LCZ696/Entresto®
Pediatric patients with heart failure

CLCZ696B2319 (PANORAMA)

AMNOG Analysis

Efficacy incl. figures

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Table 6.1 All cause death (FAS), time to event analysis

	Treatment Groups		Comparison	
All cause death (FAS)	**LCZ696 (N=182)**	**Enalapril (N=184)**	**HR [95% CI] p-value**	**Logrank test p-value**
All cause death (adjudicated)				
N'	182	184		
Patients with event, n (%)	7 (3.8)	12 (6.5)		
Median time to event (in weeks) [95% CI]	N.E.	N.E.		
Patients with event at end of study, % KM estimate [95% CI]	3.9 [1.1; 6.7]	9.9 [1.9; 17.8]	0.56 [0.22; 1.43] 0.225	0.221
All cause death (investigator reported)				
N'	182	184		
Patients with event, n (%)	7 (3.8)	12 (6.5)		
Median time to event (in weeks) [95% CI]	N.E.	N.E.		
Patients with event at end of study, % KM estimate [95% CI]	3.9 [1.1; 6.7]	9.9 [1.9; 17.8]	0.56 [0.22; 1.43] 0.225	0.221

N: Number of patients
N': Number of patients in the analysis
CI: Confidence interval
HR: Hazard ratio
KM: Kaplan-Meier
N.E.: Not estimable
.....

Analysis method:
HR obtained from Cox proportional hazards model: log(hazard ratio) = treatment + age group + NYHA/Ross class

Table 6.2 All cause death by age group (FAS), time to event analysis

	Treatment Groups		Comparison	
All cause death by age group (FAS)	**LCZ696 (N=182)**	**Enalapril (N=184)**	**HR [95% CI] p-value**	**Logrank test p-value**
6 years to < 18 years, N	109	111		
1 year to < 6 years, N	73	73		
All cause death (adjudicated)				
Interaction test	**p = 0.829**			
6 years to < 18 years				
N'	109	111		
Patients with event, n (%)	5 (4.6)	9 (8.1)		
Median time to event (in weeks) [95% CI]	N.E.	N.E.		
Patients with event at end of study, % KM estimate [95% CI]	4.7 [0.7; 8.7]	8.4 [3.1; 13.6]	0.53 [0.18; 1.58] 0.252	0.257
1 year to < 6 years				
N'	73	73		
Patients with event, n (%)	2 (2.7)	3 (4.1)		
Median time to event (in weeks) [95% CI]	N.E.	N.E.		
Patients with event at end of study, % KM estimate [95% CI]	2.8 [0.0; 6.5]	9.7 [0.0; 23.3]	0.66 [0.11; 3.98] 0.655	0.626
All cause death (investigator reported)				
Interaction test	**p = 0.829**			
6 years to < 18 years				
N'	109	111		
Patients with event, n (%)	5 (4.6)	9 (8.1)		
Median time to event (in weeks) [95% CI]	N.E.	N.E.		
Patients with event at end of study, % KM estimate [95% CI]	4.7 [0.7; 8.7]	8.4 [3.1; 13.6]	0.53 [0.18; 1.58] 0.252	0.257
1 year to < 6 years				
N'	73	73		
Patients with event, n (%)	2 (2.7)	3 (4.1)		
Median time to event (in weeks) [95% CI]	N.E.	N.E.		
Patients with event at end of study, % KM estimate [95% CI]	2.8 [0.0; 6.5]	9.7 [0.0; 23.3]	0.66 [0.11; 3.98] 0.655	0.626

	Treatment Groups		Comparison	
All cause death by age group (FAS)	**LCZ696 (N=182)**	**Enalapril (N=184)**	**HR [95% CI] p-value**	**Logrank test p-value**

N: Number of patients
N': Number of patients in the analysis
CI: Confidence interval
HR: Hazard ratio
KM: Kaplan-Meier
N.E.: Not estimable
.....

Analysis method:
Interaction test and HR obtained from Cox proportional hazards model: log(hazard ratio) = treatment + age group + treatment * age group + NYHA/Ross class

Table 6.3 All cause death by NYHA/Ross class (FAS), time to event analysis

	Treatment Groups		Comparison	
All cause death by NYHA/Ross class (FAS)	**LCZ696 (N=182)**	**Enalapril (N=184)**	**HR [95% CI] p-value**	**Logrank test p-value**
Class I/II, N	157	157		
Class III/IV, N	25	27		
All cause death (adjudicated)				
Interaction test	**p = 0.500**			
Class I/II				
N'	157	157		
Patients with event, n (%)	5 (3.2)	10 (6.4)		
Median time to event (in weeks) [95% CI]	N.E.	N.E.		
Patients with event at end of study, % KM estimate [95% CI]	3.2 [0.4; 6.0]	6.5 [2.6; 10.5]	0.47 [0.16; 1.39] 0.173	0.177
Class III/IV				
N'	25	27		
Patients with event, n (%)	2 (8.0)	2 (7.4)		
Median time to event (in weeks) [95% CI]	N.E.	56.1 [56.1; N.E.]		
Patients with event at end of study, % KM estimate [95% CI]	8.0 [0.0; 18.6]	51.9 [0.0; 100.0]	1.02 [0.14; 7.27] 0.983	0.905
All cause death (investigator reported)				
Interaction test	**p = 0.500**			
Class I/II				
N'	157	157		
Patients with event, n (%)	5 (3.2)	10 (6.4)		
Median time to event (in weeks) [95% CI]	N.E.	N.E.		
Patients with event at end of study, % KM estimate [95% CI]	3.2 [0.4; 6.0]	6.5 [2.6; 10.5]	0.47 [0.16; 1.39] 0.173	0.177
Class III/IV				
N'	25	27		
Patients with event, n (%)	2 (8.0)	2 (7.4)		
Median time to event (in weeks) [95% CI]	N.E.	56.1 [56.1; N.E.]		
Patients with event at end of study, % KM estimate [95% CI]	8.0 [0.0; 18.6]	51.9 [0.0; 100.0]	1.02 [0.14; 7.27] 0.983	0.905

	Treatment Groups		Comparison	
All cause death by NYHA/Ross class (FAS)	**LCZ696 (N=182)**	**Enalapril (N=184)**	**HR [95% CI] p-value**	**Logrank test p-value**

N: Number of patients
N': Number of patients in the analysis
CI: Confidence interval
HR: Hazard ratio
KM: Kaplan-Meier
N.E.: Not estimable
.....

Analysis method:
Interaction test and HR obtained from Cox proportional hazards model: log(hazard ratio) = treatment + NYHA/Ross class + treatment * NYHA/Ross class + age group

Table 6.4 All cause death by region (FAS), time to event analysis

	Treatment Groups		Comparison	
All cause death by region (FAS)	**LCZ696 (N=182)**	**Enalapril (N=184)**	**HR [95% CI] p-value**	**Logrank test p-value**
America, N	58	69		
Europe, N	58	55		
Asia/Pacific and other, N	66	60		
All cause death (adjudicated)				
Interaction test	**p = 0.399**			
America				
N'	58	69		
Patients with event, n (%)	1 (1.7)	6 (8.7)		
Median time to event (in weeks) [95% CI]	N.E.	N.E.		
Patients with event at end of study, % KM estimate [95% CI]	1.8 [0.0; 5.2]	8.9 [2.1; 15.7]	0.17 [0.02; 1.44] 0.105	0.085
Europe				
N'	58	55		
Patients with event, n (%)	1 (1.7)	1 (1.8)		
Median time to event (in weeks) [95% CI]	N.E.	N.E.		
Patients with event at end of study, % KM estimate [95% CI]	1.7 [0.0; 5.1]	20.0 [0.0; 55.1]	0.92 [0.06; 14.73] 0.954	0.934
Asia/Pacific and other				
N'	66	60		
Patients with event, n (%)	5 (7.6)	5 (8.3)		
Median time to event (in weeks) [95% CI]	N.E.	N.E.		
Patients with event at end of study, % KM estimate [95% CI]	7.9 [1.2; 14.5]	8.7 [1.4; 15.9]	0.91 [0.26; 3.15] 0.883	0.830

	Treatment Groups		Comparison	
All cause death by region (FAS)	**LCZ696 (N=182)**	**Enalapril (N=184)**	**HR [95% CI] p-value**	**Logrank test p-value**
All cause death (investigator reported)				
Interaction test	**p = 0.399**			
America				
N'	58	69		
Patients with event, n (%)	1 (1.7)	6 (8.7)		
Median time to event (in weeks) [95% CI]	N.E.	N.E.		
Patients with event at end of study, % KM estimate [95% CI]	1.8 [0.0; 5.2]	8.9 [2.1; 15.7]	0.17 [0.02; 1.44] 0.105	0.085
Europe				
N'	58	55		
Patients with event, n (%)	1 (1.7)	1 (1.8)		
Median time to event (in weeks) [95% CI]	N.E.	N.E.		
Patients with event at end of study, % KM estimate [95% CI]	1.7 [0.0; 5.1]	20.0 [0.0; 55.1]	0.92 [0.06; 14.73] 0.954	0.934
Asia/Pacific and other				
N'	66	60		
Patients with event, n (%)	5 (7.6)	5 (8.3)		
Median time to event (in weeks) [95% CI]	N.E.	N.E.		
Patients with event at end of study, % KM estimate [95% CI]	7.9 [1.2; 14.5]	8.7 [1.4; 15.9]	0.91 [0.26; 3.15] 0.883	0.830

N: Number of patients
N': Number of patients in the analysis
CI: Confidence interval
HR: Hazard ratio
KM: Kaplan-Meier
N.E.: Not estimable
.....

Analysis method:
Interaction test and HR obtained from Cox proportional hazards model: log(hazard ratio) = treatment + region + treatment * region + age group + NYHA/Ross class

Table 6.5 All cause death by gender (FAS), time to event analysis

	Treatment Groups		Comparison	
All cause death by gender (FAS)	**LCZ696 (N=182)**	**Enalapril (N=184)**	**HR [95% CI] p-value**	**Logrank test p-value**
Male, N	88	91		
Female, N	94	93		
All cause death (adjudicated)				
Interaction test	**p = 0.758**			
Male				
N'	88	91		
Patients with event, n (%)	4 (4.5)	6 (6.6)		
Median time to event (in weeks) [95% CI]	N.E.	N.E.		
Patients with event at end of study, % KM estimate [95% CI]	4.7 [0.2; 9.2]	12.8 [0.0; 27.2]	0.64 [0.18; 2.29] 0.497	0.524
Female				
N'	94	93		
Patients with event, n (%)	3 (3.2)	6 (6.5)		
Median time to event (in weeks) [95% CI]	N.E.	N.E.		
Patients with event at end of study, % KM estimate [95% CI]	3.2 [0.0; 6.7]	6.6 [1.5; 11.8]	0.48 [0.12; 1.92] 0.299	0.282
All cause death (investigator reported)				
Interaction test	**p = 0.758**			
Male				
N'	88	91		
Patients with event, n (%)	4 (4.5)	6 (6.6)		
Median time to event (in weeks) [95% CI]	N.E.	N.E.		
Patients with event at end of study, % KM estimate [95% CI]	4.7 [0.2; 9.2]	12.8 [0.0; 27.2]	0.64 [0.18; 2.29] 0.497	0.524
Female				
N'	94	93		
Patients with event, n (%)	3 (3.2)	6 (6.5)		
Median time to event (in weeks) [95% CI]	N.E.	N.E.		
Patients with event at end of study, % KM estimate [95% CI]	3.2 [0.0; 6.7]	6.6 [1.5; 11.8]	0.48 [0.12; 1.92] 0.299	0.282

	Treatment Groups		Comparison	
All cause death by gender (FAS)	**LCZ696 (N=182)**	**Enalapril (N=184)**	**HR [95% CI] p-value**	**Logrank test p-value**

N: Number of patients
N': Number of patients in the analysis
CI: Confidence interval
HR: Hazard ratio
KM: Kaplan-Meier
N.E.: Not estimable
.....

Analysis method:
Interaction test and HR obtained from Cox proportional hazards model: log(hazard ratio) = treatment + gender + treatment * gender + age group + NYHA/Ross class

Table 6.6 All cause death by COVID-19 period (FAS), time to event analysis

	Treatment Groups		Comparison	
All cause death by COVID-19 period (FAS)	**LCZ696 (N=182)**	**Enalapril (N=184)**	**HR [95% CI] p-value**	**Logrank test p-value**
Pre-pandemic, N	79	83		
Pre- and during-pandemic, N	62	59		
During-pandemic, N	41	42		
All cause death (adjudicated)				
Interaction test	**p = 1.000**			
Pre-pandemic				
N'	79	83		
Patients with event, n (%)	6 (7.6)	11 (13.3)		
Median time to event (in weeks) [95% CI]	N.E.	N.E.		
Patients with event at end of study, % KM estimate [95% CI]	7.8 [1.8; 13.8]	13.8 [6.2; 21.3]	0.52 [0.19; 1.40] 0.195	0.208
Pre- and during-pandemic				
N'	62	59		
Patients with event, n (%)	0 (0.0)	1 (1.7)		
Median time to event (in weeks) [95% CI]	N.E.	N.E.		
Patients with event at end of study, % KM estimate [95% CI]	0.0 [0.0; 0.0]	6.3 [0.0; 18.1]	N.E.	0.276
During-pandemic				
N'	41	42		
Patients with event, n (%)	1 (2.4)	0 (0.0)		
Median time to event (in weeks) [95% CI]	N.E.	N.E.		
Patients with event at end of study, % KM estimate [95% CI]	2.4 [0.0; 7.2]	0.0 [0.0; 0.0]	N.E.	0.317
All cause death (investigator reported)				
Interaction test	**p = 1.000**			
Pre-pandemic				
N'	79	83		
Patients with event, n (%)	6 (7.6)	11 (13.3)		
Median time to event (in weeks) [95% CI]	N.E.	N.E.		
Patients with event at end of study, % KM estimate [95% CI]	7.8 [1.8; 13.8]	13.8 [6.2; 21.3]	0.52 [0.19; 1.40] 0.195	0.208

	Treatment Groups		Comparison	
All cause death by COVID-19 period (FAS)	**LCZ696 (N=182)**	**Enalapril (N=184)**	**HR [95% CI] p-value**	**Logrank test p-value**
Pre- and during-pandemic				
N'	62	59		
Patients with event, n (%)	0 (0.0)	1 (1.7)		
Median time to event (in weeks) [95% CI]	N.E.	N.E.		
Patients with event at end of study, % KM estimate [95% CI]	0.0 [0.0; 0.0]	6.3 [0.0; 18.1]	N.E.	0.276
During-pandemic				
N'	41	42		
Patients with event, n (%)	1 (2.4)	0 (0.0)		
Median time to event (in weeks) [95% CI]	N.E.	N.E.		
Patients with event at end of study, % KM estimate [95% CI]	2.4 [0.0; 7.2]	0.0 [0.0; 0.0]	N.E.	0.317

N: Number of patients
N': Number of patients in the analysis
CI: Confidence interval
HR: Hazard ratio
KM: Kaplan-Meier
N.E.: Not estimable
.....

Analysis method:
Interaction test and HR obtained from Cox proportional hazards model: log(hazard ratio) = treatment + COVID-19 period + treatment * COVID-19 period + age group + NYHA/Ross class

Table 6.7 All cause death by race (FAS), time to event analysis

The subgroup analysis is not presented as all subgroups have less than 10 events.

7 CV death

Table 7.1 CV death (FAS), time to event analysis

	Treatment Groups		Comparison	
CV death (FAS)	**LCZ696 (N=182)**	**Enalapril (N=184)**	**HR [95% CI] p-value**	**Logrank test p-value**
CV death (adjudicated)				
N'	182	184		
Patients with event, n (%)	6 (3.3)	11 (6.0)		
Median time to event (in weeks) [95% CI]	N.E.	N.E.		
Patients with event at end of study, % KM estimate [95% CI]	3.3 [0.7; 6.0]	9.4 [1.4; 17.3]	0.52 [0.19; 1.42] 0.202	0.198
CV death (investigator reported)				
N'	182	184		
Patients with event, n (%)	4 (2.2)	9 (4.9)		
Median time to event (in weeks) [95% CI]	N.E.	N.E.		
Patients with event at end of study, % KM estimate [95% CI]	2.2 [0.1; 4.4]	8.3 [0.4; 16.2]	0.42 [0.13; 1.37] 0.149	0.144

N: Number of patients
N': Number of patients in the analysis
CI: Confidence interval
HR: Hazard ratio
KM: Kaplan-Meier
N.E.: Not estimable
.....

