Leveraging adult data to support a biomarker extrapolation: Entresto®

Ron Portman, Head of Pediatric Center of Excellence
Simon Wandel, Senior Director Biostatistics
Guenther Mueller-Velten, Global Biostatistics Development Unit Head, CRM
ADEPT 7, 1 September 2021


Ron Portman

This material may include data/information on investigational uses of compounds/drugs that have not yet been approved by regulatory authorities

NOVARTIS | Reimagining Medicine

Agenda

Entresto® (Sacubitril/Valsartan) in adult HF

Pediatric HF

Sacubitril/Valsartan pediatric program

Extrapolation approach

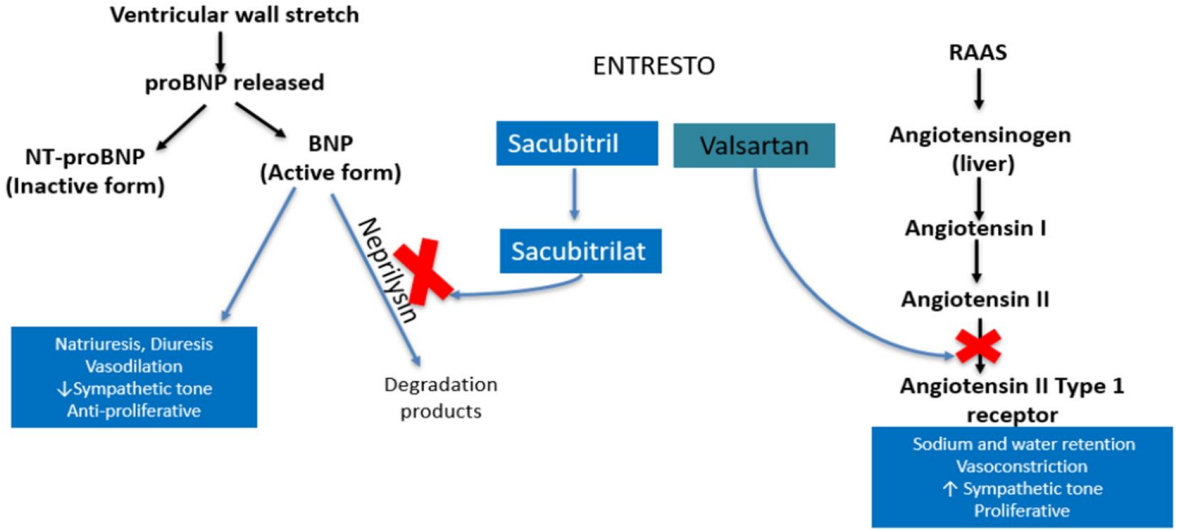
- Disease similarity (DCM)
- NT-ProBNP as bridging biomarker
- Results

Impact of extrapolation

Summary and conclusions

Entresto® in adult heart failure (HF)

- Entresto® (Sacubitril/Valsartan, oral 200mg BID)
  - First-in-class inhibitor of angiotensin II + neprilysin (ARNi)
  - Approved in 2015 for adults with chronic heart failure and reduced ejection fraction (HFrEF)
- PARADIGM-HF (N=8442) stopped early due to overwhelming efficacy
  - CV death or HFH (primary endpoint): 20% RRR compared to enalapril.

