Circulation: Heart Failure

ORIGINAL ARTICLE

Baseline Characteristics of Pediatric Patients With Heart Failure Due to Systemic Left Ventricular Systolic Dysfunction in the PANORAMA-HF Trial

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BACKGROUND: Sacubitril/valsartan has been approved for the management of heart failure (HF) with reduced ejection fraction in adults. PANORAMA-HF trial (Prospective Trial to Assess the Angiotensin Receptor Blocker Neprilysin Inhibitor LCZ696 Versus Angiotensin-Converting Enzyme Inhibitor for the Medical Treatment of Pediatric HF) investigated its effects on clinical outcomes in pediatric patients with HF.

METHODS: PANORAMA-HF is a multicenter, Phase II/III study using an adaptive, seamless, 2-part design. The study aimed to evaluate the pharmacokinetics and pharmacodynamics of single doses of sacubitril/valsartan (Part 1), and the efficacy and safety of sacubitril/valsartan versus enalapril administered twice daily for 52 weeks (Part 2) in pediatric patients with HF due to left ventricular systolic dysfunction with biventricular heart physiology. An innovative trial design using a novel global rank assessment of severity was employed. For analysis, eligible patients were stratified into 3 age groups (Group 1, 6 to <18 years; Group 2a, 2 to <6 years; and Group 3a, 1 month to <2 years) and functional classification (New York Heart Association/Ross class I/II and III/IV).

RESULTS: We report the key demographic, baseline, and clinical characteristics of 375 pediatric patients randomized to receive the study medication. The mean age for patients in Groups 1, 2a, and 3a was 12.2, 3.2, and 1.3 years, respectively. About 70% of patients had a prior HF hospitalization, 85% had New York Heart Association/Ross class I/II HF, and ≈8% were angiotensin-converting enzyme inhibitor/angiotensin receptor blocker naïve.

CONCLUSIONS: Compared to other pediatric HF studies, PANORAMA-HF recruited a relatively homogeneous pediatric HF population across 3 age groups, enabling a more robust evaluation of pharmacokinetics/pharmacodynamics and efficacy/safety of sacubitril/valsartan. Most patients had mildly symptomatic HF at baseline.

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Key Words: angiotensin receptor antagonist ■ children ■ clinical trial ■ Entresto ■ heart failure ■ neprilysin ■ ventricular dysfunction

Pediatric heart failure (HF) is associated with significant morbidity, hospitalizations, and mortality.[1–3] In the United States, pediatric HF accounts for 11 000 to 14 000 hospitalizations every year (15–18 HF-related hospitalizations per 100 000 children), ≈6000 visits to the emergency department, and an overall mortality of 7%.[1,2] According to a systematic literature review on incidence and prevalence of HF in studies on primary HF diagnoses conducted between 2003 and 2008, the incidence of HF per 100 000 children and adolescents

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WHAT IS NEW?

- 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 the largest prospective, randomized, active-controlled study in pediatric patients with heart failure (HF) to date. It is the first pediatric HF study to use a global rank primary end point, which will rank patients from worst to best based on clinical events such as death, listing for urgent heart transplant, mechanical life support requirement, worsening HF, and changes from baseline in New York Heart Association/Ross classification, Patient Global Impression of Severity score, and Pediatric Quality of Life Inventory physical functioning domain score. The seamless, 2-part clinical development methodology represents an innovative approach to clinical study design in pediatric patients with HF.

WHAT ARE THE CLINICAL IMPLICATIONS?

- PANORAMA-HF will test the hypothesis that sacubitril/valsartan is superior to enalapril in reducing mortality and morbidity as assessed using the global rank end point in pediatric patients with HF. Results from this study are expected to provide further insights into the role of sacubitril/valsartan in the management of pediatric HF, and guide clinicians on how to optimize treatment in this patient population.

Nonstandard Abbreviations and Acronyms

ACEi	angiotensin-converting enzyme inhibitor
ARNI	angiotensin receptor neprilysin inhibitor
HF	heart failure
HFrEF	heart failure with reduced ejection fraction
LVSD	left ventricular systolic dysfunction
NYHA	New York Heart Association
PANORAMA-HF	Prospective Trial to Assess the Angiotensin Receptor Blocker Neprilysin Inhibitor LCZ696 Versus Angiotensin-Converting EnzymeInhibitor for the Medical Treatment of Pediatric HF
PedsQL	Pediatric Quality of Life Inventory
PGIS	Patient Global Impression of Severity

ranged from 0.87 in the United Kingdom and Ireland through 2.0 to 3.0 in Germany, and 7.4 in Taiwan, while the reported prevalence was up to 83.3 per 100 000 children and adolescents in Spain.[4]

Although pediatric HF due to left ventricular systolic dysfunction (LVSD) has common pathophysiology with adult HF with reduced ejection fraction (HFrEF), the etiology of HF in the pediatric population differs from that in adults; ischemia is the most common cause in adults while congenital heart disease followed by cardiomyopathies are the most common causes of HF in the pediatric age group.[5,6] Additionally, the outcomes in pediatric patients with HF are significantly different from those in adults with HF. Despite the possibility of corrective cardiac surgery, which can improve the clinical course of patients with congenital heart disease, there are still 40% of patients with dilated cardiomyopathy who die or require heart transplant within 2 to 5 years from diagnosis.[7,8] Because of the lack of large, prospective, randomized clinical trials in pediatric populations with HF, guideline recommendations for the management of pediatric HF are mostly extrapolated from data collected from the clinical trials conducted on an adult population, where different recommendations are made for pediatric HF with reduced EF (systolic HF) versus preserved EF (diastolic HF).[4,9] The most recent recommendations from the International Society for Heart and Lung Transplantation Guidelines for the management of pediatric patients with HFrEF recommend the use of angiotensin-converting enzyme inhibitors ([ACEi]; class I recommendation, level of evidence B [I, B]), β-blockers (IIa, B), mineralocorticoid receptor antagonists (I, C), and angiotensin receptor blockers (IIa, C) in pediatric patients with systemic LVSD, principally based on adult HF guidelines and expert consensus.[11] Hence, there is an unmet need for prospective clinical trials to determine the safety and efficacy of different pharmacotherapies for the management of pediatric patients with HF.