Analysis method:
HR obtained from Cox proportional hazards model: log(hazard ratio) = treatment + age group + NYHA/Ross class

Table 7.2 CV death by age group (FAS), time to event analysis

	Treatment Groups		Comparison	
CV death by age group (FAS)	**LCZ696 (N=182)**	**Enalapril (N=184)**	**HR [95% CI] p-value**	**Logrank test p-value**
6 years to < 18 years, N	109	111		
1 year to < 6 years, N	73	73		
CV death (adjudicated)				
Interaction test	**p = 0.655**			
6 years to < 18 years				
N'	109	111		
Patients with event, n (%)	5 (4.6)	8 (7.2)		
Median time to event (in weeks) [95% CI]	N.E.	N.E.		
Patients with event at end of study, % KM estimate [95% CI]	4.7 [0.7; 8.7]	7.5 [2.5; 12.6]	0.59 [0.19; 1.81] 0.358	0.369
1 year to < 6 years				
N'	73	73		
Patients with event, n (%)	1 (1.4)	3 (4.1)		
Median time to event (in weeks) [95% CI]	N.E.	N.E.		
Patients with event at end of study, % KM estimate [95% CI]	1.4 [0.0; 4.0]	9.7 [0.0; 23.3]	0.33 [0.03; 3.20] 0.341	0.297
CV death (investigator reported)				
Interaction test	**p = 0.991**			
6 years to < 18 years				
N'	109	111		
Patients with event, n (%)	4 (3.7)	7 (6.3)		
Median time to event (in weeks) [95% CI]	N.E.	N.E.		
Patients with event at end of study, % KM estimate [95% CI]	3.7 [0.1; 7.3]	6.6 [1.9; 11.3]	0.54 [0.16; 1.83] 0.319	0.337
1 year to < 6 years				
N'	73	73		
Patients with event, n (%)	0 (0.0)	2 (2.7)		
Median time to event (in weeks) [95% CI]	N.E.	N.E.		
Patients with event at end of study, % KM estimate [95% CI]	0.0 [0.0; 0.0]	8.4 [0.0; 22.0]	N.E.	0.139

	Treatment Groups		Comparison	
CV death by age group (FAS)	**LCZ696 (N=182)**	**Enalapril (N=184)**	**HR [95% CI] p-value**	**Logrank test p-value**

N: Number of patients
N': Number of patients in the analysis
CI: Confidence interval
HR: Hazard ratio
KM: Kaplan-Meier
N.E.: Not estimable
.....

Analysis method:
Interaction test and HR obtained from Cox proportional hazards model: log(hazard ratio) = treatment + age group + treatment * age group + NYHA/Ross class

Table 7.3 CV death by NYHA/Ross class (FAS), time to event analysis

	Treatment Groups		Comparison	
CV death by NYHA/Ross class (FAS)	**LCZ696 (N=182)**	**Enalapril (N=184)**	**HR [95% CI] p-value**	**Logrank test p-value**
Class I/II, N	157	157		
Class III/IV, N	25	27		
CV death (adjudicated)				
Interaction test	**p = 0.452**			
Class I/II				
N'	157	157		
Patients with event, n (%)	4 (2.5)	9 (5.7)		
Median time to event (in weeks) [95% CI]	N.E.	N.E.		
Patients with event at end of study, % KM estimate [95% CI]	2.6 [0.1; 5.1]	5.9 [2.2; 9.7]	0.42 [0.13; 1.36] 0.149	0.150
Class III/IV				
N'	25	27		
Patients with event, n (%)	2 (8.0)	2 (7.4)		
Median time to event (in weeks) [95% CI]	N.E.	56.1 [56.1; N.E.]		
Patients with event at end of study, % KM estimate [95% CI]	8.0 [0.0; 18.6]	51.9 [0.0; 100.0]	1.01 [0.14; 7.18] 0.993	0.905
CV death (investigator reported)				
Interaction test	**p = 0.887**			
Class I/II				
N'	157	157		
Patients with event, n (%)	3 (1.9)	7 (4.5)		
Median time to event (in weeks) [95% CI]	N.E.	N.E.		
Patients with event at end of study, % KM estimate [95% CI]	1.9 [0.0; 4.1]	4.6 [1.3; 8.0]	0.40 [0.10; 1.55] 0.185	0.189
Class III/IV				
N'	25	27		
Patients with event, n (%)	1 (4.0)	2 (7.4)		
Median time to event (in weeks) [95% CI]	N.E.	56.1 [56.1; N.E.]		
Patients with event at end of study, % KM estimate [95% CI]	4.0 [0.0; 11.7]	51.9 [0.0; 100.0]	0.49 [0.04; 5.42] 0.560	0.453

	Treatment Groups		Comparison	
CV death by NYHA/Ross class (FAS)	**LCZ696 (N=182)**	**Enalapril (N=184)**	**HR [95% CI] p-value**	**Logrank test p-value**

N: Number of patients
N': Number of patients in the analysis
CI: Confidence interval
HR: Hazard ratio
KM: Kaplan-Meier
N.E.: Not estimable
.....

Analysis method:
Interaction test and HR obtained from Cox proportional hazards model: log(hazard ratio) = treatment + NYHA/Ross class + treatment * NYHA/Ross class + age group

Table 7.4 CV death by region (FAS), time to event analysis

The subgroup analysis is not presented as all subgroups have less than 10 events.

Table 7.5 CV death by gender (FAS), time to event analysis

The subgroup analysis is not presented as all subgroups have less than 10 events.

Table 7.6 CV death by COVID-19 period (FAS), time to event analysis

	Treatment Groups		Comparison	
CV death by COVID-19 period (FAS)	**LCZ696 (N=182)**	**Enalapril (N=184)**	**HR [95% CI] p-value**	**Logrank test p-value**
Pre-pandemic, N	79	83		
Pre- and during-pandemic, N	62	59		
During-pandemic, N	41	42		
CV death (adjudicated)				
Interaction test	**p = 1.000**			
Pre-pandemic				
N'	79	83		
Patients with event, n (%)	5 (6.3)	10 (12.0)		
Median time to event (in weeks) [95% CI]	N.E.	N.E.		
Patients with event at end of study, % KM estimate [95% CI]	6.5 [1.0; 12.0]	12.7 [5.3; 20.1]	0.47 [0.16; 1.38] 0.169	0.182
Pre- and during-pandemic				
N'	62	59		
Patients with event, n (%)	0 (0.0)	1 (1.7)		
Median time to event (in weeks) [95% CI]	N.E.	N.E.		
Patients with event at end of study, % KM estimate [95% CI]	0.0 [0.0; 0.0]	6.3 [0.0; 18.1]	N.E.	0.276
During-pandemic				
N'	41	42		
Patients with event, n (%)	1 (2.4)	0 (0.0)		
Median time to event (in weeks) [95% CI]	N.E.	N.E.		
Patients with event at end of study, % KM estimate [95% CI]	2.4 [0.0; 7.2]	0.0 [0.0; 0.0]	N.E.	0.317
CV death (investigator reported)				
Interaction test	**p = 1.000**			
Pre-pandemic				
N'	79	83		
Patients with event, n (%)	3 (3.8)	8 (9.6)		
Median time to event (in weeks) [95% CI]	N.E.	N.E.		
Patients with event at end of study, % KM estimate [95% CI]	4.0 [0.0; 8.4]	10.3 [3.5; 17.0]	0.34 [0.09; 1.30] 0.115	0.124

	Treatment Groups		Comparison	
CV death by COVID-19 period (FAS)	**LCZ696 (N=182)**	**Enalapril (N=184)**	**HR [95% CI] p-value**	**Logrank test p-value**
Pre- and during-pandemic				
N'	62	59		
Patients with event, n (%)	0 (0.0)	1 (1.7)		
Median time to event (in weeks) [95% CI]	N.E.	N.E.		
Patients with event at end of study, % KM estimate [95% CI]	0.0 [0.0; 0.0]	6.3 [0.0; 18.1]	N.E.	0.276
During-pandemic				
N'	41	42		
Patients with event, n (%)	1 (2.4)	0 (0.0)		
Median time to event (in weeks) [95% CI]	N.E.	N.E.		
Patients with event at end of study, % KM estimate [95% CI]	2.4 [0.0; 7.2]	0.0 [0.0; 0.0]	N.E.	0.317

N: Number of patients
N': Number of patients in the analysis
CI: Confidence interval
HR: Hazard ratio
KM: Kaplan-Meier
N.E.: Not estimable
.....

Analysis method:
Interaction test and HR obtained from Cox proportional hazards model: log(hazard ratio) = treatment + COVID-19 period + treatment * COVID-19 period + age group + NYHA/Ross class

Table 7.7 CV death by race (FAS), time to event analysis

The subgroup analysis is not presented as all subgroups have less than 10 events.

8 UNOS status 1A listing for heart transplant or equivalent (adjudicated)

Table 8.1 UNOS status 1A listing for heart transplant or equivalent (adjudicated) (FAS), time to event analysis

	Treatment Groups		Comparison	
UNOS status 1A listing for heart transplant or equivalent (adjudicated) (FAS)	**LCZ696 (N=182)**	**Enalapril (N=184)**	**HR [95% CI] p-value**	**Logrank test p-value**
First UNOS status 1A listing for heart transplant or equivalent (adjudicated)				
N'	182	184		
Patients with event, n (%)	5 (2.7)	7 (3.8)		
Median time to event (in weeks) [95% CI]	N.E.	N.E.		
Patients with event at end of study, % KM estimate [95% CI]	2.8 [0.4; 5.3]	4.1 [1.1; 7.0]	0.70 [0.22; 2.20] 0.541	0.532

N: Number of patients
N': Number of patients in the analysis
CI: Confidence interval
HR: Hazard ratio
KM: Kaplan-Meier
N.E.: Not estimable
.....

Analysis method:
HR obtained from Cox proportional hazards model: log(hazard ratio) = treatment + age group + NYHA/Ross class

Table 8.2 UNOS status 1A listing for heart transplant or equivalent (adjudicated) by age group (FAS), time to event analysis

The subgroup analysis is not presented as all subgroups have less than 10 events.

Table 8.3 UNOS status 1A listing for heart transplant or equivalent (adjudicated) by NYHA/Ross class (FAS), time to event analysis

The subgroup analysis is not presented as all subgroups have less than 10 events.

Table 8.4 UNOS status 1A listing for heart transplant or equivalent (adjudicated) by region (FAS), time to event analysis

The subgroup analysis is not presented as all subgroups have less than 10 events.

Table 8.5 UNOS status 1A listing for heart transplant or equivalent (adjudicated) by gender (FAS), time to event analysis

The subgroup analysis is not presented as all subgroups have less than 10 events.

Table 8.6 UNOS status 1A listing for heart transplant or equivalent (adjudicated) by COVID-19 period (FAS), time to event analysis

The subgroup analysis is not presented as all subgroups have less than 10 events.

Table 8.7 UNOS status 1A listing for heart transplant or equivalent (adjudicated) by race (FAS), time to event analysis

The subgroup analysis is not presented as all subgroups have less than 10 events.

9 VAD / ECMO / mechanical ventilation / intra-aortic balloon pump requirement for life support (adjudicated)

Table 9.1 VAD / ECMO / mechanical ventilation / intra-aortic balloon pump requirement for life support (adjudicated) (FAS), time to event analysis

	Treatment Groups		Comparison	
VAD / ECMO / mechanical ventilation / intra-aortic balloon pump requirement for life support (adjudicated) (FAS)	**LCZ696 (N=182)**	**Enalapril (N=184)**	**HR [95% CI] p-value**	**Logrank test p-value**
First VAD / ECMO / mechanical ventilation / intra-aortic balloon pump requirement for life support (adjudicated)				
N'	182	184		
Patients with event, n (%)	6 (3.3)	12 (6.5)		
Median time to event (in weeks) [95% CI]	N.E.	N.E.		
Patients with event at end of study, % KM estimate [95% CI]	3.4 [0.7; 6.0]	9.0 [2.7; 15.4]	0.48 [0.18; 1.29] 0.147	0.134

N: Number of patients
N': Number of patients in the analysis
CI: Confidence interval
HR: Hazard ratio
KM: Kaplan-Meier
N.E.: Not estimable
.....

Analysis method:
HR obtained from Cox proportional hazards model: log(hazard ratio) = treatment + age group + NYHA/Ross class

Table 9.2 VAD / ECMO / mechanical ventilation / intra-aortic balloon pump requirement for life support (adjudicated) by age group (FAS), time to event analysis

	Treatment Groups		Comparison	
VAD / ECMO / mechanical ventilation / intra-aortic balloon pump requirement for life support (adjudicated) by age group (FAS)	**LCZ696 (N=182)**	**Enalapril (N=184)**	**HR [95% CI] p-value**	**Logrank test p-value**
6 years to < 18 years, N	109	111		
1 year to < 6 years, N	73	73		
First VAD / ECMO / mechanical ventilation / intra-aortic balloon pump requirement for life support (adjudicated)				
Interaction test	**p = 0.307**			
6 years to < 18 years				
N'	109	111		
Patients with event, n (%)	5 (4.6)	7 (6.3)		
Median time to event (in weeks) [95% CI]	N.E.	N.E.		
Patients with event at end of study, % KM estimate [95% CI]	4.7 [0.7; 8.7]	6.9 [2.0; 11.9]	0.69 [0.22; 2.17] 0.526	0.518
1 year to < 6 years				
N'	73	73		
Patients with event, n (%)	1 (1.4)	5 (6.8)		
Median time to event (in weeks) [95% CI]	N.E.	N.E.		
Patients with event at end of study, % KM estimate [95% CI]	1.4 [0.0; 4.1]	12.2 [0.0; 25.9]	0.19 [0.02; 1.66] 0.135	0.082

N: Number of patients
N': Number of patients in the analysis
CI: Confidence interval
HR: Hazard ratio
KM: Kaplan-Meier
N.E.: Not estimable
.....

Analysis method:
Interaction test and HR obtained from Cox proportional hazards model: log(hazard ratio) = treatment + age group + treatment * age group + NYHA/Ross class

Table 9.3 VAD / ECMO / mechanical ventilation / intra-aortic balloon pump requirement for life support (adjudicated) by NYHA/Ross class (FAS), time to event analysis

	Treatment Groups		Comparison	
VAD / ECMO / mechanical ventilation / intra-aortic balloon pump requirement for life support (adjudicated) by NYHA/Ross class (FAS)	**LCZ696 (N=182)**	**Enalapril (N=184)**	**HR [95% CI] p-value**	**Logrank test p-value**
Class I/II, N	157	157		
Class III/IV, N	25	27		
First VAD / ECMO / mechanical ventilation / intra-aortic balloon pump requirement for life support (adjudicated)				
Interaction test	**p = 0.750**			
Class I/II				
N'	157	157		
Patients with event, n (%)	5 (3.2)	9 (5.7)		
Median time to event (in weeks) [95% CI]	N.E.	N.E.		
Patients with event at end of study, % KM estimate [95% CI]	3.2 [0.4; 6.0]	6.1 [2.2; 10.0]	0.53 [0.18; 1.57] 0.249	0.256
Class III/IV				
N'	25	27		
Patients with event, n (%)	1 (4.0)	3 (11.1)		
Median time to event (in weeks) [95% CI]	N.E.	N.E.		
Patients with event at end of study, % KM estimate [95% CI]	4.5 [0.0; 13.2]	25.9 [0.0; 59.3]	0.35 [0.04; 3.36] 0.362	0.347

N: Number of patients
N': Number of patients in the analysis
CI: Confidence interval
HR: Hazard ratio
KM: Kaplan-Meier
N.E.: Not estimable
.....

Analysis method:
Interaction test and HR obtained from Cox proportional hazards model: log(hazard ratio) = treatment + NYHA/Ross class + treatment * NYHA/Ross class + age group

Table 9.4 VAD / ECMO / mechanical ventilation / intra-aortic balloon pump requirement for life support (adjudicated) by region (FAS), time to event analysis

The subgroup analysis is not presented as all subgroups have less than 10 events.

Table 9.5 VAD / ECMO / mechanical ventilation / intra-aortic balloon pump requirement for life support (adjudicated) by gender (FAS), time to event analysis

The subgroup analysis is not presented as all subgroups have less than 10 events.