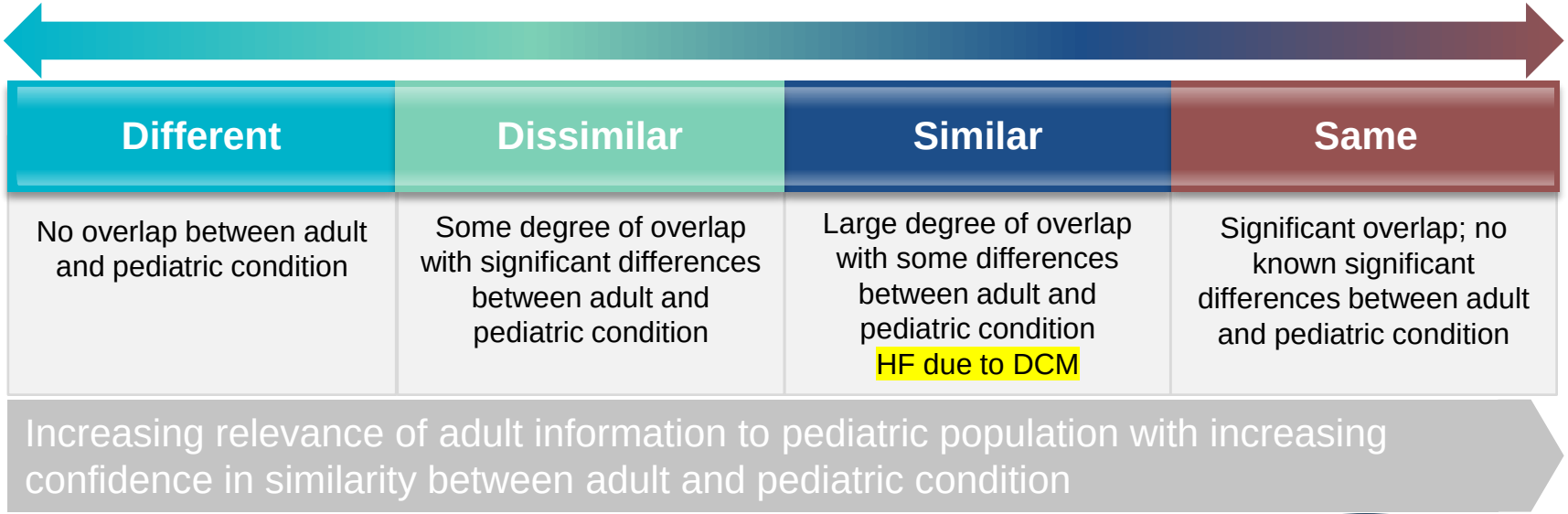


NOVARTIS | Reimagining Medicine

Pediatric CV drug development landscape and unmet medical need

- **Pediatric HF is a consequence for multiple primary and secondary cardiovascular diseases in childhood, including patients with systemic left ventricular systolic dysfunction and dilated cardiomyopathy (DCM)**
  - Characterized by increased morbidity and mortality, frequent hospitalization, extensive utilization of medical care, and poor quality of life
- **Significant unmet medical need exists for the treatment of pediatric HF patients**
  - Only prior pediatric HF pharmaceutical trial was conducted with carvedilol
  - Given lack of evidence-based pharmacologic treatment, off-label use of adult HFrEF medications is the standard of care
- **Multiple stakeholders recognize the current pediatric cardiovascular drug development landscape is inadequate and improvements are needed**

Extrapolation of Efficacy:
Disease/response "similarity" is a continuum



Ref: Lynne Yao, ACRDS Webinar Series, September 30, 2020

Road to Extrapolation – an iterative process

2015: pediatric HF etiology, presentation, clinical course understood to be *different* from adult HF → Waiver

