsartan or enalapril than adults with HF.

The 2 treatment arms did not differ in the primary end point outcome.

Similar trends were observed for measures of health-related quality of life (PedsQL and PGIC scores). Improvement in PedsQL scores at week 52 exceeded the previously reported threshold for clinically meaningful improvement for both patient self-reported (4.8) and parent proxy-reported (5.5) scores in only the sacubitril/valsartan arm, suggesting a possible health-related quality of life advantage of sacubitril/valsartan over enalapril.

In this study, through 52 weeks, the clinically relevant improvements in NYHA/Ross class and PGIS scores observed with sacubitril/valsartan were similar to those observed with enalapril across all age groups, indicating that sacubitril/valsartan was similarly as efficacious as enalapril. Overall, both treatment arms showed comparable outcomes, with the majority of the patients showing improvement.

NT-proBNP is recognized both as a prognostic biomarker for outcomes in clinical trials in adult HF,[20–22] including those for sacubitril/valsartan and for enalapril,[16] and as a bridging biomarker for extrapolation from adults with HF to the pediatric population on the basis of the Prentice criteria (International Council for Harmonisation of Technical Requirements For Pharmaceuticals For Human Use E11A).[23] These criteria include common clinical features between pediatric HF attributable to systemic LVSD and adult HFrEF with dilated cardiomyopathy.

Sacubitril/valsartan reduced NT-proBNP levels in PARADIGM-HF and was therefore considered a reasonable end point to infer improved cardiovascular outcome in pediatric patients.[7] Throughout PANORAMA-HF, NT-proBNP levels substantially decreased compared with baseline in both treatment arms. The magnitude of the

reduction from baseline to week 52 in PANORAMA-HF (≈65% in both treatment arms) is similar to the reduction observed in adult patients with HFrEF treated with sacubitril/valsartan (52% at month 8) in PARADIGM-HF. In PANORAMA-HF, the similarity in the degree of the reduction in NT-proBNP levels in both treatment arms was consistent with the lack of significant differences in the global rank end point between the 2 arms.

The safety profile of sacubitril/valsartan has been extensively evaluated and is well characterized in adults with chronic HF, with >28 000 patients in clinical studies and >6 million patient-years in the postmarketing setting. The risk of hypotension, hyperkalemia, renal impairment, and angioedema in pediatric patients treated with sacubitril/valsartan was consistent with the extensive safety profile in adults. No new safety concerns specific to the pediatric population were observed with the treatments used in this study. This study suggests that sacubitril/valsartan has an acceptable safety profile in children with HF and is consistent with studies in adults.

The limitations of this study include issues related to the low incidence of HF in children, especially when compared with adults. For instance, there are no validated end points in pediatric HF. Death and HF hospitalization as primary end points in pediatric HF trials are not feasible because of the difficulty of enrolling sufficient numbers of pediatric patients with HF to achieve such an end point. A previously described composite score, which classifies patients into 3 categories of worsened, unchanged, and improved, has been used in cardiovascular clinical trials in adults and was the end point that was used in this first large multicenter pediatric HF randomized drug trial.[13,24] The global rank end point used in PANORAMA-HF was built on this methodology of ranking clinical outcomes and on experience from previous trials.[13,18,19] It ranked 5 categories of clinical HF events that were considered clinically meaningful to the patient and caregiver, from worst to best. To compensate for the challenges of powering a trial in pediatric HF, this approach leveraged a broader scope of data from this clinical trial versus trials in adult HF. Another limitation was the difficulty in accumulating enough trial data in the youngest patients. Because only 9 patients were enrolled in group 3 (1 month to <1 year of age; 5 in the sacubitril/valsartan arm and 4 in the enalapril arm), the ability to draw a definitive conclusion on the efficacy of sacubitril/valsartan in these patients was limited.

PANORAMA-HF is the largest randomized, double-blinded clinical trial in pediatric HF ever performed. No significant differences were observed in the global rank primary end point between sacubitril/valsartan and enalapril treatment in pediatric patients with HF with systemic LVSD. There was evidence of a possible health-related quality-of-life advantage of sacubitril/valsartan over enalapril. Overall, the safety profile of sacubitril/valsartan is acceptable in children and was comparable with enalapril. In PANORAMA-HF, sacubitril/valsartan has demonstrated a favorable benefit/risk ratio in the treatment of HF in pediatric patients 1 to <18 years of age over 52 weeks.

ARTICLE INFORMATION

Received August 4, 2023; accepted August 9, 2024.