Table 9.6 VAD / ECMO / mechanical ventilation / intra-aortic balloon pump requirement for life support (adjudicated) by COVID-19 period (FAS), time to event analysis

	Treatment Groups		Comparison	
VAD / ECMO / mechanical ventilation / intra-aortic balloon pump requirement for life support (adjudicated) by COVID-19 period (FAS)	**LCZ696 (N=182)**	**Enalapril (N=184)**	**HR [95% CI] p-value**	**Logrank test p-value**
Pre-pandemic, N	79	83		
Pre- and during-pandemic, N	62	59		
During-pandemic, N	41	42		
First VAD / ECMO / mechanical ventilation / intra-aortic balloon pump requirement for life support (adjudicated)				
Interaction test	**p = 0.742**			
Pre-pandemic				
N'	79	83		
Patients with event, n (%)	5 (6.3)	8 (9.6)		
Median time to event (in weeks) [95% CI]	N.E.	N.E.		
Patients with event at end of study, % KM estimate [95% CI]	6.4 [1.0; 11.9]	10.8 [3.7; 17.8]	0.61 [0.20; 1.86] 0.385	0.397
Pre- and during-pandemic				
N'	62	59		
Patients with event, n (%)	1 (1.6)	4 (6.8)		
Median time to event (in weeks) [95% CI]	N.E.	N.E.		
Patients with event at end of study, % KM estimate [95% CI]	1.6 [0.0; 4.8]	10.1 [0.0; 21.0]	0.23 [0.03; 2.06] 0.190	0.139
During-pandemic				
N'	41	42		
Patients with event, n (%)	0 (0.0)	0 (0.0)		
Median time to event (in weeks) [95% CI]	N.E.	N.E.		
Patients with event at end of study, % KM estimate [95% CI]	0.0 [0.0; 0.0]	0.0 [0.0; 0.0]	N.E.	N.E.

	Treatment Groups		Comparison	
VAD / ECMO / mechanical ventilation / intra-aortic balloon pump requirement for life support (adjudicated) by COVID-19 period (FAS)	**LCZ696 (N=182)**	**Enalapril (N=184)**	**HR [95% CI] p-value**	**Logrank test p-value**

N: Number of patients
N': Number of patients in the analysis
CI: Confidence interval
HR: Hazard ratio
KM: Kaplan-Meier
N.E.: Not estimable
.....

Analysis method:
Interaction test and HR obtained from Cox proportional hazards model: log(hazard ratio) = treatment + COVID-19 period + treatment * COVID-19 period + age group + NYHA/Ross class

Table 9.7 VAD / ECMO / mechanical ventilation / intra-aortic balloon pump requirement for life support (adjudicated) by race (FAS), time to event analysis

The subgroup analysis is not presented as all subgroups have less than 10 events.

10 All cause hospitalization, event rate

Table 10.1 All cause hospitalization (FAS), event rate analysis

	Treatment Groups		Comparison
All cause hospitalization (FAS)	**LCZ696 (N=182)**	**Enalapril (N=184)**	**Rate ratio [95% CI] p-value**
All cause hospitalization events			
N'	182	184	
Number of patients with event	64	59	
Number of events	129	110	
Annualized event rate [95% CI]	0.71 [0.53; 0.93]	0.62 [0.46; 0.82]	1.15 [0.77; 1.71] 0.504

N: Number of patients
N': Number of patients in the analysis
CI: Confidence interval
.....

Analysis method:
Annualized event rate and rate ratio from negative binomial regression: log(events) = treatment + age group + NYHA/Ross class

Table 10.2 All cause hospitalization by age group (FAS), event rate analysis

	Treatment Groups		Comparison
All cause hospitalization by age group (FAS)	**LCZ696 (N=182)**	**Enalapril (N=184)**	**Rate ratio [95% CI] p-value**
6 years to < 18 years, N	109	111	
1 year to < 6 years, N	73	73	
All cause hospitalization events			
Interaction test	**p = 0.514**		
6 years to < 18 years			
N'	109	111	
Number of patients with event	40	39	
Number of events	80	67	
Annualized event rate [95% CI]	0.72 [0.50; 1.04]	0.70 [0.48; 1.02]	1.03 [0.61; 1.73] 0.919
1 year to < 6 years			
N'	73	73	
Number of patients with event	24	20	
Number of events	49	43	
Annualized event rate [95% CI]	0.68 [0.44; 1.06]	0.50 [0.31; 0.80]	1.36 [0.71; 2.58] 0.355

N: Number of patients
N': Number of patients in the analysis
CI: Confidence interval
.....

Analysis method:
Interaction test, annualized event rate and rate ratio from negative binomial regression: log(events) = treatment + age group + treatment * age group + NYHA/Ross class

Table 10.3 All cause hospitalization by NYHA/Ross class (FAS), event rate analysis

	Treatment Groups		Comparison
All cause hospitalization by NYHA/Ross class (FAS)	**LCZ696 (N=182)**	**Enalapril (N=184)**	**Rate ratio [95% CI] p-value**
Class I/II, N	157	157	
Class III/IV, N	25	27	
All cause hospitalization events			
Interaction test	**p = 0.914**		
Class I/II			
N'	157	157	
Number of patients with event	47	46	
Number of events	93	77	
Annualized event rate [95% CI]	0.63 [0.46; 0.85]	0.54 [0.39; 0.75]	1.16 [0.74; 1.81] 0.517
Class III/IV			
N'	25	27	
Number of patients with event	17	13	
Number of events	36	33	
Annualized event rate [95% CI]	1.48 [0.77; 2.85]	1.35 [0.70; 2.61]	1.09 [0.43; 2.79] 0.850

N: Number of patients
N': Number of patients in the analysis
CI: Confidence interval
.....

Analysis method:
Interaction test, annualized event rate and rate ratio from negative binomial regression: log(events) = treatment + NYHA/Ross class + treatment * NYHA/Ross class + age group

Table 10.4 All cause hospitalization by region (FAS), event rate analysis

	Treatment Groups		Comparison
All cause hospitalization by region (FAS)	**LCZ696 (N=182)**	**Enalapril (N=184)**	**Rate ratio [95% CI] p-value**
America, N	58	69	
Europe, N	58	55	
Asia/Pacific and other, N	66	60	
All cause hospitalization events			
Interaction test	**p = 0.747**		
America			
N'	58	69	
Number of patients with event	23	26	
Number of events	45	47	
Annualized event rate [95% CI]	0.75 [0.47; 1.21]	0.76 [0.48; 1.20]	0.99 [0.51; 1.91] 0.975
Europe			
N'	58	55	
Number of patients with event	22	21	
Number of events	45	37	
Annualized event rate [95% CI]	0.74 [0.46; 1.21]	0.51 [0.30; 0.87]	1.45 [0.71; 2.95] 0.312
Asia/Pacific and other			
N'	66	60	
Number of patients with event	19	12	
Number of events	39	26	
Annualized event rate [95% CI]	0.63 [0.39; 1.02]	0.55 [0.32; 0.95]	1.14 [0.55; 2.37] 0.723

N: Number of patients
N': Number of patients in the analysis
CI: Confidence interval
.....

Analysis method:
Interaction test, annualized event rate and rate ratio from negative binomial regression: log(events) = treatment + region + treatment * region + age group + NYHA/Ross class

Table 10.5 All cause hospitalization by gender (FAS), event rate analysis

	Treatment Groups		Comparison
All cause hospitalization by gender (FAS)	**LCZ696 (N=182)**	**Enalapril (N=184)**	**Rate ratio [95% CI] p-value**
Male, N	88	91	
Female, N	94	93	
All cause hospitalization events			
Interaction test	**p = 0.131**		
Male			
N'	88	91	
Number of patients with event	28	24	
Number of events	64	46	
Annualized event rate [95% CI]	0.78 [0.52; 1.16]	0.49 [0.32; 0.75]	1.60 [0.89; 2.88] 0.115
Female			
N'	94	93	
Number of patients with event	36	35	
Number of events	65	64	
Annualized event rate [95% CI]	0.64 [0.43; 0.95]	0.75 [0.50; 1.11]	0.86 [0.49; 1.49] 0.587

N: Number of patients
N': Number of patients in the analysis
CI: Confidence interval
.....

Analysis method:
Interaction test, annualized event rate and rate ratio from negative binomial regression: log(events) = treatment + gender + treatment * gender + age group + NYHA/Ross class

Table 10.6 All cause hospitalization by COVID-19 period (FAS), event rate analysis

	Treatment Groups		Comparison
All cause hospitalization by COVID-19 period (FAS)	**LCZ696 (N=182)**	**Enalapril (N=184)**	**Rate ratio [95% CI] p-value**
Pre-pandemic, N	79	83	
Pre- and during-pandemic, N	62	59	
During-pandemic, N	41	42	
All cause hospitalization events			
Interaction test	**p = 0.276**		
Pre-pandemic			
N'	79	83	
Number of patients with event	28	30	
Number of events	61	51	
Annualized event rate [95% CI]	0.86 [0.57; 1.29]	0.77 [0.50; 1.19]	1.11 [0.61; 2.00] 0.740
Pre- and during-pandemic			
N'	62	59	
Number of patients with event	23	20	
Number of events	38	42	
Annualized event rate [95% CI]	0.51 [0.31; 0.83]	0.61 [0.37; 0.99]	0.84 [0.42; 1.67] 0.624
During-pandemic			
N'	41	42	
Number of patients with event	13	9	
Number of events	30	17	
Annualized event rate [95% CI]	0.74 [0.41; 1.32]	0.35 [0.18; 0.69]	2.10 [0.86; 5.09] 0.101

N: Number of patients
N': Number of patients in the analysis
CI: Confidence interval
.....

Analysis method:
Interaction test, annualized event rate and rate ratio from negative binomial regression: log(events) = treatment + COVID-19 period + treatment * COVID-19 period + age group + NYHA/Ross class

Table 10.7 All cause hospitalization by race (FAS), event rate analysis

	Treatment Groups		Comparison
All cause hospitalization by race (FAS)	**LCZ696 (N=182)**	**Enalapril (N=184)**	**Rate ratio [95% CI] p-value**
Caucasian, N	86	90	
Black, N	23	25	
Asian, N	55	45	
Unknown or other, N	18	24	
All cause hospitalization events			
Interaction test	**p = 0.888**		
Caucasian			
N'	86	90	
Number of patients with event	27	28	
Number of events	52	49	
Annualized event rate [95% CI]	0.56 [0.38; 0.85]	0.50 [0.33; 0.76]	1.12 [0.63; 1.99] 0.691
Black			
N'	23	25	
Number of patients with event	12	16	
Number of events	34	30	
Annualized event rate [95% CI]	1.40 [0.73; 2.65]	1.52 [0.78; 2.95]	0.92 [0.36; 2.30] 0.853
Asian			
N'	55	45	
Number of patients with event	17	9	
Number of events	30	18	
Annualized event rate [95% CI]	0.57 [0.34; 0.96]	0.40 [0.21; 0.75]	1.44 [0.64; 3.24] 0.382
Unknown or other			
N'	18	24	
Number of patients with event	8	6	
Number of events	13	13	
Annualized event rate [95% CI]	0.81 [0.36; 1.84]	0.58 [0.26; 1.25]	1.41 [0.46; 4.34] 0.550

	Treatment Groups		Comparison
All cause hospitalization by race (FAS)	**LCZ696 (N=182)**	**Enalapril (N=184)**	**Rate ratio [95% CI] p-value**

N: Number of patients
N': Number of patients in the analysis
CI: Confidence interval
.....

Analysis method:
Interaction test, annualized event rate and rate ratio from negative binomial regression: log(events) = treatment + race + treatment * race + age group + NYHA/Ross class

11 All cause hospitalization, time to first event

Table 11.1 All cause hospitalization (FAS), time to event analysis

	Treatment Groups		Comparison	
All cause hospitalization (FAS)	**LCZ696 (N=182)**	**Enalapril (N=184)**	**HR [95% CI] p-value**	**Logrank test p-value**
First all cause hospitalization				
N'	182	184		
Patients with event, n (%)	64 (35.2)	59 (32.1)		
Median time to event (in weeks) [95% CI]	N.E.	N.E.		
Patients with event at end of study, % KM estimate [95% CI]	35.6 [28.6; 42.7]	36.1 [26.4; 45.8]	1.09 [0.76; 1.55] 0.636	0.738

N: Number of patients
N': Number of patients in the analysis
CI: Confidence interval
HR: Hazard ratio
KM: Kaplan-Meier
N.E.: Not estimable
.....

Analysis method:
HR obtained from Cox proportional hazards model: log(hazard ratio) = treatment + age group + NYHA/Ross class

Table 11.2 All cause hospitalization by age group (FAS), time to event analysis

	Treatment Groups		Comparison	
All cause hospitalization by age group (FAS)	**LCZ696 (N=182)**	**Enalapril (N=184)**	**HR [95% CI] p-value**	**Logrank test p-value**
6 years to < 18 years, N	109	111		
1 year to < 6 years, N	73	73		
First all cause hospitalization				
Interaction test	**p = 0.560**			
6 years to < 18 years				
N'	109	111		
Patients with event, n (%)	40 (36.7)	39 (35.1)		
Median time to event (in weeks) [95% CI]	N.E.	N.E.		
Patients with event at end of study, % KM estimate [95% CI]	37.3 [28.1; 46.5]	43.7 [26.9; 60.4]	1.01 [0.65; 1.57] 0.976	0.884
1 year to < 6 years				
N'	73	73		
Patients with event, n (%)	24 (32.9)	20 (27.4)		
Median time to event (in weeks) [95% CI]	N.E.	N.E.		
Patients with event at end of study, % KM estimate [95% CI]	33.3 [22.4; 44.2]	27.6 [17.3; 37.9]	1.25 [0.69; 2.27] 0.454	0.479

N: Number of patients
N': Number of patients in the analysis
CI: Confidence interval
HR: Hazard ratio
KM: Kaplan-Meier
N.E.: Not estimable
.....

Analysis method:
Interaction test and HR obtained from Cox proportional hazards model: log(hazard ratio) = treatment + age group + treatment * age group + NYHA/Ross class

Table 11.3 All cause hospitalization by NYHA/Ross class (FAS), time to event analysis

	Treatment Groups		Comparison	
All cause hospitalization by NYHA/Ross class (FAS)	**LCZ696 (N=182)**	**Enalapril (N=184)**	**HR [95% CI] p-value**	**Logrank test p-value**
Class I/II, N	157	157		
Class III/IV, N	25	27		
First all cause hospitalization				
Interaction test	**p = 0.263**			
Class I/II				
N'	157	157		
Patients with event, n (%)	47 (29.9)	46 (29.3)		
Median time to event (in weeks) [95% CI]	N.E.	N.E.		
Patients with event at end of study, % KM estimate [95% CI]	30.3 [23.1; 37.6]	33.6 [23.2; 44.1]	0.97 [0.65; 1.46] 0.886	0.908
Class III/IV				
N'	25	27		
Patients with event, n (%)	17 (68.0)	13 (48.1)		
Median time to event (in weeks) [95% CI]	27.7 [8.7; 49.3]	N.E.		
Patients with event at end of study, % KM estimate [95% CI]	69.8 [51.2; 88.5]	49.5 [30.0; 69.0]	1.56 [0.76; 3.21] 0.229	0.218

N: Number of patients
N': Number of patients in the analysis
CI: Confidence interval
HR: Hazard ratio
KM: Kaplan-Meier
N.E.: Not estimable
.....

Analysis method:
Interaction test and HR obtained from Cox proportional hazards model: log(hazard ratio) = treatment + NYHA/Ross class + treatment * NYHA/Ross class + age group

Table 11.4 All cause hospitalization by region (FAS), time to event analysis

	Treatment Groups		Comparison	
All cause hospitalization by region (FAS)	**LCZ696 (N=182)**	**Enalapril (N=184)**	**HR [95% CI] p-value**	**Logrank test p-value**
America, N	58	69		
Europe, N	58	55		
Asia/Pacific and other, N	66	60		
First all cause hospitalization				
Interaction test	**p = 0.675**			
America				
N'	58	69		
Patients with event, n (%)	23 (39.7)	26 (37.7)		
Median time to event (in weeks) [95% CI]	N.E.	N.E.		
Patients with event at end of study, % KM estimate [95% CI]	40.1 [27.4; 52.8]	44.4 [27.9; 60.9]	1.07 [0.61; 1.87] 0.821	0.909
Europe				
N'	58	55		
Patients with event, n (%)	22 (37.9)	21 (38.2)		
Median time to event (in weeks) [95% CI]	N.E.	N.E.		
Patients with event at end of study, % KM estimate [95% CI]	37.9 [25.4; 50.4]	38.2 [25.3; 51.0]	0.97 [0.53; 1.76] 0.915	0.963
Asia/Pacific and other				
N'	66	60		
Patients with event, n (%)	19 (28.8)	12 (20.0)		
Median time to event (in weeks) [95% CI]	N.E.	N.E.		
Patients with event at end of study, % KM estimate [95% CI]	29.8 [18.5; 41.0]	20.5 [10.2; 30.9]	1.47 [0.71; 3.03] 0.300	0.444

N: Number of patients
N': Number of patients in the analysis
CI: Confidence interval
HR: Hazard ratio
KM: Kaplan-Meier
N.E.: Not estimable
.....