Novartis chose to ask for written request

March 2017: FDA grants written request for Pediatric HF

Nov 2016
Fully powered PANORAMA-HF starts

Oct 2017
FDA Pediatric HF Workshop Disease Similarity with adult DCM

Novartis presented PANORAMA-HF

Aug 2018 FDA meeting
Full extrapolation of adolescents not supported

Discussed NT-ProBNP as potential bridging marker

Nov 2018 FDA meeting
Evidence for NT-ProBNP as Bridging biomarker

Jan 2019 FDA meeting
Rejected Bayesian

Accepted to amend WR – effect on bridging marker with adequate power

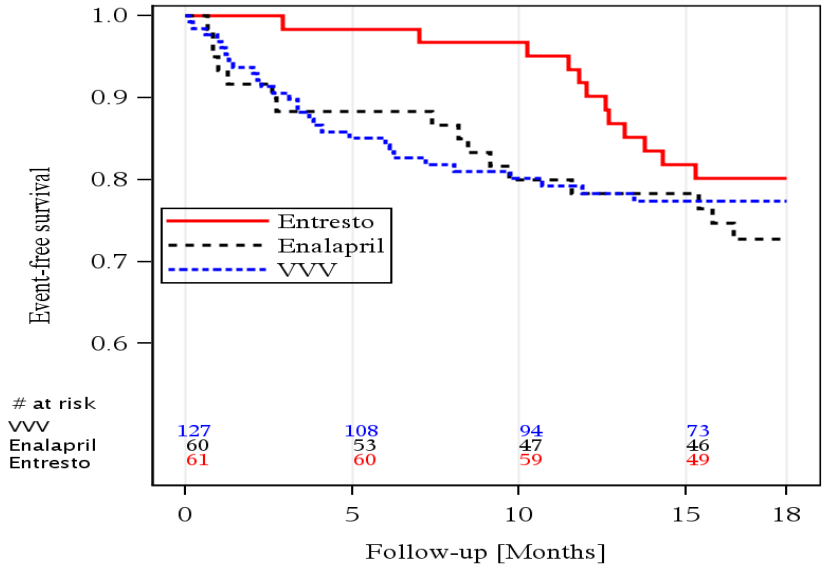
Filing on April 1st 2019
Approval on October 1st 2019

Simon Wandel

NOVARTIS | Reimagining Medicine

Disease progression: Paradigm DCM sub-population (≤ 40 years old) and VVV study

- Ventricular Volume Variability (**VVV**) Study of the Pediatric Heart Network (https://www.pediatricheartnetwork.org/studies/ventricular-volume-variability/)[#]
  - chronic DCM patients 0 - 22 years **Disease progression similarity**

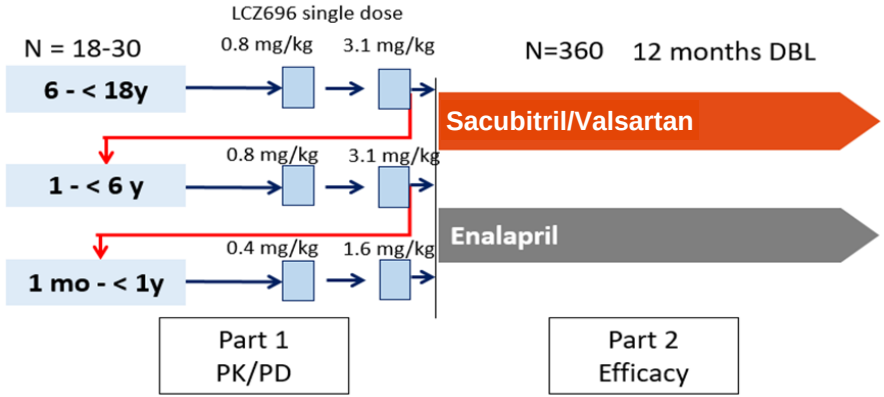


[#] *The NIH/NHLBI Pediatric Heart Network Ventricular Volume Variability Study dataset was used in preparation of this work. Data were downloaded from http://pediatricheartnetwork.org/ForResearchers/PHNPublicUseDatasets.aspx on 03/09/2019*

NOVARTIS | Reimagining Medicine

PANORAMA-HF Pediatric Study Design

Largest HF study in Children with three age groups (N=360)



Ongoing study
Started in Nov 2016

Seamless study design

- **Part 1** – PK/PD/Safety with single dose administration of two different dose levels in three age cohorts (**staggered** enrollment of age groups) primary objective is to **determine/confirm dose** for Part 2
- ***Part 2*** *employs a* ***novel global rank primary endpoint :*** 5 categories – includes death, urgent heart transplant listing, mechanical life support, worsening HF, measures of function status and QoL domains