Sacubitril/valsartan is a first-in-class angiotensin receptor neprilysin inhibitor that simultaneously inhibits neprilysin via sacubitrilat (the active metabolite of sacubitril) and blocks the angiotensin II type 1 receptor via valsartan.[12] In the PARADIGM-HF study, sacubitril/valsartan demonstrated superiority over the ACEi enalapril in reducing the risk of mortality and HF hospitalizations among adults with chronic HFrEF.[13,14] Based on the results of the PARADIGM-HF study, sacubitril/valsartan was approved by the US Food and Drug Administration[15] and the European Medicines Agency for the treatment of HFrEF in adults.[16] The effects of sacubitril/valsartan on clinical outcomes in pediatric patients with HF are, however, yet to be described.

The PANORAMA-HF study (Prospective Trial to Assess the Angiotensin Receptor Blocker Neprilysin Inhibitor LCZ696 Versus Angiotensin-Converting EnzymeInhibitor for the Medical Treatment of Pediatric HF)

was designed to assess whether treatment with sacubitril/valsartan for 52 weeks in infants, children, and adolescents (aged 1 month to <18 years) with HF offers greater clinical benefit compared to enalapril.[17] Here, we report the key demographic and baseline characteristics of the patients enrolled in the PANORAMA-HF study.

METHODS

Novartis is committed to sharing with qualified external researchers, access to patient-level data, and supporting clinical documents from eligible studies. 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. The availability of this trial data is according to the criteria and process described on http://www.clinicalstudydatarequest.com.

Study Design

The design of the PANORAMA-HF study (NCT02678312) has been published previously.[17] In brief, PANORAMA-HF is a Phase II/III, multicenter study conducted in 31 countries and 112 sites across Europe, North and South America, Asia, and South Africa. The study comprises 2 parts: Part 1 is an open-label, single-dose pharmacokinetics and pharmacodynamics study, and Part 2 is a 52-week randomized, double-blind, parallel-group, active-controlled, clinical efficacy study. This article focuses mainly on Part 2 of the study.

The study design, implementation, execution, and reporting are in accordance with the International Council for Harmonisation Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC, US Code of Federal Regulations 21, and Japanese Ministry of Health, Labor, and Welfare), and with the ethical principles laid down in the Declaration of Helsinki. The Institutional Review Board/Independent Ethics Committee at all participating centers approved the trial protocol. All patients or their legally acceptable representative(s) provided written informed consent. An informed consent was provided by the patient once he/she turned 18 years old during the study.

Patient Population

Infants, children, and adolescents (aged 1 month to <18 years) with systemic LVSD (left ventricular ejection fraction ≤45% or a fractional shortening ≤22.5%), inpatient or outpatient, with a current or past history of symptomatic HF, and on maintenance HF therapy (unless newly diagnosed) were eligible for the study; Part 2 of the study aimed to enroll at least 80% of patients with an left ventricular ejection fraction ≤40% or a fractional shortening ≤20% (original entry criteria). Excluded from the study were infants, children, and adolescents with single ventricle or systemic right ventricle; sustained or symptomatic dysrhythmias uncontrolled with drug or device therapy; renal vascular hypertension; symptomatic hypotension or blood pressure below the calculated fifth percentile systolic blood pressure for age at screening visit; and restrictive or hypertrophic cardiomyopathy. The exclusion criteria were chosen to reduce the risk of symptomatic hypotension, increase study treatment compliance, and identify a population of children with systemic LVSD, which is similar to adult HF studies such as PARADIGM-HF, thus reducing the dilution effect of complex congenital heart disease patients. The key inclusion and exclusion criteria[17] are provided in Table S1.

Eligible patients were initially stratified into age groups (Group 1, aged 6 to <18 years; Group 2, aged 1 to <6 years; and Group 3, aged 1 month to <1 year) and functional classification (New York Heart Association [NYHA]/Ross class group: I/II and III/IV) and randomized to receive sacubitril/valsartan or enalapril (Figure 1). However, it was observed that recruitment of young patients with HF for Part 1 and Part 2 of the study was going to be more challenging than anticipated. Consequently, patients were stratified by modified age groups. In line with the International Council for Harmonisation E11 recommended age ranges, the youngest age group (Group 3) was modified from the original age range of 1 month to <1 year to the modified age range of 1 month to <2 years (Group 3a). Age Group 2 was also revised accordingly from 1 to <6 years to 2 to <6 years (Group 2a). These changes in the age group stratification were included in the protocol (September 18, 2020) after approval from the PANORAMA-HF Data Monitoring Committee and Executive Committee (comprising key opinion leaders in pediatric cardiology). This protocol was submitted to all participating country health authorities, including the US Food and Drug Administration, and approved. This modification of the age groups enables a more robust analysis of the safety and efficacy data for children aged <2 years. Thus, here we report the demographic and baseline characteristics of the original age groups and patients in Groups 2a and 3a.

The randomization was stratified considering 6 strata including the modified age group and NYHA/Ross class group: (1) age Group 1 (6 years to <18 years) and NYHA/Ross class I/II; (2) age Group 1 (6 years to <18 years) and NYHA/Ross class III/IV; (3) age Group 2a (2 years to <6 years) and NYHA/Ross class I/II; (4) age Group 2a (2 years to <6 years) and NYHA/Ross class III/IV; (5) age Group 3a (1 month to <2 years) and NYHA/Ross class I/II; and (6) age Group 3a (1 month to <2 years) and NYHA/Ross class III/IV.