Analysis method:
Interaction test and HR obtained from Cox proportional hazards model: log(hazard ratio) = treatment + region + treatment * region + age group + NYHA/Ross class

Table 11.5 All cause hospitalization by gender (FAS), time to event analysis

	Treatment Groups		Comparison	
All cause hospitalization by gender (FAS)	**LCZ696 (N=182)**	**Enalapril (N=184)**	**HR [95% CI] p-value**	**Logrank test p-value**
Male, N	88	91		
Female, N	94	93		
First all cause hospitalization				
Interaction test	**p = 0.633**			
Male				
N'	88	91		
Patients with event, n (%)	28 (31.8)	24 (26.4)		
Median time to event (in weeks) [95% CI]	N.E.	N.E.		
Patients with event at end of study, % KM estimate [95% CI]	32.4 [22.5; 42.3]	32.7 [17.6; 47.8]	1.20 [0.69; 2.07] 0.515	0.551
Female				
N'	94	93		
Patients with event, n (%)	36 (38.3)	35 (37.6)		
Median time to event (in weeks) [95% CI]	N.E.	N.E.		
Patients with event at end of study, % KM estimate [95% CI]	38.7 [28.8; 48.6]	38.4 [28.4; 48.5]	1.01 [0.63; 1.60] 0.978	0.917

N: Number of patients
N': Number of patients in the analysis
CI: Confidence interval
HR: Hazard ratio
KM: Kaplan-Meier
N.E.: Not estimable
.....

Analysis method:
Interaction test and HR obtained from Cox proportional hazards model: log(hazard ratio) = treatment + gender + treatment * gender + age group + NYHA/Ross class

Table 11.6 All cause hospitalization by COVID-19 period (FAS), time to event analysis

	Treatment Groups		Comparison	
All cause hospitalization by COVID-19 period (FAS)	**LCZ696 (N=182)**	**Enalapril (N=184)**	**HR [95% CI] p-value**	**Logrank test p-value**
Pre-pandemic, N	79	83		
Pre- and during-pandemic, N	62	59		
During-pandemic, N	41	42		
First all cause hospitalization				
Interaction test	**p = 0.445**			
Pre-pandemic				
N'	79	83		
Patients with event, n (%)	28 (35.4)	30 (36.1)		
Median time to event (in weeks) [95% CI]	N.E.	N.E.		
Patients with event at end of study, % KM estimate [95% CI]	36.2 [25.5; 46.9]	45.9 [27.1; 64.7]	0.93 [0.55; 1.56] 0.777	0.751
Pre- and during-pandemic				
N'	62	59		
Patients with event, n (%)	23 (37.1)	20 (33.9)		
Median time to event (in weeks) [95% CI]	N.E.	N.E.		
Patients with event at end of study, % KM estimate [95% CI]	37.1 [25.1; 49.1]	33.9 [21.8; 46.0]	1.02 [0.56; 1.86] 0.945	0.922
During-pandemic				
N'	41	42		
Patients with event, n (%)	13 (31.7)	9 (21.4)		
Median time to event (in weeks) [95% CI]	N.E.	N.E.		
Patients with event at end of study, % KM estimate [95% CI]	32.0 [17.6; 46.4]	21.4 [9.0; 33.8]	1.76 [0.75; 4.12] 0.194	0.275

N: Number of patients
N': Number of patients in the analysis
CI: Confidence interval
HR: Hazard ratio
KM: Kaplan-Meier
N.E.: Not estimable
.....

Analysis method:
Interaction test and HR obtained from Cox proportional hazards model: log(hazard ratio) = treatment + COVID-19 period + treatment * COVID-19 period + age group + NYHA/Ross class

Table 11.7 All cause hospitalization by race (FAS), time to event analysis

	Treatment Groups		Comparison	
All cause hospitalization by race (FAS)	**LCZ696 (N=182)**	**Enalapril (N=184)**	**HR [95% CI] p-value**	**Logrank test p-value**
Caucasian, N	86	90		
Black, N	23	25		
Asian, N	55	45		
Unknown or other, N	18	24		
First all cause hospitalization				
Interaction test	**p = 0.257**			
Caucasian				
N'	86	90		
Patients with event, n (%)	27 (31.4)	28 (31.1)		
Median time to event (in weeks) [95% CI]	N.E.	N.E.		
Patients with event at end of study, % KM estimate [95% CI]	31.6 [21.7; 41.4]	40.9 [21.1; 60.6]	0.96 [0.56; 1.62] 0.869	0.989
Black				
N'	23	25		
Patients with event, n (%)	12 (52.2)	16 (64.0)		
Median time to event (in weeks) [95% CI]	45.4 [19.3; N.E.]	28.0 [9.7; N.E.]		
Patients with event at end of study, % KM estimate [95% CI]	52.2 [31.8; 72.6]	64.8 [45.8; 83.8]	0.73 [0.35; 1.55] 0.417	0.453
Asian				
N'	55	45		
Patients with event, n (%)	17 (30.9)	9 (20.0)		
Median time to event (in weeks) [95% CI]	N.E.	N.E.		
Patients with event at end of study, % KM estimate [95% CI]	32.3 [19.6; 45.0]	20.5 [8.5; 32.4]	1.77 [0.79; 3.98] 0.169	0.351
Unknown or other				
N'	18	24		
Patients with event, n (%)	8 (44.4)	6 (25.0)		
Median time to event (in weeks) [95% CI]	N.E.	N.E.		
Patients with event at end of study, % KM estimate [95% CI]	44.4 [21.5; 67.4]	25.0 [7.7; 42.3]	2.07 [0.71; 6.01] 0.182	0.267

	Treatment Groups		Comparison	
All cause hospitalization by race (FAS)	**LCZ696 (N=182)**	**Enalapril (N=184)**	**HR [95% CI] p-value**	**Logrank test p-value**

N: Number of patients
N': Number of patients in the analysis
CI: Confidence interval
HR: Hazard ratio
KM: Kaplan-Meier
N.E.: Not estimable
.....

Analysis method:
Interaction test and HR obtained from Cox proportional hazards model: log(hazard ratio) = treatment + race + treatment * race + age group + NYHA/Ross class

12 HF hospitalization and worsening of heart failure events, event rate

Table 12.1 HF hospitalization and worsening of heart failure events (FAS), event rate analysis

	Treatment Groups		Comparison
HF hospitalization and worsening of heart failure events (FAS)	**LCZ696 (N=182)**	**Enalapril (N=184)**	**Rate ratio [95% CI] p-value**
HF hospitalization events			
N'	182	184	
Number of patients with event	27	25	
Number of events	40	39	
Annualized event rate [95% CI]	0.20 [0.13; 0.32]	0.21 [0.13; 0.34]	0.95 [0.49; 1.83] 0.881
HF hospitalization events with intensive care unit stay			
N'	182	184	
Number of patients with event	20	16	
Number of events	28	21	
Annualized event rate [95% CI]	0.14 [0.09; 0.24]	0.12 [0.07; 0.20]	1.23 [0.58; 2.61] 0.585
HF hospitalization events without intensive care unit stay			
N'	182	184	
Number of patients with event	12	12	
Number of events	12	18	
Annualized event rate [95% CI]	0.06 [0.03; 0.12]	0.09 [0.05; 0.17]	0.65 [0.25; 1.67] 0.366
Worsening of heart failure events without hospitalization			
N'	182	184	
Number of patients with event	5	3	
Number of events	6	3	
Annualized event rate [95% CI]	0.02 [<0.01; 0.07]	0.01 [<0.01; 0.05]	1.99 [0.43; 9.20] 0.379

N: Number of patients
N': Number of patients in the analysis
CI: Confidence interval
.....

Analysis method:
Annualized event rate and rate ratio from negative binomial regression: log(events) = treatment + age group + NYHA/Ross class

Table 12.2 HF hospitalization and worsening of heart failure events by age group (FAS), event rate analysis

	Treatment Groups		Comparison
HF hospitalization and worsening of heart failure events by age group (FAS)	**LCZ696 (N=182)**	**Enalapril (N=184)**	**Rate ratio [95% CI] p-value**
6 years to < 18 years, N	109	111	
1 year to < 6 years, N	73	73	
HF hospitalization events			
Interaction test	**p = 0.441**		
6 years to < 18 years			
N'	109	111	
Number of patients with event	21	18	
Number of events	33	27	
Annualized event rate [95% CI]	0.33 [0.19; 0.56]	0.29 [0.16; 0.52]	1.13 [0.52; 2.47] 0.762
1 year to < 6 years			
N'	73	73	
Number of patients with event	6	7	
Number of events	7	12	
Annualized event rate [95% CI]	0.09 [0.04; 0.22]	0.14 [0.06; 0.30]	0.64 [0.20; 2.12] 0.470
HF hospitalization events with intensive care unit stay			
Interaction test	**p = 0.601**		
6 years to < 18 years			
N'	109	111	
Number of patients with event	15	11	
Number of events	22	15	
Annualized event rate [95% CI]	0.21 [0.11; 0.38]	0.15 [0.08; 0.29]	1.41 [0.57; 3.47] 0.457
1 year to < 6 years			
N'	73	73	
Number of patients with event	5	5	
Number of events	6	6	
Annualized event rate [95% CI]	0.08 [0.03; 0.20]	0.08 [0.03; 0.22]	0.91 [0.23; 3.55] 0.894

	Treatment Groups		Comparison
HF hospitalization and worsening of heart failure events by age group (FAS)	**LCZ696 (N=182)**	**Enalapril (N=184)**	**Rate ratio [95% CI] p-value**
HF hospitalization events without intensive care unit stay			
Interaction test	**p = 0.203**		
6 years to < 18 years			
N'	109	111	
Number of patients with event	11	9	
Number of events	11	12	
Annualized event rate [95% CI]	0.11 [0.05; 0.24]	0.13 [0.06; 0.28]	0.84 [0.29; 2.46] 0.756
1 year to < 6 years			
N'	73	73	
Number of patients with event	1	3	
Number of events	1	6	
Annualized event rate [95% CI]	0.01 [<0.01; 0.10]	0.08 [0.03; 0.22]	0.17 [0.02; 1.60] 0.120
Worsening of heart failure events without hospitalization			
Interaction test	**N.E.**		
6 years to < 18 years			
N'	109	111	
Number of patients with event	5	2	
Number of events	6	2	
Annualized event rate [95% CI]	0.05 [0.02; 0.14]	0.02 [<0.01; 0.08]	3.33 [0.55; 20.28] 0.192
1 year to < 6 years			
N'	73	73	
Number of patients with event	0	1	
Number of events	0	1	
Annualized event rate [95% CI]	N.E.	N.E.	N.E.

N: Number of patients
N': Number of patients in the analysis
CI: Confidence interval
N.E.: Not estimable
.....

Analysis method:
Interaction test, annualized event rate and rate ratio from negative binomial regression: log(events) = treatment + age group + treatment * age group + NYHA/Ross class

Exceptionally applied model(s) due to non-convergence:
HF hospitalization events without intensive care unit stay: log(events) = treatment + age group + treatment * age group
Worsening of heart failure events without hospitalization: log(events) = treatment + NYHA/Ross class, by age group

Table 12.3 HF hospitalization and worsening of heart failure events by NYHA/Ross class (FAS), event rate analysis

	Treatment Groups		Comparison
HF hospitalization and worsening of heart failure events by NYHA/Ross class (FAS)	**LCZ696 (N=182)**	**Enalapril (N=184)**	**Rate ratio [95% CI] p-value**
Class I/II, N	157	157	
Class III/IV, N	25	27	
HF hospitalization events			
Interaction test	**p = 0.470**		
Class I/II			
N'	157	157	
Number of patients with event	18	18	
Number of events	30	25	
Annualized event rate [95% CI]	0.18 [0.11; 0.31]	0.17 [0.10; 0.29]	1.07 [0.52; 2.23] 0.851
Class III/IV			
N'	25	27	
Number of patients with event	9	7	
Number of events	10	14	
Annualized event rate [95% CI]	0.39 [0.13; 1.11]	0.66 [0.24; 1.78]	0.59 [0.14; 2.54] 0.476
HF hospitalization events with intensive care unit stay			
Interaction test	**p = 0.957**		
Class I/II			
N'	157	157	
Number of patients with event	13	12	
Number of events	20	15	
Annualized event rate [95% CI]	0.13 [0.07; 0.22]	0.10 [0.05; 0.19]	1.22 [0.52; 2.84] 0.645
Class III/IV			
N'	25	27	
Number of patients with event	7	4	
Number of events	8	6	
Annualized event rate [95% CI]	0.31 [0.10; 0.94]	0.24 [0.07; 0.80]	1.28 [0.25; 6.61] 0.765

	Treatment Groups		Comparison
HF hospitalization and worsening of heart failure events by NYHA/Ross class (FAS)	**LCZ696 (N=182)**	**Enalapril (N=184)**	**Rate ratio [95% CI] p-value**
HF hospitalization events without intensive care unit stay			
Interaction test	**p = 0.170**		
Class I/II			
N'	157	157	
Number of patients with event	10	7	
Number of events	10	10	
Annualized event rate [95% CI]	0.05 [0.02; 0.12]	0.06 [0.03; 0.13]	0.92 [0.32; 2.67] 0.880
Class III/IV			
N'	25	27	
Number of patients with event	2	5	
Number of events	2	8	
Annualized event rate [95% CI]	0.07 [0.01; 0.41]	0.44 [0.12; 1.63]	0.16 [0.02; 1.53] 0.112
Worsening of heart failure events without hospitalization			
Interaction test	**N.E.**		
Class I/II			
N'	157	157	
Number of patients with event	3	2	
Number of events	4	2	
Annualized event rate [95% CI]	0.02 [<0.01; 0.07]	0.01 [<0.01; 0.06]	1.70 [0.24; 11.83] 0.591
Class III/IV			
N'	25	27	
Number of patients with event	2	1	
Number of events	2	1	
Annualized event rate [95% CI]	N.E.	N.E.	N.E.

N: Number of patients
N': Number of patients in the analysis
CI: Confidence interval
N.E.: Not estimable
.....