Pharmacodynamic biomarker to predict and bridge efficacy across populations

NT-proBNP Change from Baseline

- N-terminal prohormone of brain natriuretic peptide (NT-ProBNP) used in clinical practice for disease severity, easy to measure, has been known to be a strong (actually the strongest) independent prognostic factor for outcomes in CHF, but is not an established surrogate
- The diagnostic and prognostic value of natriuretic peptides in the acute and chronic setting of adult heart failure is well recognized for the management of Heart Failure with reduced ejection fraction by the US ACC/AHA/HFSA and ESC guidelines
- Data on the use of Entresto® in adult HFrEF patients from PARADIGM-HF (N=2,080 in biomarker substudy) and data from other studies support Δ NT-proBNP as a **bridging biomarker** of treatment effect on outcome (time first event of CV death or HF hospitalization)
- NT-ProBNP is measured in PANORAMA (early read-out at Week 12)

Guenther Mueller-Velten

Biomarker (*NT-proBNP Change from Baseline*) to predict and bridge efficacy (Time to first event of CV death or HFH) across populations – Prentice criteria[1]

1	2	3	4
Treatment has a significant impact on the true clinical endpoint	Treatment has a significant impact on the biomarker	Biomarker significantly associated with true clinical endpoint	The effect of treatment on true clinical endpoint is explained by the biomarker
• Entresto® reduced the hazard rate of the primary endpoint by 20% in PARADIGM-HF (McMurray et al, 2014)	• Entresto® NT-proBNP ratio to baseline 25% lower vs enalapril in PARADIGM-HF	• **Adults:** PARADIGM-HF (Zile et al, 2016), ValHeFT (Masson et al, 2008) and GUIDE IT (Januzzi et al, 2018) • **Pediatrics:** Changes in NT-proBNP are associated with markers of left ventricular systolic function and heart failure outcomes in pediatric patients (den Boer et al, 2016; Rusconi et al, 2010)	• **85.5%** of treatment effect for CVD/HFH explained by change in NT-proBNP over time; **82.5%** by change in NT-ProBNP at 1 month

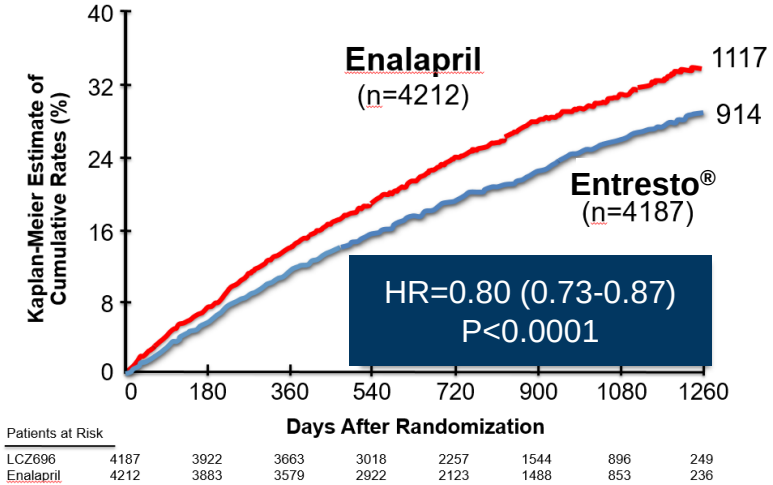
[1] Prentice RL (1989) Surrogate endpoints in clinical trials: definition and operational criteria. *Statistics in Medicine* 8:431–40
See also FREEDMAN et al (1992). Statistics in Medicine 11, 167–178 and FLEMING et al (1994). Statistics in Medicine 13, 955–968.