Affiliations

Children's Hospital Los Angeles and the Keck School of Medicine of the University of Southern California, Los Angeles (R.S., P.F.K., J.M.). Great Ormond Street Hospital for Children, London, UK (M.B.). Novartis Pharmaceuticals Corporation, East Hanover, NJ (S.S.-Y., M.K.). Novartis Pharma AG, Basel, Switzerland (T.G.). Novartis, Shanghai, China (S.Z.). Children's Healthcare of Atlanta and Emory University, GA (C.M.). Chris Hani Baragwanath Academic Hospital, University of the Witwatersrand, Johannesburg, South Africa (A.C.). National Center for Cardiovascular Disease and Fuwai Hospital, Chinese Academy of Medical Sciences, Peking Union Medical College, Beijing, China (X.W.). Washington University School of Medicine, St. Louis, MO (C.C.). Children's Hospital of Philadelphia, PA (J.R.). Levine Children's Hospital, Charlotte, NC (G.W.). Hotel Dieu de France Hospital, Beirut, Lebanon (L.D.). Regional Specialist Hospital in Wroclaw, Poland (J.K.). Baskent University Medical Faculty, Ankara, Turkey (K.T.). University Hospital Centre, Zagreb, Croatia (D.D.). Shanghai Children's Medical Center, Shanghai Jiao Tong University School of Medicine, China (Z.X.). Children's Hospital of Shanghai, China (T.X.). Mattel Children's Hospital and David Geffen School of Medicine, UCLA, Los Angeles, CA (N.H.). Boston Children's Hospital and Harvard Medical School, MA (K.P.D., T.P.S.). Pediatrics, Division of Cardiology, Loma Linda University Children's Hospital, CA (M.J.B.). Columbia University Medical Center, Morgan Stanley Children's Hospital of New York, New York (W.Z.). Department of Congenital & Pediatric Cardiology, Indraprastha Apollo Hospitals, New Delhi, India (M.C.). Division of Pediatric Cardiology, Soroka University Medical Center, Ben-Gurion University of the Negev, Beer-Sheva, Israel (A.L.). University of Milan–Bicocca, A.S.S.T. Papa Giovanni XXIII, Bergamo, Italy (M.S.). Bambino Gesù Children Hospital, IRCSS, Rome, Italy (G.G.). Seoul National University College of Medicine, Seoul National University Children's Hospital, Korea (G.B.K.). Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea (J.S.). Pusan National University Yangsan Hospital Yangsan-si, Gyeongsangnam-Do, Korea (H.D.L.). Department of Paediatrics, Yong Loo Lin School of Medicine, National University of Singapore (C.K.C.). Hospital Sant Joan de Deu Esplugues de Llobregat, Spain (J.S.-d.-T.). Seattle Children's Hospital, WA (Y.L.). Ramathibodi Hospital Mahidol University, Bangkok, Thailand (S.W.). Guangzhou Women and Children's Medical Center Guangzhou, Guangdong, China (Y.C.). Centro Hospitalar Lisboa Ocidental EPE Hospital de Santa Cruz Carnaxide, Lisboa, Portugal (R.A.). University of Health Sciences Turkey Dr. Behcet Uz Childrens Hospital-Konak/Izmir, Turkey (T.M.). M3C-Necker, Congenital and Paediatric Cardiology Department, Hospital Necker-Enfants Malades, University of Paris Cité, France (D.B.).

Acknowledgments

The study was sponsored by Novartis Pharma AG, Basel, Switzerland. The authors thank the clinical investigators, study personnel, and study participants for their contributions, as well as Nupur Chaubey, Novartis Healthcare Pvt. Ltd. (Hyderabad, India), for medical writing assistance. The authors directed the development of the manuscript and are fully responsible for all content and editorial decisions made.

Sources of Funding

Novartis Pharma AG, Basel, Switzerland.

Disclosures

Dr Shaddy is a consultant for Novartis, American Regent Inc., CRI Biotech, and Rocket Pharmaceuticals. S. Solar-Yohay is an employee of US Novartis Pharmaceuticals Corporation and owns stocks in Novartis Pharma AG, Basel, Switzerland. Dr Garito is an employee of Novartis Pharma AG, Basel, Switzerland, and owns its shares. Dr Zhang is an employee of Novartis, Shanghai, China. M. Kocun is an employee of US Novartis Pharmaceuticals Corporation and owns stocks in Novartis Pharma AG, Basel, Switzerland. Dr Canter holds a Data and Safety Monitoring Board chairman position at the Mayo Research Foundation and has participated on an advisory board for CareDx. Dr Rossano reports receiving consulting fees from Bayer, Enzyvant, Merck, AskBio, American Regent, and Bristol Myers Squibb. Dr Halnon reports receiving consulting fees from Novartis and grants