Analysis method:
Interaction test, annualized event rate and rate ratio from negative binomial regression: log(events) = treatment + NYHA/Ross class + treatment * NYHA/Ross class + age group

Exceptionally applied model(s) due to non-convergence:
Worsening of heart failure events without hospitalization: log(events) = treatment + age group, by NYHA/Ross class

Table 12.4 HF hospitalization and worsening of heart failure events by region (FAS), event rate analysis

	Treatment Groups		Comparison
HF hospitalization and worsening of heart failure events by region (FAS)	**LCZ696 (N=182)**	**Enalapril (N=184)**	**Rate ratio [95% CI] p-value**
America, N	58	69	
Europe, N	58	55	
Asia/Pacific and other, N	66	60	
HF hospitalization events			
Interaction test	**p = 0.745**		
America			
N'	58	69	
Number of patients with event	8	8	
Number of events	11	13	
Annualized event rate [95% CI]	0.17 [0.07; 0.40]	0.22 [0.10; 0.48]	0.78 [0.25; 2.43] 0.668
Europe			
N'	58	55	
Number of patients with event	10	9	
Number of events	18	16	
Annualized event rate [95% CI]	0.28 [0.13; 0.59]	0.21 [0.09; 0.47]	1.34 [0.44; 4.10] 0.603
Asia/Pacific and other			
N'	66	60	
Number of patients with event	9	8	
Number of events	11	10	
Annualized event rate [95% CI]	0.16 [0.07; 0.37]	0.21 [0.09; 0.51]	0.77 [0.23; 2.55] 0.673
HF hospitalization events with intensive care unit stay			
Interaction test	**p = 0.465**		
America			
N'	58	69	
Number of patients with event	4	6	
Number of events	6	8	
Annualized event rate [95% CI]	0.10 [0.04; 0.27]	0.14 [0.05; 0.33]	0.73 [0.19; 2.78] 0.646

	Treatment Groups		Comparison
HF hospitalization and worsening of heart failure events by region (FAS)	**LCZ696 (N=182)**	**Enalapril (N=184)**	**Rate ratio [95% CI] p-value**
Europe			
N'	58	55	
Number of patients with event	9	5	
Number of events	14	7	
Annualized event rate [95% CI]	0.22 [0.10; 0.48]	0.10 [0.03; 0.26]	2.25 [0.63; 7.99] 0.209
Asia/Pacific and other			
N'	66	60	
Number of patients with event	7	5	
Number of events	8	6	
Annualized event rate [95% CI]	0.12 [0.05; 0.29]	0.12 [0.04; 0.33]	1.00 [0.26; 3.86] 0.996
HF hospitalization events without intensive care unit stay			
Interaction test	**p = 0.836**		
America			
N'	58	69	
Number of patients with event	5	3	
Number of events	5	5	
Annualized event rate [95% CI]	0.06 [0.02; 0.20]	0.07 [0.02; 0.20]	0.94 [0.20; 4.44] 0.933
Europe			
N'	58	55	
Number of patients with event	4	6	
Number of events	4	9	
Annualized event rate [95% CI]	0.06 [0.02; 0.20]	0.12 [0.04; 0.33]	0.48 [0.10; 2.31] 0.357
Asia/Pacific and other			
N'	66	60	
Number of patients with event	3	3	
Number of events	3	4	
Annualized event rate [95% CI]	0.05 [0.01; 0.18]	0.08 [0.02; 0.26]	0.63 [0.10; 3.77] 0.609

	Treatment Groups		Comparison
HF hospitalization and worsening of heart failure events by region (FAS)	**LCZ696 (N=182)**	**Enalapril (N=184)**	**Rate ratio [95% CI] p-value**
Worsening of heart failure events without hospitalization			
Interaction test	**N.E.**		
America			
N'	58	69	
Number of patients with event	3	2	
Number of events	4	2	
Annualized event rate [95% CI]	0.06 [0.02; 0.23]	0.03 [<0.01; 0.14]	2.06 [0.28; 15.06] 0.477
Europe			
N'	58	55	
Number of patients with event	0	1	
Number of events	0	1	
Annualized event rate [95% CI]	N.E.	N.E.	N.E.
Asia/Pacific and other			
N'	66	60	
Number of patients with event	2	0	
Number of events	2	0	
Annualized event rate [95% CI]	N.E.	N.E.	N.E.

N: Number of patients
N': Number of patients in the analysis
CI: Confidence interval
N.E.: Not estimable
.....

Analysis method:
Interaction test, annualized event rate and rate ratio from negative binomial regression: log(events) = treatment + region + treatment * region + age group + NYHA/Ross class

Exceptionally applied model(s) due to non-convergence:
Worsening of heart failure events without hospitalization: log(events) = treatment + age group + NYHA/Ross class, by region

Table 12.5 HF hospitalization and worsening of heart failure events by gender (FAS), event rate analysis

	Treatment Groups		Comparison
HF hospitalization and worsening of heart failure events by gender (FAS)	**LCZ696 (N=182)**	**Enalapril (N=184)**	**Rate ratio [95% CI] p-value**
Male, N	88	91	
Female, N	94	93	
HF hospitalization events			
Interaction test	**p = 0.753**		
Male			
N'	88	91	
Number of patients with event	15	12	
Number of events	22	20	
Annualized event rate [95% CI]	0.23 [0.12; 0.44]	0.22 [0.12; 0.42]	1.05 [0.42; 2.62] 0.912
Female			
N'	94	93	
Number of patients with event	12	13	
Number of events	18	19	
Annualized event rate [95% CI]	0.17 [0.09; 0.34]	0.20 [0.10; 0.40]	0.85 [0.33; 2.19] 0.741
HF hospitalization events with intensive care unit stay			
Interaction test	**p = 0.591**		
Male			
N'	88	91	
Number of patients with event	10	7	
Number of events	14	8	
Annualized event rate [95% CI]	0.15 [0.07; 0.30]	0.09 [0.04; 0.22]	1.55 [0.51; 4.73] 0.439
Female			
N'	94	93	
Number of patients with event	10	9	
Number of events	14	13	
Annualized event rate [95% CI]	0.14 [0.07; 0.29]	0.14 [0.06; 0.29]	1.03 [0.37; 2.84] 0.961

	Treatment Groups		Comparison
HF hospitalization and worsening of heart failure events by gender (FAS)	**LCZ696 (N=182)**	**Enalapril (N=184)**	**Rate ratio [95% CI] p-value**
HF hospitalization events without intensive care unit stay			
Interaction test	**p = 0.871**		
Male			
N'	88	91	
Number of patients with event	8	7	
Number of events	8	12	
Annualized event rate [95% CI]	0.08 [0.03; 0.20]	0.12 [0.05; 0.25]	0.70 [0.21; 2.29] 0.554
Female			
N'	94	93	
Number of patients with event	4	5	
Number of events	4	6	
Annualized event rate [95% CI]	0.03 [0.01; 0.11]	0.06 [0.02; 0.16]	0.60 [0.13; 2.69] 0.501
Worsening of heart failure events without hospitalization			
Interaction test	**p = 0.700**		
Male			
N'	88	91	
Number of patients with event	3	1	
Number of events	3	1	
Annualized event rate [95% CI]	0.02 [<0.01; 0.10]	<0.01 [<0.01; 0.07]	2.85 [0.25; 32.30] 0.398
Female			
N'	94	93	
Number of patients with event	2	2	
Number of events	3	2	
Annualized event rate [95% CI]	0.02 [<0.01; 0.09]	0.01 [<0.01; 0.08]	1.53 [0.21; 11.46] 0.677

N: Number of patients
N': Number of patients in the analysis
CI: Confidence interval
.....

Analysis method:
Interaction test, annualized event rate and rate ratio from negative binomial regression: log(events) = treatment + gender + treatment * gender + age group + NYHA/Ross class

Table 12.6 HF hospitalization and worsening of heart failure events by COVID-19 period (FAS), event rate analysis

	Treatment Groups		Comparison
HF hospitalization and worsening of heart failure events by COVID-19 period (FAS)	**LCZ696 (N=182)**	**Enalapril (N=184)**	**Rate ratio [95% CI] p-value**
Pre-pandemic, N	79	83	
Pre- and during-pandemic, N	62	59	
During-pandemic, N	41	42	
HF hospitalization events			
Interaction test	**p = 0.535**		
Pre-pandemic			
N'	79	83	
Number of patients with event	14	13	
Number of events	22	19	
Annualized event rate [95% CI]	0.30 [0.16; 0.58]	0.27 [0.14; 0.55]	1.10 [0.43; 2.81] 0.835
Pre- and during-pandemic			
N'	62	59	
Number of patients with event	7	8	
Number of events	9	15	
Annualized event rate [95% CI]	0.12 [0.05; 0.28]	0.21 [0.09; 0.46]	0.57 [0.17; 1.84] 0.345
During-pandemic			
N'	41	42	
Number of patients with event	6	4	
Number of events	9	5	
Annualized event rate [95% CI]	0.17 [0.06; 0.45]	0.11 [0.04; 0.35]	1.54 [0.34; 6.88] 0.574
HF hospitalization events with intensive care unit stay			
Interaction test	**p = 0.201**		
Pre-pandemic			
N'	79	83	
Number of patients with event	10	9	
Number of events	15	11	
Annualized event rate [95% CI]	0.20 [0.10; 0.41]	0.14 [0.07; 0.32]	1.38 [0.49; 3.93] 0.546

	Treatment Groups		Comparison
HF hospitalization and worsening of heart failure events by COVID-19 period (FAS)	**LCZ696 (N=182)**	**Enalapril (N=184)**	**Rate ratio [95% CI] p-value**
Pre- and during-pandemic			
N'	62	59	
Number of patients with event	5	6	
Number of events	6	9	
Annualized event rate [95% CI]	0.08 [0.03; 0.21]	0.14 [0.06; 0.33]	0.57 [0.15; 2.11] 0.398
During-pandemic			
N'	41	42	
Number of patients with event	5	1	
Number of events	7	1	
Annualized event rate [95% CI]	0.14 [0.05; 0.40]	0.02 [<0.01; 0.19]	6.15 [0.60; 63.25] 0.126
HF hospitalization events without intensive care unit stay			
Interaction test	**p = 0.923**		
Pre-pandemic			
N'	79	83	
Number of patients with event	7	5	
Number of events	7	8	
Annualized event rate [95% CI]	0.08 [0.03; 0.22]	0.11 [0.04; 0.29]	0.75 [0.20; 2.87] 0.676
Pre- and during-pandemic			
N'	62	59	
Number of patients with event	3	4	
Number of events	3	6	
Annualized event rate [95% CI]	0.04 [0.01; 0.16]	0.07 [0.02; 0.22]	0.62 [0.10; 3.69] 0.600
During-pandemic			
N'	41	42	
Number of patients with event	2	3	
Number of events	2	4	
Annualized event rate [95% CI]	0.03 [<0.01; 0.20]	0.08 [0.02; 0.30]	0.45 [0.05; 3.94] 0.468

	Treatment Groups		Comparison
HF hospitalization and worsening of heart failure events by COVID-19 period (FAS)	**LCZ696 (N=182)**	**Enalapril (N=184)**	**Rate ratio [95% CI] p-value**
Worsening of heart failure events without hospitalization			
Interaction test	**N.E.**		
Pre-pandemic			
N'	79	83	
Number of patients with event	3	1	
Number of events	4	1	
Annualized event rate [95% CI]	<0.01 [<0.01; <0.01]	<0.01 [<0.01; <0.01]	4.08 [0.32; 51.84] 0.278
Pre- and during-pandemic			
N'	62	59	
Number of patients with event	2	2	
Number of events	2	2	
Annualized event rate [95% CI]	0.03 [<0.01; 0.12]	0.03 [<0.01; 0.13]	0.95 [0.13; 6.76] 0.961
During-pandemic			
N'	41	42	
Number of patients with event	0	0	
Number of events	0	0	
Annualized event rate [95% CI]	N.E.	N.E.	N.E.

N: Number of patients
N': Number of patients in the analysis
CI: Confidence interval
N.E.: Not estimable
.....

Analysis method:
Interaction test, annualized event rate and rate ratio from negative binomial regression: log(events) = treatment + COVID-19 period + treatment * COVID-19 period + age group + NYHA/Ross class

Exceptionally applied model(s) due to non-convergence:
Worsening of heart failure events without hospitalization: log(events) = treatment + age group, by COVID-19 period

Table 12.7 HF hospitalization and worsening of heart failure events by race (FAS), event rate analysis

	Treatment Groups		Comparison
HF hospitalization and worsening of heart failure events by race (FAS)	**LCZ696 (N=182)**	**Enalapril (N=184)**	**Rate ratio [95% CI] p-value**
Caucasian, N	86	90	
Black, N	23	25	
Asian, N	55	45	
Unknown or other, N	18	24	
HF hospitalization events			
Interaction test	**p = 0.982**		
Caucasian			
N'	86	90	
Number of patients with event	9	8	
Number of events	13	13	
Annualized event rate [95% CI]	0.12 [0.06; 0.25]	0.12 [0.06; 0.24]	1.04 [0.40; 2.75] 0.933
Black			
N'	23	25	
Number of patients with event	9	8	
Number of events	15	16	
Annualized event rate [95% CI]	0.58 [0.24; 1.40]	0.70 [0.29; 1.71]	0.83 [0.24; 2.87] 0.763
Asian			
N'	55	45	
Number of patients with event	7	6	
Number of events	8	6	
Annualized event rate [95% CI]	0.15 [0.06; 0.35]	0.14 [0.05; 0.37]	1.06 [0.28; 4.01] 0.927
Unknown or other			
N'	18	24	
Number of patients with event	2	3	
Number of events	4	4	
Annualized event rate [95% CI]	0.26 [0.07; 0.93]	0.20 [0.06; 0.74]	1.28 [0.21; 7.89] 0.792

	Treatment Groups		Comparison
HF hospitalization and worsening of heart failure events by race (FAS)	**LCZ696 (N=182)**	**Enalapril (N=184)**	**Rate ratio [95% CI] p-value**
HF hospitalization events with intensive care unit stay			
Interaction test	**p = 0.940**		
Caucasian			
N'	86	90	
Number of patients with event	7	5	
Number of events	10	6	
Annualized event rate [95% CI]	0.09 [0.04; 0.21]	0.06 [0.02; 0.14]	1.67 [0.52; 5.39] 0.392
Black			
N'	23	25	
Number of patients with event	6	5	
Number of events	10	8	
Annualized event rate [95% CI]	0.39 [0.15; 1.02]	0.29 [0.10; 0.82]	1.34 [0.33; 5.43] 0.684
Asian			
N'	55	45	
Number of patients with event	5	4	
Number of events	5	4	
Annualized event rate [95% CI]	0.09 [0.03; 0.25]	0.10 [0.03; 0.31]	0.91 [0.19; 4.30] 0.905
Unknown or other			
N'	18	24	
Number of patients with event	2	2	
Number of events	3	3	
Annualized event rate [95% CI]	0.19 [0.05; 0.80]	0.17 [0.04; 0.72]	1.11 [0.15; 8.10] 0.916
HF hospitalization events without intensive care unit stay			
Interaction test	**N.E.**		
Caucasian			
N'	86	90	
Number of patients with event	3	4	
Number of events	3	7	
Annualized event rate [95% CI]	0.04 [<0.01; 0.19]	0.08 [0.03; 0.25]	0.54 [0.08; 3.58] 0.525

	Treatment Groups		Comparison
HF hospitalization and worsening of heart failure events by race (FAS)	**LCZ696 (N=182)**	**Enalapril (N=184)**	**Rate ratio [95% CI] p-value**
Black			
N'	23	25	
Number of patients with event	5	5	
Number of events	5	8	
Annualized event rate [95% CI]	0.21 [0.07; 0.62]	0.42 [0.16; 1.14]	0.49 [0.11; 2.14] 0.345
Asian			
N'	55	45	
Number of patients with event	3	2	
Number of events	3	2	
Annualized event rate [95% CI]	0.06 [0.02; 0.18]	0.05 [0.01; 0.19]	1.21 [0.20; 7.24] 0.835
Unknown or other			
N'	18	24	
Number of patients with event	1	1	
Number of events	1	1	
Annualized event rate [95% CI]	N.E.	N.E.	N.E.
Worsening of heart failure events without hospitalization			
Interaction test	**N.E.**		
Caucasian			
N'	86	90	
Number of patients with event	3	1	
Number of events	4	1	
Annualized event rate [95% CI]	<0.01 [<0.01; <0.01]	<0.01 [<0.01; <0.01]	4.13 [0.34; 50.57] 0.267
Black			
N'	23	25	
Number of patients with event	0	1	
Number of events	0	1	
Annualized event rate [95% CI]	N.E.	N.E.	N.E.
Asian			
N'	55	45	
Number of patients with event	2	0	
Number of events	2	0	
Annualized event rate [95% CI]	N.E.	N.E.	N.E.

	Treatment Groups		Comparison
HF hospitalization and worsening of heart failure events by race (FAS)	**LCZ696 (N=182)**	**Enalapril (N=184)**	**Rate ratio [95% CI] p-value**
Unknown or other			
N'	18	24	
Number of patients with event	0	1	
Number of events	0	1	
Annualized event rate [95% CI]	N.E.	N.E.	N.E.

N: Number of patients
N': Number of patients in the analysis
CI: Confidence interval
N.E.: Not estimable
.....