Entresto® in Adult Heart Failure (HF)

1 CV death or HFH (primary endpoint)

PARADIGM-HF (N=8,399):
HR=0.80 (0.73-0.87), p<0.001

PARADIGM-HF DCM (N=1,810):
HR=0.75 (0.62,0.91), p=0.004



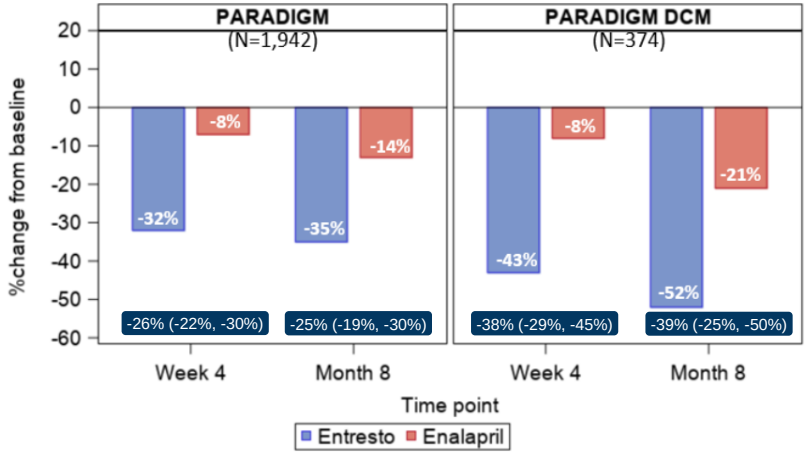
2 NT-ProBNP ratio to baseline (V2/2a)

PARADIGM-HF (N=1,942)

- Greater NT-proBNP reduction (approx. 25%) in Entresto® compared to enalapril

PARADIGM-HF DCM (N=374)

- Greater NT-proBNP reduction (approx. 38%) in Entresto® compared to enalapril

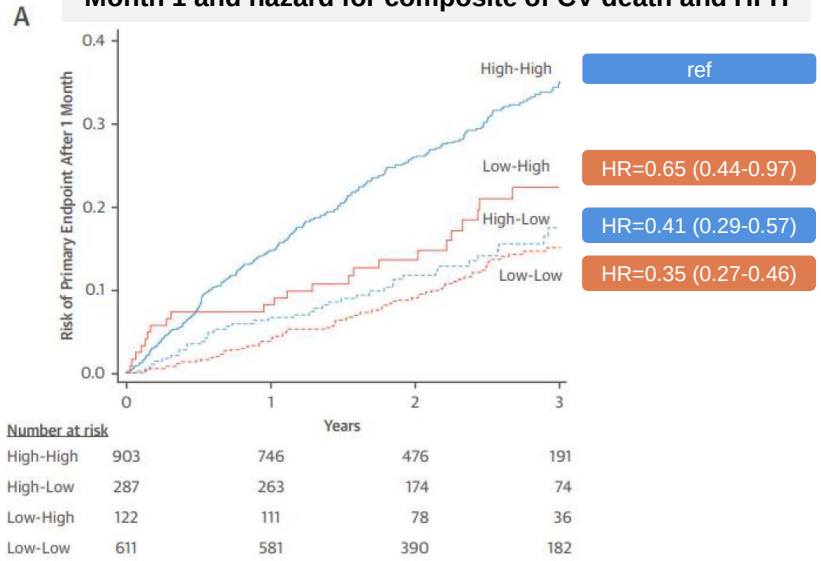


Dark blue shapes represent relative effect size (Entresto® vs enalapril) with 95% CI