Objectives and End Points

The primary objective of the PANORAMA-HF study is to determine whether sacubitril/valsartan is superior to the ACEi enalapril for the treatment of HF, as assessed using a global rank end point through 52 weeks of treatment in pediatric patients with HF due to systemic LVSD (Part 2 study). The primary end point is the global rank end point through 52 weeks of treatment, which will be constructed through 2 steps within each of the 6 strata. In Step 1, patients are classified into 5 ordinal categories. In Step 2, within each category, patients are ranked from worst to best based first on the subcategory if applicable. The 5 categories are as follows: (1) Category 1, death: United Network for Organ Sharing status 1A listing for heart transplant or equivalent; ventricular assist device/extracorporeal membrane oxygenation/mechanical ventilation/intra-aortic balloon pump requirement for life support; (2) Category 2, worsening HF: defined by signs and symptoms of worsening HF that requires an intensification of HF therapy; (3) Category 3, worsened: worse NYHA/Ross or worse Patient Global Impression of Severity (PGIS); and

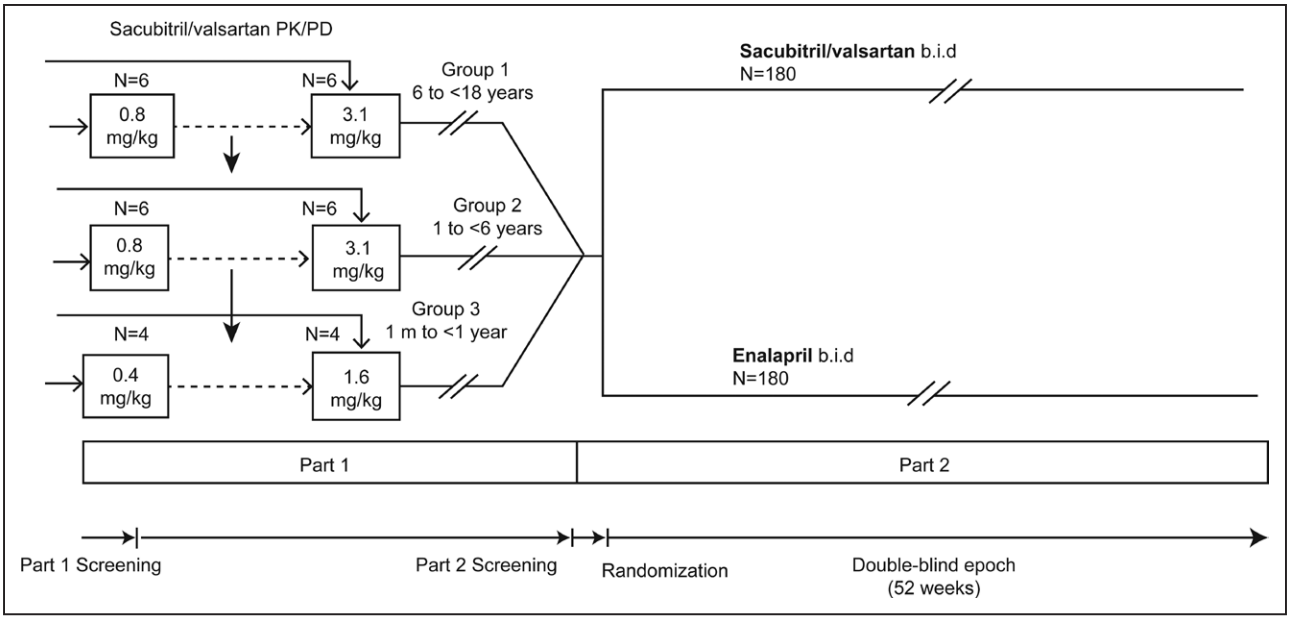

Figure 1. PANORAMA-HF study design.
b.i.d. indicates twice daily; N, number of patients; PANORAMA-HF, Prospective Trial to Assess the Angiotensin Receptor Blocker Neprilysin Inhibitor LCZ696 Versus Angiotensin-Converting Enzyme Inhibitor for the Medical Treatment of Pediatric HF; and PK/PD, pharmacokinetics/pharmacodynamics.

further ranking by Pediatric Quality of Life Inventory (PedsQL) physical functioning domain; (4) Category 4, unchanged: unchanged NYHA/Ross and unchanged PGIS; and further ranking by PedsQL physical functioning domain; and (5) Category 5, improved: improved NYHA/Ross or improved PGIS (neither can be worse); and further ranking by PedsQL physical functioning domain. Within each stratum, the Mann-Whitney (MW) probability is defined as the probability of the patient from the sacubitril/valsartan group having a better outcome than the patient from the enalapril group plus half of the probability of the patient from the sacubitril/valsartan group having equal outcome to the one from the enalapril group, when the 2 patients are independently sampled from the sacubitril/valsartan group and the enalapril group. Correspondingly, the MW odds is defined as 1 minus the MW probability divided by the MW probability.

Enalapril was chosen as the comparator since it is the most commonly used renin-angiotensin system blocker in pediatric patients with HF and is considered as the standard of care in the treatment of chronic HF in most geographic areas. Additionally, enalapril has a twice daily dosing regimen similar to sacubitril/valsartan. The secondary objectives and exploratory end points are provided in Table S2.