Analysis method:
Interaction test, annualized event rate and rate ratio from negative binomial regression: log(events) = treatment + race + treatment * race + age group + NYHA/Ross class

Exceptionally applied model(s) due to non-convergence:
HF hospitalization events without intensive care unit stay: log(events) = treatment, by race
Worsening of heart failure events without hospitalization: log(events) = treatment + age group + NYHA/Ross class, by race

13 HF hospitalization and worsening of heart failure events, time to first event

Table 13.1 HF hospitalization and worsening of heart failure events (FAS), time to event analysis

	Treatment Groups		Comparison	
HF hospitalization and worsening of heart failure events (FAS)	**LCZ696 (N=182)**	**Enalapril (N=184)**	**HR [95% CI] p-value**	**Logrank test p-value**
First HF hospitalization				
N'	182	184		
Patients with event, n (%)	27 (14.8)	25 (13.6)		
Median time to event (in weeks) [95% CI]	N.E.	N.E.		
Patients with event at end of study, % KM estimate [95% CI]	15.1 [9.8; 20.3]	13.9 [8.8; 18.9]	1.10 [0.64; 1.89] 0.741	0.807
First HF hospitalization with intensive care unit stay				
N'	182	184		
Patients with event, n (%)	20 (11.0)	16 (8.7)		
Median time to event (in weeks) [95% CI]	N.E.	N.E.		
Patients with event at end of study, % KM estimate [95% CI]	11.2 [6.6; 15.8]	9.0 [4.8; 13.2]	1.28 [0.66; 2.47] 0.466	0.508
First HF hospitalization without intensive care unit stay				
N'	182	184		
Patients with event, n (%)	12 (6.6)	12 (6.5)		
Median time to event (in weeks) [95% CI]	N.E.	N.E.		
Patients with event at end of study, % KM estimate [95% CI]	6.7 [3.0; 10.4]	6.8 [3.1; 10.5]	0.99 [0.45; 2.21] 0.989	0.964
First worsening of heart failure without hospitalization				
N'	182	184		
Patients with event, n (%)	5 (2.7)	3 (1.6)		
Median time to event (in weeks) [95% CI]	N.E.	N.E.		
Patients with event at end of study, % KM estimate [95% CI]	2.8 [0.4; 5.3]	1.7 [0.0; 3.5]	1.65 [0.39; 6.90] 0.494	0.498

	Treatment Groups		Comparison	
HF hospitalization and worsening of heart failure events (FAS)	**LCZ696 (N=182)**	**Enalapril (N=184)**	**HR [95% CI] p-value**	**Logrank test p-value**

N: Number of patients
N': Number of patients in the analysis
CI: Confidence interval
HR: Hazard ratio
KM: Kaplan-Meier
N.E.: Not estimable
.....

Analysis method:
HR obtained from Cox proportional hazards model: log(hazard ratio) = treatment + age group + NYHA/Ross class

Table 13.2 HF hospitalization and worsening of heart failure events by age group (FAS), time to event analysis

	Treatment Groups		Comparison	
HF hospitalization and worsening of heart failure events by age group (FAS)	**LCZ696 (N=182)**	**Enalapril (N=184)**	**HR [95% CI] p-value**	**Logrank test p-value**
6 years to < 18 years, N	109	111		
1 year to < 6 years, N	73	73		
First HF hospitalization				
Interaction test	**p = 0.665**			
6 years to < 18 years				
N'	109	111		
Patients with event, n (%)	21 (19.3)	18 (16.2)		
Median time to event (in weeks) [95% CI]	N.E.	N.E.		
Patients with event at end of study, % KM estimate [95% CI]	19.5 [12.0; 27.0]	16.9 [9.7; 24.0]	1.18 [0.63; 2.21] 0.615	0.684
1 year to < 6 years				
N'	73	73		
Patients with event, n (%)	6 (8.2)	7 (9.6)		
Median time to event (in weeks) [95% CI]	N.E.	N.E.		
Patients with event at end of study, % KM estimate [95% CI]	8.4 [2.0; 14.8]	9.6 [2.8; 16.3]	0.89 [0.30; 2.65] 0.834	0.811
First HF hospitalization with intensive care unit stay				
Interaction test	**p = 0.755**			
6 years to < 18 years				
N'	109	111		
Patients with event, n (%)	15 (13.8)	11 (9.9)		
Median time to event (in weeks) [95% CI]	N.E.	N.E.		
Patients with event at end of study, % KM estimate [95% CI]	14.0 [7.4; 20.6]	10.5 [4.6; 16.3]	1.36 [0.63; 2.97] 0.435	0.465
1 year to < 6 years				
N'	73	73		
Patients with event, n (%)	5 (6.8)	5 (6.8)		
Median time to event (in weeks) [95% CI]	N.E.	N.E.		
Patients with event at end of study, % KM estimate [95% CI]	7.0 [1.1; 12.9]	6.9 [1.1; 12.7]	1.08 [0.31; 3.73] 0.904	0.973

	Treatment Groups		Comparison	
HF hospitalization and worsening of heart failure events by age group (FAS)	**LCZ696 (N=182)**	**Enalapril (N=184)**	**HR [95% CI] p-value**	**Logrank test p-value**
First HF hospitalization without intensive care unit stay				
Interaction test	**p = 0.289**			
6 years to < 18 years				
N'	109	111		
Patients with event, n (%)	11 (10.1)	9 (8.1)		
Median time to event (in weeks) [95% CI]	N.E.	N.E.		
Patients with event at end of study, % KM estimate [95% CI]	10.3 [4.5; 16.1]	8.7 [3.2; 14.1]	1.22 [0.50; 2.94] 0.661	0.697
1 year to < 6 years				
N'	73	73		
Patients with event, n (%)	1 (1.4)	3 (4.1)		
Median time to event (in weeks) [95% CI]	N.E.	N.E.		
Patients with event at end of study, % KM estimate [95% CI]	1.4 [0.0; 4.1]	4.1 [0.0; 8.7]	0.33 [0.03; 3.15] 0.334	0.324
First worsening of heart failure without hospitalization				
N.A.[1]				

N: Number of patients
N': Number of patients in the analysis
CI: Confidence interval
HR: Hazard ratio
KM: Kaplan-Meier
N.A.: Not analyzed
N.E.: Not estimable
.....

Analysis method:
Interaction test and HR obtained from Cox proportional hazards model: log(hazard ratio) = treatment + age group + treatment * age group + NYHA/Ross class

[1] The subgroup analysis is not presented as all subgroups have less than 10 events.

Table 13.3 HF hospitalization and worsening of heart failure events by NYHA/Ross class (FAS), time to event analysis

	Treatment Groups		Comparison	
HF hospitalization and worsening of heart failure events by NYHA/Ross class (FAS)	**LCZ696 (N=182)**	**Enalapril (N=184)**	**HR [95% CI] p-value**	**Logrank test p-value**
Class I/II, N	157	157		
Class III/IV, N	25	27		
First HF hospitalization				
Interaction test	**p = 0.488**			
Class I/II				
N'	157	157		
Patients with event, n (%)	18 (11.5)	18 (11.5)		
Median time to event (in weeks) [95% CI]	N.E.	N.E.		
Patients with event at end of study, % KM estimate [95% CI]	11.7 [6.6; 16.7]	11.8 [6.7; 16.9]	0.96 [0.50; 1.85] 0.912	0.930
Class III/IV				
N'	25	27		
Patients with event, n (%)	9 (36.0)	7 (25.9)		
Median time to event (in weeks) [95% CI]	N.E.	N.E.		
Patients with event at end of study, % KM estimate [95% CI]	36.2 [17.3; 55.2]	25.9 [9.4; 42.5]	1.47 [0.55; 3.94] 0.448	0.454
First HF hospitalization with intensive care unit stay				
Interaction test	**p = 0.386**			
Class I/II				
N'	157	157		
Patients with event, n (%)	13 (8.3)	12 (7.6)		
Median time to event (in weeks) [95% CI]	N.E.	N.E.		
Patients with event at end of study, % KM estimate [95% CI]	8.4 [4.1; 12.8]	7.9 [3.6; 12.2]	1.05 [0.48; 2.31] 0.899	0.893
Class III/IV				
N'	25	27		
Patients with event, n (%)	7 (28.0)	4 (14.8)		
Median time to event (in weeks) [95% CI]	N.E.	N.E.		
Patients with event at end of study, % KM estimate [95% CI]	28.7 [10.7; 46.7]	14.8 [1.4; 28.2]	2.01 [0.59; 6.86] 0.267	0.248

	Treatment Groups		Comparison	
HF hospitalization and worsening of heart failure events by NYHA/Ross class (FAS)	**LCZ696 (N=182)**	**Enalapril (N=184)**	**HR [95% CI] p-value**	**Logrank test p-value**
First HF hospitalization without intensive care unit stay				
Interaction test	**p = 0.232**			
Class I/II				
N'	157	157		
Patients with event, n (%)	10 (6.4)	7 (4.5)		
Median time to event (in weeks) [95% CI]	N.E.	N.E.		
Patients with event at end of study, % KM estimate [95% CI]	6.5 [2.6; 10.4]	4.6 [1.3; 8.0]	1.37 [0.52; 3.61] 0.519	0.503
Class III/IV				
N'	25	27		
Patients with event, n (%)	2 (8.0)	5 (18.5)		
Median time to event (in weeks) [95% CI]	N.E.	N.E.		
Patients with event at end of study, % KM estimate [95% CI]	8.0 [0.0; 18.6]	19.8 [4.2; 35.5]	0.43 [0.08; 2.22] 0.314	0.281
First worsening of heart failure without hospitalization				
N.A.[1]				

N: Number of patients
N': Number of patients in the analysis
CI: Confidence interval
HR: Hazard ratio
KM: Kaplan-Meier
N.A.: Not analyzed
N.E.: Not estimable
.....

Analysis method:
Interaction test and HR obtained from Cox proportional hazards model: log(hazard ratio) = treatment + NYHA/Ross class + treatment * NYHA/Ross class + age group

[1] The subgroup analysis is not presented as all subgroups have less than 10 events.

Table 13.4 HF hospitalization and worsening of heart failure events by region (FAS), time to event analysis

	Treatment Groups		Comparison	
HF hospitalization and worsening of heart failure events by region (FAS)	**LCZ696 (N=182)**	**Enalapril (N=184)**	**HR [95% CI] p-value**	**Logrank test p-value**
America, N	58	69		
Europe, N	58	55		
Asia/Pacific and other, N	66	60		
First HF hospitalization				
Interaction test	**p = 0.989**			
America				
N'	58	69		
Patients with event, n (%)	8 (13.8)	8 (11.6)		
Median time to event (in weeks) [95% CI]	N.E.	N.E.		
Patients with event at end of study, % KM estimate [95% CI]	13.9 [4.9; 22.8]	12.0 [4.2; 19.8]	1.15 [0.43; 3.06] 0.780	0.727
Europe				
N'	58	55		
Patients with event, n (%)	10 (17.2)	9 (16.4)		
Median time to event (in weeks) [95% CI]	N.E.	N.E.		
Patients with event at end of study, % KM estimate [95% CI]	17.2 [7.5; 27.0]	16.4 [6.6; 26.1]	1.04 [0.42; 2.56] 0.930	0.886
Asia/Pacific and other				
N'	66	60		
Patients with event, n (%)	9 (13.6)	8 (13.3)		
Median time to event (in weeks) [95% CI]	N.E.	N.E.		
Patients with event at end of study, % KM estimate [95% CI]	14.3 [5.6; 23.0]	13.7 [4.9; 22.5]	1.08 [0.41; 2.80] 0.881	0.922

	Treatment Groups		Comparison	
HF hospitalization and worsening of heart failure events by region (FAS)	**LCZ696 (N=182)**	**Enalapril (N=184)**	**HR [95% CI] p-value**	**Logrank test p-value**
First HF hospitalization with intensive care unit stay				
Interaction test	**p = 0.566**			
America				
N'	58	69		
Patients with event, n (%)	4 (6.9)	6 (8.7)		
Median time to event (in weeks) [95% CI]	N.E.	N.E.		
Patients with event at end of study, % KM estimate [95% CI]	7.0 [0.4; 13.7]	9.1 [2.2; 16.1]	0.73 [0.20; 2.58] 0.621	0.669
Europe				
N'	58	55		
Patients with event, n (%)	9 (15.5)	5 (9.1)		
Median time to event (in weeks) [95% CI]	N.E.	N.E.		
Patients with event at end of study, % KM estimate [95% CI]	15.5 [6.2; 24.8]	9.1 [1.5; 16.7]	1.79 [0.60; 5.35] 0.298	0.301
Asia/Pacific and other				
N'	66	60		
Patients with event, n (%)	7 (10.6)	5 (8.3)		
Median time to event (in weeks) [95% CI]	N.E.	N.E.		
Patients with event at end of study, % KM estimate [95% CI]	11.2 [3.4; 19.1]	8.6 [1.4; 15.9]	1.37 [0.43; 4.32] 0.594	0.729
First HF hospitalization without intensive care unit stay				
Interaction test	**p = 0.514**			
America				
N'	58	69		
Patients with event, n (%)	5 (8.6)	3 (4.3)		
Median time to event (in weeks) [95% CI]	N.E.	N.E.		
Patients with event at end of study, % KM estimate [95% CI]	8.7 [1.4; 15.9]	4.5 [0.0; 9.5]	1.87 [0.45; 7.83] 0.391	0.342

	Treatment Groups		Comparison	
HF hospitalization and worsening of heart failure events by region (FAS)	**LCZ696 (N=182)**	**Enalapril (N=184)**	**HR [95% CI] p-value**	**Logrank test p-value**
Europe				
N'	58	55		
Patients with event, n (%)	4 (6.9)	6 (10.9)		
Median time to event (in weeks) [95% CI]	N.E.	N.E.		
Patients with event at end of study, % KM estimate [95% CI]	6.9 [0.4; 13.4]	10.9 [2.7; 19.1]	0.61 [0.17; 2.16] 0.442	0.469
Asia/Pacific and other				
N'	66	60		
Patients with event, n (%)	3 (4.5)	3 (5.0)		
Median time to event (in weeks) [95% CI]	N.E.	N.E.		
Patients with event at end of study, % KM estimate [95% CI]	5.0 [0.0; 10.4]	5.1 [0.0; 10.6]	0.95 [0.19; 4.70] 0.947	0.846
First worsening of heart failure without hospitalization				
N.A.[1]				

N: Number of patients
N': Number of patients in the analysis
CI: Confidence interval
HR: Hazard ratio
KM: Kaplan-Meier
N.A.: Not analyzed
N.E.: Not estimable
.....

Analysis method:
Interaction test and HR obtained from Cox proportional hazards model: log(hazard ratio) = treatment + region + treatment * region + age group + NYHA/Ross class

[1] The subgroup analysis is not presented as all subgroups have less than 10 events.

Table 13.5 HF hospitalization and worsening of heart failure events by gender (FAS), time to event analysis

	Treatment Groups		Comparison	
HF hospitalization and worsening of heart failure events by gender (FAS)	**LCZ696 (N=182)**	**Enalapril (N=184)**	**HR [95% CI] p-value**	**Logrank test p-value**
Male, N	88	91		
Female, N	94	93		
First HF hospitalization				
Interaction test	**p = 0.630**			
Male				
N'	88	91		
Patients with event, n (%)	15 (17.0)	12 (13.2)		
Median time to event (in weeks) [95% CI]	N.E.	N.E.		
Patients with event at end of study, % KM estimate [95% CI]	17.5 [9.4; 25.5]	13.6 [6.4; 20.8]	1.25 [0.58; 2.67] 0.569	0.532
Female				
N'	94	93		
Patients with event, n (%)	12 (12.8)	13 (14.0)		
Median time to event (in weeks) [95% CI]	N.E.	N.E.		
Patients with event at end of study, % KM estimate [95% CI]	12.8 [6.1; 19.6]	14.2 [7.0; 21.3]	0.95 [0.43; 2.09] 0.905	0.779
First HF hospitalization with intensive care unit stay				
Interaction test	**p = 0.680**			
Male				
N'	88	91		
Patients with event, n (%)	10 (11.4)	7 (7.7)		
Median time to event (in weeks) [95% CI]	N.E.	N.E.		
Patients with event at end of study, % KM estimate [95% CI]	11.8 [4.9; 18.6]	8.0 [2.3; 13.8]	1.48 [0.56; 3.90] 0.427	0.422
Female				
N'	94	93		
Patients with event, n (%)	10 (10.6)	9 (9.7)		
Median time to event (in weeks) [95% CI]	N.E.	N.E.		
Patients with event at end of study, % KM estimate [95% CI]	10.7 [4.4; 17.0]	9.9 [3.7; 16.0]	1.12 [0.45; 2.76] 0.805	0.872

	Treatment Groups		Comparison	
HF hospitalization and worsening of heart failure events by gender (FAS)	**LCZ696 (N=182)**	**Enalapril (N=184)**	**HR [95% CI] p-value**	**Logrank test p-value**
First HF hospitalization without intensive care unit stay				
Interaction test	**p = 0.791**			
Male				
N'	88	91		
Patients with event, n (%)	8 (9.1)	7 (7.7)		
Median time to event (in weeks) [95% CI]	N.E.	N.E.		
Patients with event at end of study, % KM estimate [95% CI]	9.5 [3.2; 15.7]	8.1 [2.3; 13.8]	1.06 [0.38; 2.94] 0.907	0.798
Female				
N'	94	93		
Patients with event, n (%)	4 (4.3)	5 (5.4)		
Median time to event (in weeks) [95% CI]	N.E.	N.E.		
Patients with event at end of study, % KM estimate [95% CI]	4.3 [0.2; 8.3]	5.6 [0.8; 10.4]	0.85 [0.23; 3.17] 0.807	0.705
First worsening of heart failure without hospitalization				
N.A.[1]				

N: Number of patients
N': Number of patients in the analysis
CI: Confidence interval
HR: Hazard ratio
KM: Kaplan-Meier
N.A.: Not analyzed
N.E.: Not estimable
.....