3 NT-ProBNP change significantly associated with time to first event of CV death or HFH

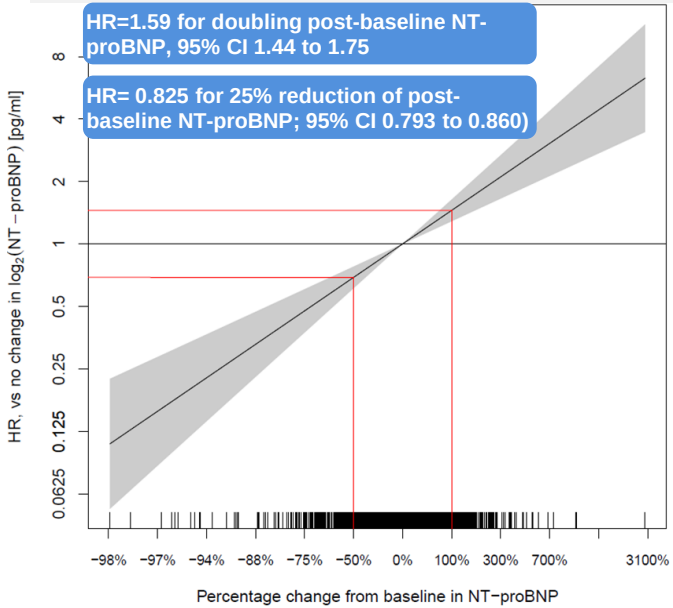
- Biomarker substudy of PARADIGM-HF (N=2,080)
  - Change from baseline in NT-proBNP when adjusted for baseline NT-proBNP and treatment was significantly associated with the risk of the true clinical endpoint (first event of CV death or HF hospitalization)

Categorical* relationship between ΔNT-proBNP at Month 1 and hazard for composite of CV death and HFH



* NT-proBNP treshold ≤1,000 (low) vs >1,000 pg/ml (high) (Zile et al, 2016)

Linear relationship between ΔNT-proBNP at Month 1 and hazard for composite of CV death and HFH



NOVARTIS | Reimagining Medicine

4 More than 80% of treatment effect on first primary endpoint captured by NT-proBNP change at month 1 on top of baseline NT-proBNP – PARADIGM-HF biomarker substudy

Explanatory Variable	N	n	**Model 1***		**Model 2***		**Proportion (%) of treatment effect explained by change from baseline to Month 1 in log_2 (NT-proBNP) (95% CI)**
			HR (95%CI)	P-value	HR (95% CI)	P-value	
Entresto	1007	197	0.81 (0.67, 0.98)	0.0302	0.96 (0.79, 1.18)	0.7169	**82.50** (1.26, 163.74)
Enalapril	983	230					
Change from baseline in log_2(NT-proBNP) at Month 1					1.45 (1.29,1.63)	<0.0001	
Baseline log_2(NT-proBNP)			1.49 (1.38, 1.60)	<0.0001	1.60 (1.47,1.73)	<0.0001	

Treatment effect disappears after inclusion of change from baseline in NT-ProBNP in the model

The analysis is performed using Cox regression.
- *Model 1 contains treatment, region and baseline log_2(NT-proBNP) as explanatory variables and Model 2 contains treatment, region, baseline log_2(NT-proBNP) and change from baseline in log(NT-proBNP) at Month 1 as explanatory variables.

Extrapolation based on early biomarker readout in PANORAMA-HF study

- A study protocol amendment was initiated to introduce an interim analysis to evaluate the effect of Sacubitril/Valsartan on NT-ProBNP at Week 12 in at least 100 pediatric patients with age ≥ 1 year
  - change in NT-proBNP as primary endpoint to for the purpose of extrapolation
- The submission interim analysis included results of 110 patients (55 per treatment group) evaluated for efficacy and 143 patients (73 in the Sacubitril/Valsartan group and 70 in the enalapril group) evaluated for safety
- PANORAMA-HF study will be completed as agreed with FDA and EMA

Extrapolation

PANORAMA-HF 12-weeks interim analysis PD results and comparison to adult HFrEF DCM

Change from baseline (Ratio to BL) in NT-proBNP

- A decrease in NT-proBNP was observed in both the Sacubitril/Valsartan and enalapril groups at Week 12
- While the between-group difference was not statistically significant (p=0.1466), the within-group reductions for Sacubitril/Valsartan were similar to what was seen in adults