Sample Size

The planned sample size was 180 patients per group (360 patients total). The sample size calculation is based on the MW probability; the power analysis is done for Part 2 of the study and calculated based on the global rank end point. The power calculation is based on the data from the pediatric HF carvedilol study within the subgroup of patients with HF due to systemic LVSD.[18] Referring from the article, this sample size will provide 80% power for the comparison of the primary end point (alpha 0.05) following the assumed percentage of patients in each category.[19]

Statistical Methods

The null hypothesis is that the MW odds in all strata are equal to 1, while the alternative hypothesis is that the MW odds are not equal to 1 in at least 1 stratum. The hypothesis will be tested by the stratified Wilcoxon rank-sum test. The test will be performed at an overall significance level of 2-sided 0.05. No multiple testing was considered.

Key demographic and clinical findings will be reported for patients aged 1 month to <18 years with systemic LVSD, with a current or past history of symptomatic HF, and on maintenance HF therapy. Summary analyses will be performed for each baseline parameter. Continuous variables will be summarized using number of observations, mean, SD, median, quartiles, minimum, and maximum. Categorical variables will be summarized using frequencies and percentages.

RESULTS

Between November 2016 and January 2021, 422 patients were screened for Part 2, among whom 377 eligible patients were enrolled in Part 2 of the study. Among the 377 patients enrolled, 375 were randomized to double-blind sacubitril/valsartan or enalapril twice daily for 52 weeks; 2 patients were misrandomized and did not receive study drug; misrandomized patients refer to patients who were not qualified for randomization and did not receive study drug but were inadvertently randomized into the study. The last patient visit for the study population was January 3, 2022.

Demographic and Baseline Characteristics

The demographic and baseline characteristics of the original age group patients, and those in Groups 2a

and 3a are shown in Table 1.[20] Focusing on the modified age groups, the mean age was 12.2, 3.2, and 1.3 years in Groups 1, 2a, and 3a, respectively. The proportion of female-to-male patients was similar in this population. Overall, the proportion of patients enrolled from the American region (35.2%), Asia (34.1%), and Europe (30.7%) was similar; however, in Group 2a, 49.4% of the patients were from Asia. In Group 1, 54.6% of the patients were White, 21.4% were Asians, and 15% were Black or African Americans. In Group 2a and 3a, 34.1% and 44.3% of the patients were White, 40% and 30% were Asians, and 11.8% and 7.1% were Black or African Americans, respectively. The mean LV ejection fraction was 32.2 overall and comparable across Groups 1, 2a, and 3a (32.8, 32.1, and 30.7, respectively). Of note, 93.3% of patients were enrolled with the original EF/fractional shortening entry criteria (≤40%/≤20%, respectively) while only 6.7% of patients enrolled utilizing the amended EF/fractional shortening entry criteria (≤45%/≤22.5%, respectively). Most patients (85%) had NYHA/Ross class I/II HF at baseline (Group 1, 10.9%/72.3%; Group 2a, 23.5%/68.2%; Group 3a, 21.4%/61.4%), but all patients had a history of NYHA/Ross class II or worse to be eligible. Overall, 68.5% of the patients had prior HF hospitalizations and at screening most (90%) were outpatients. For renin-angiotensin system inhibition, 88.5% of the patients were on an ACEi, 2.1% were on an angiotensin receptor blocker, and 1.9% were on an ACEi and an angiotensin receptor blocker. Other HF and cardiovascular medications included mineralocorticoid receptor antagonists and β-blockers (each in 69.3% of the patients), diuretics (69.1%, of which furosemide accounted for the 63.7%), aspirin (41.6% of the patients), and digoxin (36.8% of the patients). The mean systolic blood pressure was 103.0±12.1 mm Hg, 95.6±12.4 mm Hg, and 99.0±13.5 mm Hg in Groups 1, 2a, and 3a, respectively. The mean diastolic blood pressure was 62.0±9.6 mm Hg, 57.6±10.0 mm Hg, and 59.0±12.7 mm Hg, in Groups 1, 2a and 3a, respectively. The mean heart rate in Groups 1, 2a, and 3a was 84.3, 100.1, and 122.2 bpm, respectively.

Heart Failure Etiology

Overall, cardiomyopathy was observed in >60% of patients, with the cause being idiopathic in 34.7% of patients, followed by familial/genetic conditions in 17.6% and LV noncompaction in 11.2% of patients (Figure 2). Uncommon causes of HF associated with cardiomyopathy were neuromuscular disease (3.5%), inborn errors of metabolism (1.1%), and mitochondrial disorders in 0.5%.

Heart failure secondary to other causes was noted in 27% of patients, with congenital cardiac malformations in 13.9% of patients and myocarditis-induced HF in 13.1% of patients. Ischemic heart disease was observed in 4.3% and acquired/chemotherapy-related HF in 3.7% of patients.

Patient Global Impression of Severity Score

The PGIS uses a 5-point patient evaluation scale for patient self-report in those aged ≥7 years. While a 5-point evaluation scale was used for parents/caregivers for patients aged <5 years, a 3-point faces scale (good, neither good nor bad, or bad) was used for patient self-report by children aged 5 to <7 years. At randomization, PGIS score was assessed in 366 patients overall, most of whom reported no or mild HF symptoms (Table 2). Symptoms were rated as moderate in 17.8% of the patients, as severe in 4% and as very severe in 0.8%.

Pediatric Quality of Life (Physical Functioning Domain) Score

Overall, the majority of parents (96.3%) and patients (78.1% from Groups 1 and 2a) responded to the PedsQL physical functioning domain questionnaire at the randomization visit. The mean patient-reported PedsQL total summary score (Groups 1 and 2a) was 71.2 (Table 3) and the mean parent-reported total summary score was 71.6 (Table 4).[21,22] Inputs were collected only from those patients who were aged ≥5 years. For patients aged between 1 month to 4 years at randomization, inputs were collected from the parent/caregiver only.

