PANORAMA-HF Trial

Written by: Robert E. Shaddy, MD

Based on the results of the landmark PARADIGM-HF trial in adults (1), and the subsequent approval of the neprilysin/angiotensin receptor inhibitor, sacubitril/valsartan, for the treatment of adults with heart failure with reduced ejection fraction (HFrEF), a group of pediatric cardiologists worked with Novartis and the US Food and Drug Administration (FDA) and the European Medicines Agency to develop a study for comparing sacubitril/valsartan to enalapril in children. The result of these discussions was the launching of the PANORAMA-HF trial in children (2). Neprilysin is a nearly ubiquitous enzyme in the human body which has multiple effects. One of the primary cardiovascular effects of neprilysin is to break down natriuretic peptides. As a neprilysin inhibitor, sacubritil inhibits the breakdown of natriuretic peptides, thus resulting in increased circulating levels of the natriuretic peptides and subsequent increased vasodilation and diuresis in addition to other hemodynamic effects. It has been known for some time that neprilysin inhibition also results in activation of the renin-angiotensin-aldosterone system (RAAS), an unwanted effect in heart failure. Previous attempts to develop a combination drug that could block both the RAAS and to inhibit neprilysin were unsuccessful. For example, attempts to combine an angiotensin-converting enzyme inhibitor with a neprilysin inhibitor resulted in an unacceptably high incidence of angioedema (3). Thus, efforts toward developing a neprilysin inhibitor, sacubritil, combined with an angiotensin-receptor blocker, valsartan, resulted in the current medication of sacubitril/valsartan.

The PANORAMA-HF trial was launched several years ago with the intention of determining if sacubitril/valsartan was superior to enalapril in the treatment of HFrEF in children whose systemic ventricle is a morphologic left ventricle. This study has a unique study design in that it is a two-part study. The first part of the study is the pharmacokinetic/pharmacodynamic (PK/PD) part of the trial where two different doses of sacubitril-valsartan were administered to children in three different age groups: 6 years to <18 years of age, one year to < six years of age, an one month to < one year of age. Each PK/PD portion of the study was done sequentially such that the older children were enrolled first in part one of PANORAMA-HF. Once the PK/PD data was obtained and analyzed in each age group and the target dose for part 2 of the study confirmed, part 2 of the trial was opened up for those patients in that age group, initially for children 6 years to <18 years of age. Simultaneously, part one was opened up for the next youngest age group. Subsequent age groups were then enrolled into part one and then part 2 of the trial as described above. The trial is also unique in that it uses a unique study endpoint for a pediatric heart failure trial. This end point is called a global rank end point and has previously been proposed for acute heart failure studies (4). In working with the FDA, PANORAMA-HF adopted this end point and devised a ranking of outcomes. For the global rank endpoint used in this study, patients are classified into 5 ordinal categories and ranked from worst to best based on clinical events such as death, urgent listing for heart transplant, mechanical life support, worsening heart failure, measures of functional assessment in NYHA/Ross classification, and patient-reported outcomes. The patient-reported outcomes for the primary endpoint include the Patient Global Impression of Severity (PGIS) and the Pediatric Quality of Life Inventory (PedsQL; physical functioning sub-group of questions) (2).

PANORAMA-HF Trial

Written by: Robert E. Shaddy, MD

This study was opened up to children in over 130 centers in more than 30 countries worldwide. The study was complicated by the coronavirus pandemic which made enrollment in PANORAMA-HF much more difficult than it was before the pandemic. However, we were able to persist through this and patient enrollment is complete. At the current time, we are waiting for patients to complete the one-year enrollment period for part 2. There was an unusual occurrence in the middle of this trial (October 2019) whereby the FDA approved the use of sacubritil/valsartan for pediatric patients with symptomatic heart failure with systemic left ventricular systolic dysfunction, one year of age and older. This was based upon the analysis of 110 subjects in the PANORAMA-HF trial, where they analyzed NT-proBNP levels at baseline and 12 weeks into the study. Based on this data, the FDA was able to show comparable reductions in NT-proBNP between enalapril and sacubitril/valsartan. These changes paralleled what was seen in the PARADIGM-HF trial and therefore was felt to be adequate data to infer that sacubritil/valsartan could be approved for use in children ≥1 year.

References

1. *McMurray JJ, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure. The New England journal of medicine. 2014;371(11):993-1004.*
2. *Shaddy R, Canter C, Halnon N, Kochilas L, Rossano J, Bonnet D, 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). American heart journal. 2017;193:23-34.*
3. *Packer M, Califf RM, Konstam MA, Krum H, McMurray JJ, Rouleau JL, et al. Comparison of omapatrilat and enalapril in patients with chronic heart failure: the Omapatrilat Versus Enalapril Randomized Trial of Utility in Reducing Events (OVERTURE). Circulation. 2002;106(8):920-6.*
4. *Felker G. Michael and Maisel Alan S. 2010. "A Global Rank End Point for Clinical Trials in Acute Heart Failure." Circulation: Heart Failure 3 (5): 643–46.*