		Sacubitril/Valsartan		Enalapril		Sacubitril/Valsartan over Enalapril	
Study	**Time point**	**n**	**Geo. Mean (95% CI)**	**n**	**Geo. Mean (95% CI)**	**Geo. Mean Ratio**	**2-sided p-value**
PANORAMA-HF (1 - <18 yrs)	W 12	54	0.565 (0.480, 0.665) -44%	54	0.670 (0.569, 0.788)	0.844 (0.671, 1.061) -33%	0.1466
PARADIGM-HF (adult DCM)	W 4	196	0.57 (0.52, 0.62) -43%	188	0.92 (0.84, 1.00)		
	M 8	178	0.48 (0.42, 0.56) -52%	167	0.79 (0.68, 0.91)		

Estimates based on ANCOVA model including age group, NYHA/ROSS class group at randomization, region and treatment group as fixed-effect factors and baseline log(NT-proBNP) and age-group-by-baseline-log(NT-proBNP) as covariates.

Impact of extrapolation

- Entresto® first approved treatment for children (age ≥ 1 year) with HF in the US!

- **Approximately 3 years earlier label update to describe pediatric use**

  1.2 Pediatric Heart Failure
  ENTRESTO is indicated for the treatment of symptomatic heart failure with systemic left ventricular systolic dysfunction in pediatric patients aged one year and older. ENTRESTO reduces NT-proBNP and is expected to improve cardiovascular outcomes.

Summary and Conclusion

- **Significant unmet medical** need exists for the treatment of **pediatric HF patients**
- **Disease similarity** between pediatric HF patients and adult HFrEF patients with DCM
- Empirical evidence was provided to support the use of **NT-proBNP as a bridging marker for clinical efficacy of Entresto®** from adults to a pediatric HF population
- As a result, a **label update** to for the treatment of pediatric HF patients could be obtained **earlier** based on **extrapolation** and inclusion of relevant pediatric PK, dosing, PD and safety information
- **PANORAMA-HF study** is fully enrolled and **will be completed** as agreed with FDA and EMA

Thank you

NOVARTIS | Reimagining Medicine

References

- den Boer SL, Rizopoulos D, du Marchie Sarvaas GJ, et al (2016) Usefulness of Serial N-terminal Pro-B-type Natriuretic Peptide Measurements to Predict Cardiac Death in Acute and Chronic Dilated Cardiomyopathy in Children. Am J Cardiol; 118(11):1723-9
- Fleming et al (1994). Surrogate and auxiliary endpoints in clinical trials, with potential applications in cancer and AIDS research. Statistics in Medicine 13, 955–968
- Freedman et al (1992). Statistical validation of intermediate endpoints for chronic diseases. Statistics in Medicine 11, 167–178
- Januzzi, J, Heart Failure Society of America (2018) (HFSA) 22nd Annual Scientific Meeting. Late Breaking Insights from Trials and Novel Investigations: The Importance of Natriuretic Peptide Response to Predict Outcomes in Chronic HF with Reduced Ejection Fraction: Insights from the GUIDE-IT Clinical Trial. Presented September 17, 2018. Available from : https://www.medscape.com/viewarticle/902580#vp_1 (Accessed 25 March 2019).
- Masson S, Latini R, Anand IS, et al (2008) Prognostic value of changes in N-terminal pro-brain natriuretic peptide in Val-HeFT (Valsartan Heart Failure Trial). J Am Coll Cardiol; 52(12):997-1003
- McMurray et al (2014). Angiotensin–Neprilysin Inhibition versus Enalapril in Heart Failure. N Engl J Med 371:993-1004
- Prentice RL (1989) Surrogate endpoints in clinical trials: definition and operational criteria. Stat Med 8 (4):431-40
- Rusconi PG, Ludwig DA, Ratnasamy C, et al (2010) Serial measurements of serum NT-proBNP as markers of left ventricular systolic function and remodeling in children with heart failure. Am Heart J; 160(4):776-83
- Zile MR, Claggett BL, Prescott MF, et al (2016) Prognostic Implications of Changes in N-Terminal Pro-B-Type Natriuretic Peptide in Patients With Heart Failure, J Am Coll Cardiol; 68(22):2425-2436