DISCUSSION

To date, PANORAMA-HF is the largest prospective, randomized study conducted in pediatric patients with HF. PANORAMA-HF included pediatric patients with biventricular heart physiology and HF due to systemic left ventricle dysfunction. The baseline cardiac function and symptom status characteristics of patients in the PANORAMA-HF study were generally consistent with those in previous trials involving pediatric patients with HF (Table 5).[17,23,24] Most of the patients were categorized as NYHA/Ross class I or II and for the majority of patients the global impression of disease severity (PGIS) was mild, while only a minority reported their symptoms as moderate or severe.

The PedsQL physical functioning domain assessment was employed as a tool to determine the health-related quality of life in these children and adolescents and has been used in several studies involving pediatric patients with cardiovascular disease. In the PedsQL score from 0 through 100 points, higher scores indicate a better quality of life. In the current study, the baseline PedsQL scores reported by parents and patients well reflect the NYHA/Ross class and were lower than in healthy children as reported previously.[21,22] The findings from

Table 1. Demographic and Baseline Characteristics

Variables	Overall (N=375)	Group 1 (6 to <18 y; n=220)	Group 2 (1 to <6 y; n=146)	Group 2a (2 to <6 y; n=85)	Group 3 (1 mo to <1 y; n=9)	Group 3a (1 mo to <2 y; n=70)
Age, y, mean±SD	8.1±5.6	12.2±3.4	2.4±1.2	3.2±1.0	0.7±0.3	1.3±0.4
Female, n (%)	193 (51.5)	108 (49.1)	79 (54.1)	44 (51.8)	6 (66.7)	41 (58.6)
Height (age-adjusted percentile) at screening, mean±SD	43.9±34.7	44.6±34.7	43.9±34.9	51.9±35.8	27.9±32.5	32.0±30.6
Weight (age-adjusted percentile), mean±SD	46.0±34.9	53.0±36.3	36.5±30.5	40.3±32.8	29.3±26.1	31.0±26.0
BMI, kg/m²*; mean±SD	18.4±5.7	20.4±6.4	15.5±2.1	15.2±1.9	15.8±2.1	15.9±2.3
Region of enrollment, n (%)						
America	132 (35.2)	86 (39.1)	41 (28.1)	20 (23.5)	5 (55.6)	26 (37.1)
Asia	128 (34.1)	63 (28.6)	63 (43.2)	42 (49.4)	2 (22.2)	23 (32.9)
Europe	115 (30.7)	71 (32.3)	42 (28.8)	23 (27.1)	2 (22.2)	21 (30.0)
Race, n (%)						
White	180 (48.0)	120 (54.6)	56 (38.4)	29 (34.1)	4 (44.4)	31 (44.3)
Black or African American	48 (12.8)	33 (15.0)	15 (10.3)	10 (11.8)	0 (0)	5 (7.1)
Asian	102 (27.2)	47 (21.4)	53 (36.3)	34 (40.0)	2 (22.2)	21 (30.0)
American Indian or Alaska Native	5 (1.3)	2 (0.9)	3 (2.1)	2 (2.4)	0 (0)	1 (1.4)
Native Hawaiian or other Pacific Islander	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Unknown	14 (3.7)	8 (3.6)	4 (2.7)	0 (0)	2 (22.2)	6 (8.6)
Other	26 (6.9)	10 (4.6)	15 (10.3)	10 (11.8)	1 (11.1)	6 (8.6)
LVEF at screening, mean±SD	32.2±7.7	32.8±7.5	31.1±8.0	32.1±7.5	37.1±5.7	30.7±8.4
NYHA/Ross class, n (%)						
I	59 (15.7)	24 (10.9)	34 (23.3)	20 (23.5)	1 (11.1)	15 (21.4)
II	260 (69.3)	159 (72.3)	94 (64.4)	58 (68.2)	7 (77.8)	43 (61.4)
III	54 (14.4)	36 (16.4)	17 (11.6)	7 (8.2)	1 (11.1)	11 (15.7)
IV	2 (0.5)	1 (0.5)	1 (0.7)	0 (0)	0 (0)	1 (1.4)
Prior HF hospitalization, n (%)	257 (68.5)	140 (63.6)	108 (74.0)	61 (71.8)	9 (100)	56 (80.0)
Hospitalization status at screening, n (%)						
Inpatient	37 (9.9)	17 (7.7)	18 (12.3)	9 (10.6)	2 (22.2)	11 (15.7)
Outpatient	338 (90.1)	203 (92.3)	128 (87.7)	76 (89.4)	7 (77.8)	59 (84.3)
Prior HF and cardiovascular medication, n (%)						
ACEi only	332 (88.5)	195 (88.6)	128 (87.7)	75 (88.2)	9 (100)	62 (88.6)
ARB only	8 (2.1)	7 (3.2)	1 (0.7)	0 (0)	0 (0)	1 (1.4)
ACEi and ARB	7 (1.9)	6 (2.7)	1 (0.7)	0 (0)	0 (0)	1 (1.4)
β-blockers	260 (69.3)	158 (71.8)	95 (65.1)	55 (64.7)	7 (77.8)	47 (67.1)
MRAs (including spironolactone)	260 (69.3)	150 (68.2)	103 (70.6)	60 (70.6)	7 (77.8)	50 (71.4)
Diuretics other than MRAs	259 (69.1)	142 (64.6)	111 (76.0)	67 (78.8)	6 (66.7)	50 (71.4)
Furosemide	239 (63.7)	134 (60.9)	99 (67.8)	60 (70.6)	6 (66.7)	45 (64.3)
Aspirin	156 (41.6)	90 (40.9)	60 (41.1)	30 (35.3)	6 (66.7)	36 (51.4)
Digoxin	138 (36.8)	78 (35.5)	58 (39.7)	40 (47.1)	2 (22.2)	20 (28.6)
Oral anticoagulants	40 (10.7)	30 (13.6)	10 (6.9)	8 (9.4)	NA	2 (2.9)
Blood pressure, mm Hg†, mean±SD						
Systolic	100.6±12.8	103.0±12.1	97.0±13.2	95.6±12.4	98.6±9.8	99.0±13.5
Diastolic	60.4±10.5	62.0±9.6	58.3±11.4	57.6±10.0	56.4±10.9	59.0±12.7
Heart rate, bpm, mean±SD	94.9±22.0	84.3±16.1	108.9±19.9	100.1±17.7	129.6±18.0	122.2±16.4

Data collected at randomization unless specified otherwise. ACEi indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; bpm, beats per minute; HF, heart failure; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NA, not available; and NYHA, New York Heart Association.