Analysis method:
Interaction test and HR obtained from Cox proportional hazards model: log(hazard ratio) = treatment + gender + treatment * gender + age group + NYHA/Ross class

[1] The subgroup analysis is not presented as all subgroups have less than 10 events.

Table 13.6 HF hospitalization and worsening of heart failure events by COVID-19 period (FAS), time to event analysis

	Treatment Groups		Comparison	
HF hospitalization and worsening of heart failure events by COVID-19 period (FAS)	**LCZ696 (N=182)**	**Enalapril (N=184)**	**HR [95% CI] p-value**	**Logrank test p-value**
Pre-pandemic, N	79	83		
Pre- and during-pandemic, N	62	59		
During-pandemic, N	41	42		
First HF hospitalization				
Interaction test	**p = 0.542**			
Pre-pandemic				
N'	79	83		
Patients with event, n (%)	14 (17.7)	13 (15.7)		
Median time to event (in weeks) [95% CI]	N.E.	N.E.		
Patients with event at end of study, % KM estimate [95% CI]	18.0 [9.4; 26.5]	16.6 [8.3; 24.9]	1.08 [0.51; 2.29] 0.847	0.787
Pre- and during-pandemic				
N'	62	59		
Patients with event, n (%)	7 (11.3)	8 (13.6)		
Median time to event (in weeks) [95% CI]	N.E.	N.E.		
Patients with event at end of study, % KM estimate [95% CI]	11.3 [3.4; 19.2]	13.6 [4.8; 22.3]	0.77 [0.28; 2.13] 0.620	0.636
During-pandemic				
N'	41	42		
Patients with event, n (%)	6 (14.6)	4 (9.5)		
Median time to event (in weeks) [95% CI]	N.E.	N.E.		
Patients with event at end of study, % KM estimate [95% CI]	14.8 [3.9; 25.7]	9.5 [0.6; 18.4]	1.93 [0.54; 6.89] 0.308	0.483

	Treatment Groups		Comparison	
HF hospitalization and worsening of heart failure events by COVID-19 period (FAS)	**LCZ696 (N=182)**	**Enalapril (N=184)**	**HR [95% CI] p-value**	**Logrank test p-value**
First HF hospitalization with intensive care unit stay				
Interaction test	**p = 0.237**			
Pre-pandemic				
N'	79	83		
Patients with event, n (%)	10 (12.7)	9 (10.8)		
Median time to event (in weeks) [95% CI]	N.E.	N.E.		
Patients with event at end of study, % KM estimate [95% CI]	13.0 [5.5; 20.6]	11.9 [4.6; 19.2]	1.11 [0.45; 2.74] 0.818	0.781
Pre- and during-pandemic				
N'	62	59		
Patients with event, n (%)	5 (8.1)	6 (10.2)		
Median time to event (in weeks) [95% CI]	N.E.	N.E.		
Patients with event at end of study, % KM estimate [95% CI]	8.1 [1.3; 14.8]	10.2 [2.5; 17.9]	0.76 [0.23; 2.49] 0.650	0.652
During-pandemic				
N'	41	42		
Patients with event, n (%)	5 (12.2)	1 (2.4)		
Median time to event (in weeks) [95% CI]	N.E.	N.E.		
Patients with event at end of study, % KM estimate [95% CI]	12.3 [2.2; 22.4]	2.4 [0.0; 7.0]	6.31 [0.74; 54.11] 0.093	0.087
First HF hospitalization without intensive care unit stay				
Interaction test	**p = 0.759**			
Pre-pandemic				
N'	79	83		
Patients with event, n (%)	7 (8.9)	5 (6.0)		
Median time to event (in weeks) [95% CI]	N.E.	N.E.		
Patients with event at end of study, % KM estimate [95% CI]	9.0 [2.7; 15.4]	6.4 [1.0; 11.8]	1.35 [0.43; 4.25] 0.609	0.562

	Treatment Groups		Comparison	
HF hospitalization and worsening of heart failure events by COVID-19 period (FAS)	**LCZ696 (N=182)**	**Enalapril (N=184)**	**HR [95% CI] p-value**	**Logrank test p-value**
Pre- and during-pandemic				
N'	62	59		
Patients with event, n (%)	3 (4.8)	4 (6.8)		
Median time to event (in weeks) [95% CI]	N.E.	N.E.		
Patients with event at end of study, % KM estimate [95% CI]	4.9 [0.0; 10.3]	6.8 [0.4; 13.3]	0.71 [0.16; 3.17] 0.654	0.639
During-pandemic				
N'	41	42		
Patients with event, n (%)	2 (4.9)	3 (7.1)		
Median time to event (in weeks) [95% CI]	N.E.	N.E.		
Patients with event at end of study, % KM estimate [95% CI]	4.9 [0.0; 11.5]	7.2 [0.0; 15.1]	0.76 [0.13; 4.56] 0.765	0.679
First worsening of heart failure without hospitalization				
N.A.[1]				

N: Number of patients
N': Number of patients in the analysis
CI: Confidence interval
HR: Hazard ratio
KM: Kaplan-Meier
N.A.: Not analyzed
N.E.: Not estimable
.....

Analysis method:
Interaction test and HR obtained from Cox proportional hazards model: log(hazard ratio) = treatment + COVID-19 period + treatment * COVID-19 period + age group + NYHA/Ross class

[1] The subgroup analysis is not presented as all subgroups have less than 10 events.

Table 13.7 HF hospitalization and worsening of heart failure events by race (FAS), time to event analysis

	Treatment Groups		Comparison	
HF hospitalization and worsening of heart failure events by race (FAS)	**LCZ696 (N=182)**	**Enalapril (N=184)**	**HR [95% CI] p-value**	**Logrank test p-value**
Caucasian, N	86	90		
Black, N	23	25		
Asian, N	55	45		
Unknown or other, N	18	24		
First HF hospitalization				
Interaction test	**p = 0.974**			
Caucasian				
N'	86	90		
Patients with event, n (%)	9 (10.5)	8 (8.9)		
Median time to event (in weeks) [95% CI]	N.E.	N.E.		
Patients with event at end of study, % KM estimate [95% CI]	10.5 [4.0; 17.0]	9.1 [3.1; 15.2]	1.11 [0.43; 2.89] 0.825	0.736
Black				
N'	23	25		
Patients with event, n (%)	9 (39.1)	8 (32.0)		
Median time to event (in weeks) [95% CI]	N.E.	N.E.		
Patients with event at end of study, % KM estimate [95% CI]	39.1 [19.2; 59.1]	32.9 [14.1; 51.7]	1.38 [0.53; 3.59] 0.507	0.636
Asian				
N'	55	45		
Patients with event, n (%)	7 (12.7)	6 (13.3)		
Median time to event (in weeks) [95% CI]	N.E.	N.E.		
Patients with event at end of study, % KM estimate [95% CI]	13.7 [4.2; 23.1]	13.6 [3.5; 23.8]	1.08 [0.36; 3.23] 0.888	0.825
Unknown or other				
N'	18	24		
Patients with event, n (%)	2 (11.1)	3 (12.5)		
Median time to event (in weeks) [95% CI]	N.E.	N.E.		
Patients with event at end of study, % KM estimate [95% CI]	11.1 [0.0; 25.6]	12.5 [0.0; 25.7]	0.91 [0.15; 5.49] 0.916	0.830

	Treatment Groups		Comparison	
HF hospitalization and worsening of heart failure events by race (FAS)	**LCZ696 (N=182)**	**Enalapril (N=184)**	**HR [95% CI] p-value**	**Logrank test p-value**
First HF hospitalization with intensive care unit stay				
Interaction test	**p = 0.996**			
Caucasian				
N'	86	90		
Patients with event, n (%)	7 (8.1)	5 (5.6)		
Median time to event (in weeks) [95% CI]	N.E.	N.E.		
Patients with event at end of study, % KM estimate [95% CI]	8.2 [2.4; 14.0]	5.7 [0.9; 10.6]	1.41 [0.45; 4.46] 0.555	0.503
Black				
N'	23	25		
Patients with event, n (%)	6 (26.1)	5 (20.0)		
Median time to event (in weeks) [95% CI]	N.E.	N.E.		
Patients with event at end of study, % KM estimate [95% CI]	26.1 [8.1; 44.0]	22.3 [4.9; 39.7]	1.24 [0.38; 4.05] 0.727	0.722
Asian				
N'	55	45		
Patients with event, n (%)	5 (9.1)	4 (8.9)		
Median time to event (in weeks) [95% CI]	N.E.	N.E.		
Patients with event at end of study, % KM estimate [95% CI]	9.9 [1.6; 18.2]	9.1 [0.6; 17.6]	1.18 [0.32; 4.42] 0.806	0.987
Unknown or other				
N'	18	24		
Patients with event, n (%)	2 (11.1)	2 (8.3)		
Median time to event (in weeks) [95% CI]	N.E.	N.E.		
Patients with event at end of study, % KM estimate [95% CI]	11.1 [0.0; 25.6]	8.3 [0.0; 19.4]	1.45 [0.20; 10.48] 0.711	0.822

	Treatment Groups		Comparison	
HF hospitalization and worsening of heart failure events by race (FAS)	**LCZ696 (N=182)**	**Enalapril (N=184)**	**HR [95% CI] p-value**	**Logrank test p-value**
First HF hospitalization without intensive care unit stay				
Interaction test	**p = 0.952**			
Caucasian				
N'	86	90		
Patients with event, n (%)	3 (3.5)	4 (4.4)		
Median time to event (in weeks) [95% CI]	N.E.	N.E.		
Patients with event at end of study, % KM estimate [95% CI]	3.5 [0.0; 7.4]	4.6 [0.2; 9.1]	0.73 [0.16; 3.27] 0.681	0.713
Black				
N'	23	25		
Patients with event, n (%)	5 (21.7)	5 (20.0)		
Median time to event (in weeks) [95% CI]	N.E.	N.E.		
Patients with event at end of study, % KM estimate [95% CI]	21.7 [4.9; 38.6]	20.8 [4.5; 37.2]	1.16 [0.34; 4.02] 0.813	0.909
Asian				
N'	55	45		
Patients with event, n (%)	3 (5.5)	2 (4.4)		
Median time to event (in weeks) [95% CI]	N.E.	N.E.		
Patients with event at end of study, % KM estimate [95% CI]	6.1 [0.0; 12.7]	4.6 [0.0; 10.8]	1.36 [0.23; 8.18] 0.735	0.873
Unknown or other				
N'	18	24		
Patients with event, n (%)	1 (5.6)	1 (4.2)		
Median time to event (in weeks) [95% CI]	N.E.	N.E.		
Patients with event at end of study, % KM estimate [95% CI]	5.6 [0.0; 16.1]	4.2 [0.0; 12.2]	1.20 [0.07; 19.53] 0.896	0.850

	Treatment Groups		Comparison	
HF hospitalization and worsening of heart failure events by race (FAS)	**LCZ696 (N=182)**	**Enalapril (N=184)**	**HR [95% CI] p-value**	**Logrank test p-value**
First worsening of heart failure without hospitalization				
N.A.[1]				

N: Number of patients
N': Number of patients in the analysis
CI: Confidence interval
HR: Hazard ratio
KM: Kaplan-Meier
N.A.: Not analyzed
N.E.: Not estimable
.....

Analysis method:
Interaction test and HR obtained from Cox proportional hazards model: log(hazard ratio) = treatment + race + treatment * race + age group + NYHA/Ross class

[1] The subgroup analysis is not presented as all subgroups have less than 10 events.

14 PGI-S change, considering cutoff date for the last visit

Table 14.1 PGI-S change considering cutoff (FAS), proportional odds model analysis

	Treatment Groups		Comparison
PGI-S change considering cutoff (FAS)	**LCZ696 (N=182)**	**Enalapril (N=184)**	**Cumulative OR [95% CI] p-value**
PGI-S score			
Week 52			
N' / N''	149 / 137	156 / 139	
Improved, n (%)	53 (35.6)	53 (34.0)	
Unchanged, n (%)	71 (47.7)	76 (48.7)	
Worsened, n (%)	25 (16.8)	27 (17.3)	1.16 [0.74; 1.82] 0.520

N: Number of patients
N': Number of patients in the analysis
N'': Number of patients with non-missing value (not imputed)
n (%): Number and percentage of patients in this category, percentage based on the number of patients in the analysis
CI: Confidence interval
OR: Odds ratio
.....

Imputation method: Missing values after the first category-1-event (investigator reported or positively adjudicated) were set to the worst category.

Analysis method:
Cumulative odds ratio from proportional cumulative odds model for ordinal response: logit(cumulative proportion) = treatment + baseline value + age group + NYHA/Ross class

Considering cutoff date: Nominal week 52 assessments that were performed later than 58 weeks after baseline were excluded from the analysis.

Table 14.2 PGI-S change considering cutoff by age group (FAS), proportional odds model analysis

	Treatment Groups		Comparison
PGI-S change considering cutoff by age group (FAS)	**LCZ696 (N=182)**	**Enalapril (N=184)**	**Cumulative OR [95% CI] p-value**
6 years to < 18 years, N	109	111	
1 year to < 6 years, N	73	73	
PGI-S score			
Week 52			
Interaction test	**p = 0.449**		
6 years to < 18 years			
N' / N"	91 / 82	94 / 81	
Improved, n (%)	31 (34.1)	36 (38.3)	
Unchanged, n (%)	42 (46.2)	42 (44.7)	
Worsened, n (%)	18 (19.8)	16 (17.0)	1.00 [0.56; 1.80] 0.996
1 year to < 6 years			
N' / N"	58 / 55	62 / 58	
Improved, n (%)	22 (37.9)	17 (27.4)	
Unchanged, n (%)	29 (50.0)	34 (54.8)	
Worsened, n (%)	7 (12.1)	11 (17.7)	1.43 [0.70; 2.93] 0.325

N: Number of patients
N': Number of patients in the analysis
N": Number of patients with non-missing value (not imputed)
n (%): Number and percentage of patients in this category, percentage based on the number of patients in the analysis
CI: Confidence interval
OR: Odds ratio
.....

Imputation method: Missing values after the first category-1-event (investigator reported or positively adjudicated) were set to the worst category.

Analysis method:
Interaction test and cumulative odds ratio from proportional cumulative odds model for ordinal response: logit(cumulative proportion) = treatment + age group + treatment * age group + baseline value + NYHA/Ross class

Considering cutoff date: Nominal week 52 assessments that were performed later than 58 weeks after baseline were excluded from the analysis.

Table 14.3 PGI-S change considering cutoff by NYHA/Ross class (FAS), proportional odds model analysis

	Treatment Groups		Comparison
PGI-S change considering cutoff by NYHA/Ross class (FAS)	**LCZ696 (N=182)**	**Enalapril (N=184)**	**Cumulative OR [95% CI] p-value**
Class I/II, N	157	157	
Class III/IV, N	25	27	
PGI-S score			
Week 52			
Interaction test	**p = 0.335**		
Class I/II			
N' / N"	128 / 119	132 / 118	
Improved, n (%)	42 (32.8)	40 (30.3)	
Unchanged, n (%)	66 (51.6)	69 (52.3)	
Worsened, n (%)	20 (15.6)	23 (17.4)	1.07 [0.66; 1.74] 0.788
Class III/IV			
N' / N"	21 / 18	24 / 21	
Improved, n (%)	11 (52.4)	13 (54.2)	
Unchanged, n (%)	5 (23.8)	7 (29.2)	
Worsened, n (%)	5 (23.8)	4 (16.7)	2.06 [0.60; 7.11] 0.254

N: Number of patients
N': Number of patients in the analysis
N": Number of patients with non-missing value (not imputed)
n (%): Number and percentage of patients in this category, percentage based on the number of patients in the analysis
CI: Confidence interval
OR: Odds ratio
.....

Imputation method: Missing values after the first category-1-event (investigator reported or positively adjudicated) were set to the worst category.

Analysis method:
Interaction test and cumulative odds ratio from proportional cumulative odds model for ordinal response: logit(cumulative proportion) = treatment + NYHA/Ross class + treatment * NYHA/Ross class + baseline value + age group

Considering cutoff date: Nominal week 52 assessments that were performed later than 58 weeks after baseline were excluded from the analysis.