or contracts to her institution from Novartis. Dr Daly reports grants or contracts for the TEAMMATE multicenter trial of post–heart transplant immunosuppression (different patient population; Novartis holds the nonexclusive rights to one of the drugs that was studied [everolimus] but Novartis did not provide any support for the TEAMMATE study) and for American Heart Association/Enduring Hearts (ancillary studies to the TEAMMATE study in heart transplant recipients [different drug and patient population]); consulting fees from AstraZeneca (consultation regarding a different pediatric heart failure drug and possible study in children); payment or honoraria for lectures, presentations, speaker bureaus, manuscript writing, or educational events from CareDx (pediatric research board related to the use of Allosure Heart in transplant recipients); leadership or fiduciary role in other board, society, committee or advocacy group, paid or unpaid in ISHLT program committee 2021–2023 (developed ISHLT scientific sessions program) and AST trainee and young faculty community of practice chair (developed content for fellows and young faculty as part of the AST). Dr Singh is co-chair of the end point adjudication committee at Novartis for PANORAMA-HF. Dr Senni reports receiving consulting fees and payment or honoraria for lectures, presentations, speaker bureaus, manuscript writing, or educational events from Novartis, Bayer, Merck, MSD, Abbott, AstraZeneca, Boehringer, Vifor, and Novo Nordisk. Dr Anjos reports an unpaid position as a board member of the pediatric cardiology section of the Portuguese Medical Association. Dr Bonnet reports consulting fees from Novartis paid to his institution for being the steering committee member for the current study and participating in an advisory board for the current study. The other authors declare no competing interests.