*N=374.

†Normal blood pressure: <90th percentile for children aged 1 to 13 years and <120/<80 mm Hg for children aged ≥13 years.[20]

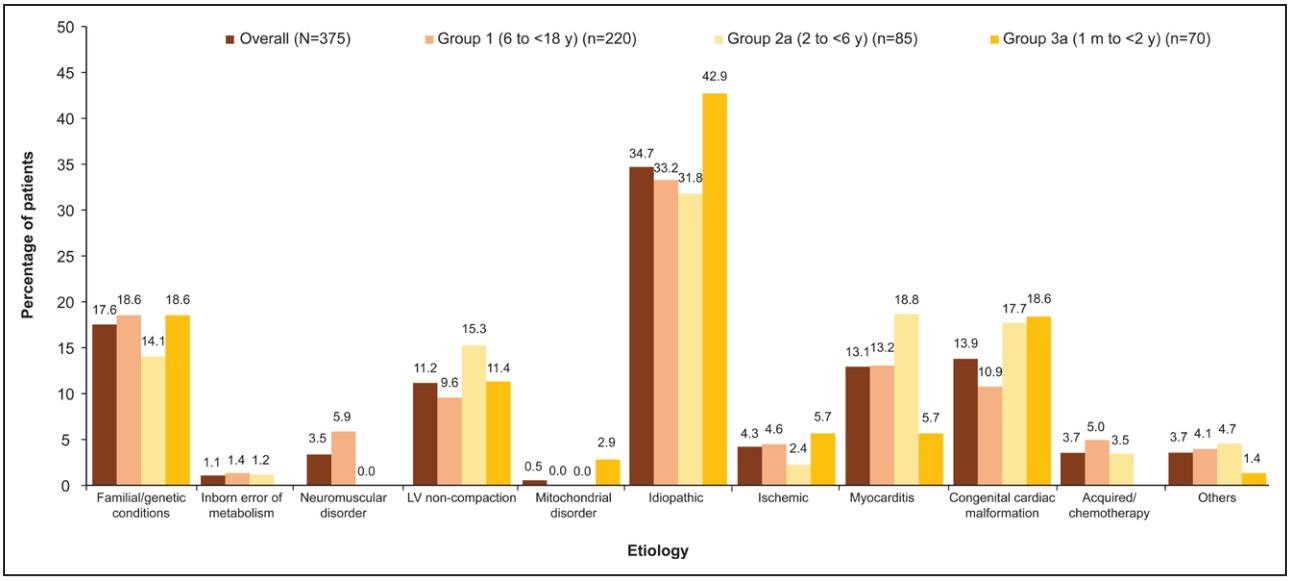

Figure 2. Heart failure etiology.
LV indicates left ventricular.

the PANORAMA-HF study are consistent with those reported in studies involving pediatric patients with cardiovascular disease.[21,25]

The innovative design of PANORAMA-HF consists of 2 seamless parts, with Part 1 patients in Group 1 enrolled first to determine the dose based on pharmacokinetics results, followed by patients in Group 2 and Group 3. The evaluation of pharmacokinetics/pharmacodynamics in Part 1 in a staggered manner based on age allowed for the safe enrollment of younger children and determination of a target dose for a predefined age group, which was subsequently used in Part 2. In Part 2, eligible patients were stratified by the modified age group, adapting the approach to the recruitment challenges and to International Council for Harmonisation predefined age groups,[26] also allowing a better analysis of Group 3 data in the long-term portion of the Part 2 study, as patients would better stay within the same age group from baseline to end of study. This approach is statistically more appropriate because it allows the collection of data over a broader age range, that is, 1 month to <2 years, also reducing the numerical imbalance in the age groups resulting from the original design.

Prior to entry into PANORAMA-HF, >88% of patients in the current study were on an ACEi, while only a small proportion were on an angiotensin receptor blocker (2.1%). Sixty-nine percent of the patients were on β-blockers, mineralocorticoid receptor antagonists (including spironolactone), or diuretics (ie, furosemide). Although there is a lack of strong evidence from prospective randomized studies in children, clinical experience has resulted in the widespread adoption of ACEi as first-line therapy, while many consider β-blockers as second-line therapy in pediatric patients with HF.[10] In contrast, the most recent adult HF guidelines from the European Society of Cardiology now recommend the use of sacubitril/valsartan, an angiotensin receptor neprilysin inhibitor, as a replacement for an ACEi in patients with HFrEF to reduce the risk of hospitalization and death.[27] Other groups are now recommending a direct-to-angiotensin receptor neprilysin inhibitor approach when instituting HF medications.[28]

Table 2. Patient Global Impression of Severity

Score	Overall (N=375)	Group 1 (6 to <18 y; n=220)	Group 2 (1 to <6 y; n=146)	Group 2a (2 to < 6 y; n=85)	Group 3 (1 month to <1 y; n=9)	Group 3a (1 month to <2 y; n=70)
C1	153 (41.8)	83 (38.6)	65 (45.8)	41 (50.6)	5 (55.6)	29 (41.4)
C2	131 (35.8)	77 (35.8)	52 (36.6)	28 (34.6)	2 (22.2)	26 (37.1)
C3	65 (17.8)	41 (19.1)	22 (15.5)	11 (13.6)	2 (22.2)	13 (18.6)
C4	14 (3.8)	12 (5.6)	2 (1.4)	0 (0)	0 (0)	2 (2.9)
C5	3 (0.8)	2 (0.9)	1 (0.7)	1 (1.2)	0 (0)	0 (0)
Total	366 (100)	215 (100)	142 (100)	81 (100)	9 (100)	70 (100)

Data collected at randomization and presented as n (%). PGIS symptom score: C1, none; C2, mild; C3, moderate; C4, severe; C5, very severe. PGIS indicates Patient Global Impression of Severity.

Table 3. Patient-Reported Pediatric Quality of Life Scores (PedsQL Physical Functioning Domain)

	Overall (N=278)	Group 1 (6 to <18 y; n=268)	Group 2a (2 to <6 y; n=10)
Total summary score*, n (mean±SD)	217 (71.2±17.1)	208 (70.9±17.3)	9 (77.9±9.5)

Data collected at randomization. Mean±SD PedsQL scores (self-reported) for physical health domain in healthy children are 86.2±13.2 in children aged 5 to 7 years, 88.0±13.8 in children aged 8 to 12 years, and 88.8±13.2 in adolescents aged 13 to 18 years.[21,22]

*Among the 375 patients overall, only 278 patients responded to the PedsQL score, because inputs were received only from those patients aged 5 years and older. For those patients aged between 1 month and 4 years at randomization, only parental input was collected, and it is reported in Table 4. Thus, among Group 2a patients (2 to <6 years), only those aged 5 years at randomization could have potentially contributed to the patient PedsQL data.

Pharmacotherapy for the management of pediatric patients with HF is based mainly on core principles of adult HF therapy and consensus guidelines, which in turn are largely derived from adult HF clinical trials. The prospective treatment trials conducted to date in pediatric HF populations are small and therefore difficult to interpret. Moreover, as compared to adults, the manifestation of HF is diverse in the pediatric population, and there exists age-dependent variability in pharmacokinetics and pharmacodynamics of the drugs from birth to adolescence. Hence, pharmacotherapies for management of HF that have been proven effective in adults might not necessarily have similar benefits in pediatric patients with HF.[29]

Currently, only a few trials have evaluated the efficacy and safety of different pharmacotherapeutic agents in pediatric patients with HF (Table 5). The Pediatric Carvedilol study was the first large randomized controlled trial that evaluated the effects of a pharmacotherapeutic agent in a pediatric HF population. It included 161 children and adolescents (aged 8 months to 14 years) with symptomatic systemic ventricular systolic dysfunction.[18] Carvedilol, a nonselective β- and α-blocker, did not significantly improve the primary composite end point of clinical HF outcomes in children and adolescents with chronic HF, despite showing benefits in adult populations. However, in a prespecified subgroup analysis, a significant interaction (P=0.02) was observed between ventricular morphology and carvedilol. The findings suggest that carvedilol may potentially confer a differential effect (beneficial trend) in those with a systemic left ventricle compared with those with a systemic ventricle not of LV morphology (nonbeneficial trend).[17,18] The primary results of the Pediatric Carvedilol study are in contrast to the findings in adult patients with HF, where carvedilol has been shown to improve survival and symptoms of HF. The differences in the etiology of HF in adults (primary ischemic heart disease) compared with children and adolescents (congenital heart disease and dilated cardiomyopathy) as well as the heterogeneity of the pediatric patient population included in the Pediatric Carvedilol trial may well have impacted the efficacy of carvedilol in this study.[17,18]

Both PANORAMA-HF and the Pediatric Carvedilol study use a form of composite clinical end point as the primary end point; the global rank end point in PANORAMA-HF is chosen in order to have a more robust way of differentiating the 2 treatment arms.[30] However, unlike the Pediatric Carvedilol study, the PANORAMA-HF study excludes patients with a single-ventricle physiology and enrolled a more homogeneous population that more closely mimics adult HF study populations in which sacubitril/valsartan has been shown to be more effective than enalapril in improving symptoms and reducing mortality and HF hospitalization.[17]

A double-blind, placebo-controlled, randomized, Phase II/III study by Bonnet et al[28] determined the effect of ivabradine in children (n=116; aged 6 months to 18 years) with dilated cardiomyopathy and symptomatic chronic HF. The cause for the dilated cardiomyopathy was idiopathic in 56% of the patients, postviral myocarditis in 22%, LV noncompaction in 19%, ischemic in 2%, and postanthracycline induced in 2% of the patients. Eligible patients were stratified into 3 subgroups (age 6–12 months; >1 to <3 years; and 3–18 years) and randomized in a 2:1 ratio to ivabradine or placebo. Among the children receiving ivabradine, 70% achieved the primary end point (a ≥20% decrease in heart rate from baseline without inducing bradycardia or its symptoms). Treatment with ivabradine was associated with a significant improvement in the secondary end point of left ventricular ejection fraction (P=0.024) at 12 months. Other secondary end points such as clinical HF status (ie, NYHA/Ross class) and quality of life demonstrated a trend toward improvement at 12 months in the ivabradine arm. The beneficial effects of ivabradine in this study were broadly consistent with those demonstrated in adults with HF.[31]

There have also been attempts to identify treatments to reduce or prevent HF in pediatric patients with

Table 4. Parent-Reported Pediatric Quality of Life Scores (PedsQL Physical Functioning Domain)