Supplemental Material

Methods

Tables S1–S7

Figures S1–S2

REFERENCES

1. Shaw TB, Blitzer D, Carter KT, Lirette S, Mohammed A, Copeland J, Baran DA, Copeland H. Functional status of heart transplant recipients predicts survival. *Clin Transplant*. 2022;36:e14748. doi: 10.1111/ctr.14748
2. Peng DM, Zhang Y, Rosenthal DN, Palmon M, Chen S, Kaufman BD, Maeda K, Hollander SA, McDonald N, Smoot LB, et al. Impact of heart transplantation on the functional status of US children with end-stage heart failure. *Circulation*. 2017;135:939–950. doi: 10.1161/CIRCULATIONAHA.115.016520
3. Ahmed H, VanderPluym C. Medical management of pediatric heart failure. *Cardiovasc Diagn Ther*. 2021;11:323–335. doi: 10.21037/cdt-20-358
4. Masarone D, Valente F, Rubino M, Vastarella R, Gravino R, Rea A, Russo MG, Pacileo G, Limongelli G. Pediatric heart failure: a practical guide to diagnosis and management. *Pediatr Neonatol*. 2017;58:303–312. doi: 10.1016/j.pedneo.2017.01.001
5. Kirk R, Dipchand AI, Rosenthal DN, Addonizio L, Burch M, Chrisant M, Dubin A, Everitt M, Gajarski R, Mertens L, et al. The International Society for Heart and Lung Transplantation guidelines for the management of pediatric heart failure: executive summary [corrected]. *J Heart Lung Transplant*. 2014;33:888–909. doi: 10.1016/j.healun.2014.06.002
6. McMurray JJ, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, Rouleau JL, Shi VC, Solomon SD, Swedberg K, et al; PARADIGM-HF Investigators and Committees. Angiotensin-neprilysin inhibition versus enalapril in heart failure. *N Engl J Med*. 2014;371:993–1004. doi: 10.1056/NEJMoa1409077
7. Novartis. Entresto (sacubitril and valsartan). Prescribing information. Novartis; 2021.
8. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Bohm M, Burri H, Butler J, Celutkiene J, Chioncel O, et al; ESC Scientific Document Group. 2021 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J*. 2021;42:3599–3726. doi: 10.1093/eurheartj/ehab368
9. Heidenreich PA, Bozkurt B, Aguilar D, Allen LA, Byun JJ, Colvin MM, Deswal A, Drazner MH, Dunlay SM, Evers LR, et al. 2022 AHA/ACC/HFSA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association joint committee on clinical practice guidelines. *J Am Coll Cardiol*. 2022;79:e263–e421. doi: 10.1016/j.jacc.2021.12.012
10. Maddox TM, Januzzi JL Jr, Allen LA, Breathett K, Brouse S, Butler J, Davis LL, Fonarow GC, Ibrahim NE, Lindenfeld J, et al. 2024 ACC expert consensus decision pathway for treatment of heart failure with reduced ejection fraction: a report of the American College of Cardiology solution set oversight committee. *J Am Coll Cardiol*. 2024;83:1444–1488. doi: 10.1016/j.jacc.2023.12.024
11. Shaddy R, Canter C, Halnon N, Kochilas L, Rossano J, Bonnet D, Bush C, Zhao Z, Kantor P, Burch M, et al. Design for the sacubitril/valsartan (LCZ696) compared with enalapril study of pediatric patients with heart failure due to systemic left ventricle systolic dysfunction (PANORAMA-HF study). *Am Heart J*. 2017;193:23–34. doi: 10.1016/j.ahj.2017.07.006
12. Shaddy R, Burch M, Kantor PF, Solar-Yohay S, Garito T, Zhang S, Kocun M, Bonnet D. Baseline characteristics of pediatric patients with heart failure due to systemic left ventricular systolic dysfunction in the PANORAMA-HF trial. *Circ Heart Fail*. 2023;16:e009816. doi: 10.1161/CIRCHEARTFAILURE.122.009816
13. Shaddy RE, Boucek MM, Hsu DT, Boucek RJ, Canter CE, Mahony L, Ross RD, Pahl E, Blume ED, Dodd DA, et al; Pediatric Carvedilol Study Group. Carvedilol for children and adolescents with heart failure: a randomized controlled trial. *JAMA*. 2007;298:1171–1179. doi: 10.1001/jama.298.10.1171
14. Varni JW, Burwinkle TM, Seid M, Skarr D. The PedsQL 4.0 as a pediatric population health measure: feasibility, reliability, and validity. *Ambul Pediatr*. 2003;3:329–341. doi: 10.1367/1539-4409(2003)003<0329:tpaapp>2.0.co;2
15. Bonnet D, Berger F, Jokinen E, Kantor PF, Daubeney PEF. Ivabradine in children with dilated cardiomyopathy and symptomatic chronic heart failure. *J Am Coll Cardiol*. 2017;70:1262–1272. doi: 10.1016/j.jacc.2017.07.725
16. Zile MR, Claggett BL, Prescott MF, McMurray JJ, Packer M, Rouleau JL, Swedberg K, Desai AS, Gong J, Shi VC, et al. Prognostic implications of changes in N-terminal pro-B-type natriuretic peptide in patients with heart failure. *J Am Coll Cardiol*. 2016;68:2425–2436. doi: 10.1016/j.jacc.2016.09.931
17. European Medicines Agency. Report on the Expert Group Meeting of Paediatric Heart Failure; London, UK; November 29, 2010.
18. Sun H, Davison BA, Cotter G, Pencina MJ, Koch GG. Evaluating treatment efficacy by multiple end points in phase II acute heart failure clinical trials: analyzing data using a global method. *Circ Heart Fail*. 2012;5:742–749. doi: 10.1161/CIRCHEARTFAILURE.112.969154
19. Felker GM, Maisel AS. A global rank end point for clinical trials in acute heart failure. *Circ Heart Fail*. 2010;3:643–646. doi: 10.1161/CIRCHEARTFAILURE.109.926030
20. Januzzi JL Jr, Ahmad T, Mulder H, Coles A, Anstrom KJ, Adams KF, Ezekowitz JA, Fiuzat M, Houston-Miller N, Mark DB, et al. Natriuretic peptide response and outcomes in chronic heart failure with reduced ejection fraction. *J Am Coll Cardiol*. 2019;74:1205–1217. doi: 10.1016/j.jacc.2019.06.055
21. Masson S, Latini R, Anand IS, Barlera S, Angelici L, Vago T, Tognoni G, Cohn JN; Val-HeFT Investigators. Prognostic value of changes in N-terminal pro-brain natriuretic peptide in Val-HeFT (Valsartan Heart Failure Trial). *J Am Coll Cardiol*. 2008;52:997–1003. doi: 10.1016/j.jacc.2008.04.069
22. Schmitt W, Ruhs H, Burghaus R, Diedrich C, Duwal S, Eissing T, Garmann D, Meyer M, Ploeger B, Lippert J. NT-proBNP qualifies as a surrogate for clinical end points in heart failure. *Clin Pharmacol Ther*. 2021;110:498–507. doi: 10.1002/cpt.2222
23. Prentice RL. Surrogate end points in clinical trials: definition and operational criteria. *Stat Med*. 1989;8:431–440. doi: 10.1002/sim.4780080407
24. Packer M. Proposal for a new clinical end point to evaluate the efficacy of drugs and devices in the treatment of chronic heart failure. *J Card Fail*. 2001;7:176–182. doi: 10.1054/jcaf.2001.25652