	Overall (N=375)	Group 1 (6 to <18 y; n=220)	Group 2 (1 to <6 y; n=146)	Group 2a (2 to <6 y; n=85)	Group 3 (1 month to <1 y; n=9)	Group 3a (1 month to <2 y; n=70)
Total summary score, n (mean±SD)	362 (71.6±18.3)	212 (67.2±17.8)	141 (77.2±17.4)	80 (76.7±17.7)	9 (87.6±9.1)	70 (79.2±16.6)

Data collected at randomization. Mean±SD PedsQL scores (proxy reported) for physical health domain in healthy children are 89.8±15.4 in toddlers aged 2 to 4 years, 80.1±20.9 in children aged 5 to 7 years, 83.0±20.6 in children aged 8 to 12 years, and 83.9±20.1 in adolescents aged 13 to 18 years.[21,22] PedsQL indicates Pediatric Quality of Life Inventory.

Table 5. Comparison of the Baseline Characteristics of Pediatric HF Studies

Characteristic	PANORAMA-HF study	Pediatric Carvedilol study[18]			Ivabradine study[23]	Pediatric Heart Network study[24]	
Country	31 countries	United States			16 countries	United States and Canada	
Study sites	112	26			47	10	
Number of patients	375	161			116	230	
Treatment arm	Sacubitril/valsartan vs enalapril (double-blind period)	Placebo	Low-dose carvedilol	High-dose carvedilol	Ivabradine vs placebo	Enalapril	Placebo
Enrollment age, mean±SD	8.13±5.6 y	1.8 (0.8–6.1)* y	3.6 (1.2–12.8)* y	2.8 (1.08–10.2)* y	5.8±4.9 y	20.1±8.9 d	20.7±9.1d
Male, %	48.5	54.5	52.8	47.2	55	65	76
Systemic ventricle dysfunction, %	100	100	100	100	100	17	22
Systemic ventricle EF (%), mean±SD	32.2±7.7‡	25.1±9.0	28.1±7.0	27.5±6.7	33±8	57.9±9.8 (systemic ventricle)	56.6±10.2 (systemic ventricle)
NYHA/Ross HF classification, %							
I	15.7	0	0	0	NR	NR	NR
II	69.3	69.1	67.9	77.4	80	NR	NR
III	14.4	30.9	30.2	20.8	16	NR	NR
IV	0.5	0	1.9	1.9	4	NR	NR
BNP, pg/mL, median (IQR)†	NA	116 (45–294)	91 (19–270)	123 (20–497)	NR	79 (30–182)	84 (36–196)
Diagnosis	HF with systemic left ventricular systolic dysfunction	Chronic symptomatic HF due to systemic ventricular systolic dysfunction			Dilated cardiomyopathy and symptomatic chronic HF	Single-ventricle physiology	
Primary end point	Global rank end point through 52 wks of treatment	Composite measure of HF outcomes (worsened, improved, or unchanged HF)			≥20% reduction of the baseline resting heart rate without bradycardia or symptoms of bradycardia	Weight-for-age *Z*-score at 14 mo	

BNP indicates B-type natriuretic peptide; EF, ejection fraction; HF, heart failure; IQR, interquartile range; NA, not applicable; NR, not reported; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; and 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.

*Data presented as median (IQR).

†NT-proBNP data were collected in the Ivabradine study, and the overall geometric mean value was 484 pg/mL.

‡Mean±SD of LV shortening fraction was 16.2±4.2%.

single-ventricle physiology. The Pediatric Heart Network conducted a double-blind, placebo-controlled, randomized study to determine whether the ACEi enalapril preserves ventricular function and improves somatic growth and outcomes in 230 infants with single-ventricle physiology. The study found that in infants with single-ventricle physiology, enalapril does not confer a beneficial effect on weight-for-age at 14 months, height-for-age, head circumference-for-age, ventricular structure and function, or clinical HF, and therefore has no favorable effect on ventricular function, somatic growth, or overall neurodevelopmental and clinical outcomes. These findings, along with the results of the Pediatric Carvedilol study, emphasize the need for development of more specific-targeted therapy in this patient population with single-ventricle physiology and in general that treatment of pediatric HF is dependent on the physiology of HF itself.[24]

The current study reports the baseline characteristics of patients in Part 2 of the PANORAMA-HF study and provides insights into the clinical characteristics of pediatric patients with HF. More importantly, our study recruited a relatively homogenous pediatric population that more closely resembles adult patients with HF. Results from the PANORAMA-HF study will help determine whether sacubitril/valsartan offers greater clinical benefit compared to enalapril in pediatric patients with HF. Future prospective studies involving a homogenous pediatric population are warranted to provide a strong evidence-base for the management of pediatric HF.

Limitations

The original age group definition selected for the PANORAMA-HF study would have resulted in an imbalance within the groups; however, with the modified age group stratification this imbalance is resolved. Also, in this study, there were more pediatric patients with NYHA/Ross class I and II HF compared with adult

studies, which may make it difficult to compare the efficacy of sacubitril/valsartan between this pediatric and other similar adult trials.

Conclusions

In this prospective study, the largest of its kind in pediatric patients with HF, cardiomyopathy due to idiopathic, familial/genetic causes, and LV noncompaction accounted for >60% of cases; HF secondary to congenital cardiac malformations (13.9%) and myocarditis (13.1%) were the next largest groups. All patients had a biventricular physiology, and the systemic ventricle was of LV morphology. There was no difference between primary HF etiology among the 3 age groups. Only a small proportion of HF was due to ischemic and acquired conditions, in contrast to adult studies where they are the most common causes. Most participants had NYHA/Ross class II HF and were on prior ACEi therapy.

ARTICLE INFORMATION

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Supplemental Material

Tables S1–S3

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