Table 14.4 PGI-S change considering cutoff by region (FAS), proportional odds model analysis

	Treatment Groups		Comparison
PGI-S change considering cutoff by region (FAS)	**LCZ696 (N=182)**	**Enalapril (N=184)**	**Cumulative OR [95% CI] p-value**
America, N	58	69	
Europe, N	58	55	
Asia/Pacific and other, N	66	60	
PGI-S score			
Week 52			
Interaction test	**p = 0.669**		
America			
N' / N''	43 / 41	54 / 45	
Improved, n (%)	14 (32.6)	15 (27.8)	
Unchanged, n (%)	23 (53.5)	27 (50.0)	
Worsened, n (%)	6 (14.0)	12 (22.2)	1.51 [0.67; 3.38] 0.316
Europe			
N' / N''	50 / 47	51 / 49	
Improved, n (%)	18 (36.0)	18 (35.3)	
Unchanged, n (%)	24 (48.0)	28 (54.9)	
Worsened, n (%)	8 (16.0)	5 (9.8)	1.13 [0.52; 2.48] 0.761
Asia/Pacific and other			
N' / N''	56 / 49	51 / 45	
Improved, n (%)	21 (37.5)	20 (39.2)	
Unchanged, n (%)	24 (42.9)	21 (41.2)	
Worsened, n (%)	11 (19.6)	10 (19.6)	0.91 [0.42; 1.96] 0.805

	Treatment Groups		Comparison
PGI-S change considering cutoff by region (FAS)	**LCZ696 (N=182)**	**Enalapril (N=184)**	**Cumulative OR [95% CI] p-value**

N: Number of patients
N': Number of patients in the analysis
N'': Number of patients with non-missing value (not imputed)
n (%): Number and percentage of patients in this category, percentage based on the number of patients in the analysis
CI: Confidence interval
OR: Odds ratio
.....

Imputation method: Missing values after the first category-1-event (investigator reported or positively adjudicated) were set to the worst category.

Analysis method:
Interaction test and cumulative odds ratio from proportional cumulative odds model for ordinal response: logit(cumulative proportion) = treatment + region + treatment * region + baseline value + age group + NYHA/Ross class

Considering cutoff date: Nominal week 52 assessments that were performed later than 58 weeks after baseline were excluded from the analysis.

Table 14.5 PGI-S change considering cutoff by gender (FAS), proportional odds model analysis

	Treatment Groups		Comparison
PGI-S change considering cutoff by gender (FAS)	**LCZ696 (N=182)**	**Enalapril (N=184)**	**Cumulative OR [95% CI] p-value**
Male, N	88	91	
Female, N	94	93	
PGI-S score			
Week 52			
Interaction test	**p = 0.375**		
Male			
N' / N''	74 / 67	75 / 68	
Improved, n (%)	21 (28.4)	22 (29.3)	
Unchanged, n (%)	40 (54.1)	43 (57.3)	
Worsened, n (%)	13 (17.6)	10 (13.3)	0.95 [0.50; 1.80] 0.875
Female			
N' / N''	75 / 70	81 / 71	
Improved, n (%)	32 (42.7)	31 (38.3)	
Unchanged, n (%)	31 (41.3)	33 (40.7)	
Worsened, n (%)	12 (16.0)	17 (21.0)	1.43 [0.75; 2.72] 0.272

N: Number of patients
N': Number of patients in the analysis
N'': Number of patients with non-missing value (not imputed)
n (%): Number and percentage of patients in this category, percentage based on the number of patients in the analysis
CI: Confidence interval
OR: Odds ratio
.....

Imputation method: Missing values after the first category-1-event (investigator reported or positively adjudicated) were set to the worst category.

Analysis method:
Interaction test and cumulative odds ratio from proportional cumulative odds model for ordinal response: logit(cumulative proportion) = treatment + gender + treatment * gender + baseline value + age group + NYHA/Ross class

Considering cutoff date: Nominal week 52 assessments that were performed later than 58 weeks after baseline were excluded from the analysis.

Table 14.6 PGI-S change considering cutoff by COVID-19 period (FAS), proportional odds model analysis

	Treatment Groups		Comparison
PGI-S change considering cutoff by COVID-19 period (FAS)	**LCZ696 (N=182)**	**Enalapril (N=184)**	**Cumulative OR [95% CI] p-value**
Pre-pandemic, N	79	83	
Pre- and during-pandemic, N	62	59	
During-pandemic, N	41	42	
PGI-S score			
Week 52			
Interaction test	**p = 0.896**		
Pre-pandemic			
N' / N''	69 / 59	67 / 54	
Improved, n (%)	22 (31.9)	22 (32.8)	
Unchanged, n (%)	32 (46.4)	29 (43.3)	
Worsened, n (%)	15 (21.7)	16 (23.9)	1.16 [0.59; 2.28] 0.657
Pre- and during-pandemic			
N' / N''	43 / 42	48 / 45	
Improved, n (%)	16 (37.2)	15 (31.3)	
Unchanged, n (%)	22 (51.2)	26 (54.2)	
Worsened, n (%)	5 (11.6)	7 (14.6)	1.37 [0.59; 3.17] 0.458
During-pandemic			
N' / N''	37 / 36	41 / 40	
Improved, n (%)	15 (40.5)	16 (39.0)	
Unchanged, n (%)	17 (45.9)	21 (51.2)	
Worsened, n (%)	5 (13.5)	4 (9.8)	1.02 [0.42; 2.52] 0.957

	Treatment Groups		Comparison
PGI-S change considering cutoff by COVID-19 period (FAS)	**LCZ696 (N=182)**	**Enalapril (N=184)**	**Cumulative OR [95% CI] p-value**

N: Number of patients
N': Number of patients in the analysis
N'': Number of patients with non-missing value (not imputed)
n (%): Number and percentage of patients in this category, percentage based on the number of patients in the analysis
CI: Confidence interval
OR: Odds ratio
.....

Imputation method: Missing values after the first category-1-event (investigator reported or positively adjudicated) were set to the worst category.

Analysis method:
Interaction test and cumulative odds ratio from proportional cumulative odds model for ordinal response: logit(cumulative proportion) = treatment + COVID-19 period + treatment * COVID-19 period + baseline value + age group + NYHA/Ross class

Considering cutoff date: Nominal week 52 assessments that were performed later than 58 weeks after baseline were excluded from the analysis.

Table 14.7 PGI-S change considering cutoff by race (FAS), proportional odds model analysis

	Treatment Groups		Comparison
PGI-S change considering cutoff by race (FAS)	**LCZ696 (N=182)**	**Enalapril (N=184)**	**Cumulative OR [95% CI] p-value**
Caucasian, N	86	90	
Black, N	23	25	
Asian, N	55	45	
Unknown or other, N	18	24	
PGI-S score			
Week 52			
Interaction test	**p = 0.032 ***		
Caucasian			
N' / N"	74 / 69	79 / 72	
Improved, n (%)	28 (37.8)	23 (29.1)	
Unchanged, n (%)	35 (47.3)	43 (54.4)	
Worsened, n (%)	11 (14.9)	13 (16.5)	1.55 [0.81; 2.95] 0.182
Black			
N' / N"	17 / 17	21 / 16	
Improved, n (%)	9 (52.9)	7 (33.3)	
Unchanged, n (%)	8 (47.1)	8 (38.1)	
Worsened, n (%)	0 (0.0)	6 (28.6)	4.17 [1.05; 16.52] 0.042 *
Asian			
N' / N"	45 / 39	37 / 34	
Improved, n (%)	16 (35.6)	17 (45.9)	
Unchanged, n (%)	19 (42.2)	16 (43.2)	
Worsened, n (%)	10 (22.2)	4 (10.8)	0.57 [0.24; 1.38] 0.213
Unknown or other			
N' / N"	13 / 12	19 / 17	
Improved, n (%)	0 (0.0)	6 (31.6)	
Unchanged, n (%)	9 (69.2)	9 (47.4)	
Worsened, n (%)	4 (30.8)	4 (21.1)	0.39 [0.09; 1.58] 0.186

	Treatment Groups		Comparison
PGI-S change considering cutoff by race (FAS)	**LCZ696 (N=182)**	**Enalapril (N=184)**	**Cumulative OR [95% CI] p-value**

N: Number of patients
N': Number of patients in the analysis
N'': Number of patients with non-missing value (not imputed)
n (%): Number and percentage of patients in this category, percentage based on the number of patients in the analysis
CI: Confidence interval
OR: Odds ratio
*: $p < 0.05$
.....

Imputation method: Missing values after the first category-1-event (investigator reported or positively adjudicated) were set to the worst category.

Analysis method:
Interaction test and cumulative odds ratio from proportional cumulative odds model for ordinal response: logit(cumulative proportion) = treatment + race + treatment * race + baseline value + age group + NYHA/Ross class

Considering cutoff date: Nominal week 52 assessments that were performed later than 58 weeks after baseline were excluded from the analysis.

15 PGI-S change, not considering cutoff date for the last visit

Table 15.1 PGI-S change not considering cutoff (FAS), proportional odds model analysis

	Treatment Groups		Comparison
PGI-S change not considering cutoff (FAS)	**LCZ696 (N=182)**	**Enalapril (N=184)**	**Cumulative OR [95% CI] p-value**
PGI-S score			
Week 52			
N' / N''	169 / 157	170 / 154	
Improved, n (%)	58 (34.3)	59 (34.7)	
Unchanged, n (%)	83 (49.1)	84 (49.4)	
Worsened, n (%)	28 (16.6)	27 (15.9)	1.02 [0.66; 1.57] 0.931

N: Number of patients
N': Number of patients in the analysis
N'': Number of patients with non-missing value (not imputed)
n (%): Number and percentage of patients in this category, percentage based on the number of patients in the analysis
CI: Confidence interval
OR: Odds ratio
.....

Imputation method: Missing values after the first category-1-event (investigator reported or positively adjudicated) were set to the worst category.

Analysis method:
Cumulative odds ratio from proportional cumulative odds model for ordinal response: logit(cumulative proportion) = treatment + baseline value + age group + NYHA/Ross class

Not considering cutoff date: Nominal week 52 assessments that were performed later than 58 weeks after baseline were included in the analysis.

Table 15.2 PGI-S change not considering cutoff by age group (FAS), proportional odds model analysis

	Treatment Groups		Comparison
PGI-S change not considering cutoff by age group (FAS)	**LCZ696 (N=182)**	**Enalapril (N=184)**	**Cumulative OR [95% CI] p-value**
6 years to < 18 years, N	109	111	
1 year to < 6 years, N	73	73	
PGI-S score			
Week 52			
Interaction test	**p = 0.356**		
6 years to < 18 years			
N' / N"	101 / 92	101 / 89	
Improved, n (%)	34 (33.7)	40 (39.6)	
Unchanged, n (%)	47 (46.5)	45 (44.6)	
Worsened, n (%)	20 (19.8)	16 (15.8)	0.86 [0.49; 1.51] 0.588
1 year to < 6 years			
N' / N"	68 / 65	69 / 65	
Improved, n (%)	24 (35.3)	19 (27.5)	
Unchanged, n (%)	36 (52.9)	39 (56.5)	
Worsened, n (%)	8 (11.8)	11 (15.9)	1.29 [0.66; 2.54] 0.453

N: Number of patients
N': Number of patients in the analysis
N": Number of patients with non-missing value (not imputed)
n (%): Number and percentage of patients in this category, percentage based on the number of patients in the analysis
CI: Confidence interval
OR: Odds ratio
.....

Imputation method: Missing values after the first category-1-event (investigator reported or positively adjudicated) were set to the worst category.

Analysis method:
Interaction test and cumulative odds ratio from proportional cumulative odds model for ordinal response: logit(cumulative proportion) = treatment + age group + treatment * age group + baseline value + NYHA/Ross class

Not considering cutoff date: Nominal week 52 assessments that were performed later than 58 weeks after baseline were included in the analysis.

Table 15.3 PGI-S change not considering cutoff by NYHA/Ross class (FAS), proportional odds model analysis

	Treatment Groups		Comparison
PGI-S change not considering cutoff by NYHA/Ross class (FAS)	**LCZ696 (N=182)**	**Enalapril (N=184)**	**Cumulative OR [95% CI] p-value**
Class I/II, N	157	157	
Class III/IV, N	25	27	
PGI-S score			
Week 52			
Interaction test	**p = 0.364**		
Class I/II			
N' / N''	147 / 138	145 / 132	
Improved, n (%)	47 (32.0)	46 (31.7)	
Unchanged, n (%)	77 (52.4)	76 (52.4)	
Worsened, n (%)	23 (15.6)	23 (15.9)	0.95 [0.60; 1.51] 0.823
Class III/IV			
N' / N''	22 / 19	25 / 22	
Improved, n (%)	11 (50.0)	13 (52.0)	
Unchanged, n (%)	6 (27.3)	8 (32.0)	
Worsened, n (%)	5 (22.7)	4 (16.0)	1.73 [0.52; 5.80] 0.376

N: Number of patients
N': Number of patients in the analysis
N'': Number of patients with non-missing value (not imputed)
n (%): Number and percentage of patients in this category, percentage based on the number of patients in the analysis
CI: Confidence interval
OR: Odds ratio
.....

Imputation method: Missing values after the first category-1-event (investigator reported or positively adjudicated) were set to the worst category.

Analysis method:
Interaction test and cumulative odds ratio from proportional cumulative odds model for ordinal response: logit(cumulative proportion) = treatment + NYHA/Ross class + treatment * NYHA/Ross class + baseline value + age group

Not considering cutoff date: Nominal week 52 assessments that were performed later than 58 weeks after baseline were included in the analysis.

Table 15.4 PGI-S change not considering cutoff by region (FAS), proportional odds model analysis

	Treatment Groups		Comparison
PGI-S change not considering cutoff by region (FAS)	**LCZ696 (N=182)**	**Enalapril (N=184)**	**Cumulative OR [95% CI] p-value**
America, N	58	69	
Europe, N	58	55	
Asia/Pacific and other, N	66	60	
PGI-S score			
Week 52			
Interaction test	**p = 0.933**		
America			
N' / N''	52 / 50	62 / 54	
Improved, n (%)	17 (32.7)	18 (29.0)	
Unchanged, n (%)	26 (50.0)	33 (53.2)	
Worsened, n (%)	9 (17.3)	11 (17.7)	1.07 [0.51; 2.27] 0.851
Europe			
N' / N''	55 / 52	52 / 50	
Improved, n (%)	19 (34.5)	19 (36.5)	
Unchanged, n (%)	28 (50.9)	28 (53.8)	
Worsened, n (%)	8 (14.5)	5 (9.6)	1.07 [0.49; 2.31] 0.866
Asia/Pacific and other			
N' / N''	62 / 55	56 / 50	
Improved, n (%)	22 (35.5)	22 (39.3)	
Unchanged, n (%)	29 (46.8)	23 (41.1)	
Worsened, n (%)	11 (17.7)	11 (19.6)	0.90 [0.43; 1.89] 0.782

	Treatment Groups		Comparison
PGI-S change not considering cutoff by region (FAS)	**LCZ696 (N=182)**	**Enalapril (N=184)**	**Cumulative OR [95% CI] p-value**

N: Number of patients
N': Number of patients in the analysis
N'': Number of patients with non-missing value (not imputed)
n (%): Number and percentage of patients in this category, percentage based on the number of patients in the analysis
CI: Confidence interval
OR: Odds ratio
.....

Imputation method: Missing values after the first category-1-event (investigator reported or positively adjudicated) were set to the worst category.

Analysis method:
Interaction test and cumulative odds ratio from proportional cumulative odds model for ordinal response: logit(cumulative proportion) = treatment + region + treatment * region + baseline value + age group + NYHA/Ross class

Not considering cutoff date: Nominal week 52 assessments that were performed later than 58 weeks after baseline were included in the analysis.

Table 15.5 PGI-S change not considering cutoff by gender (FAS), proportional odds model analysis

	Treatment Groups		Comparison
PGI-S change not considering cutoff by gender (FAS)	**LCZ696 (N=182)**	**Enalapril (N=184)**	**Cumulative OR [95% CI] p-value**
Male, N	88	91	
Female, N	94	93	
PGI-S score			
Week 52			
Interaction test	**p = 0.204**		
Male			
N' / N"	81 / 74	84 / 77	
Improved, n (%)	22 (27.2)	27 (32.1)	
Unchanged, n (%)	44 (54.3)	47 (56.0)	
Worsened, n (%)	15 (18.5)	10 (11.9)	0.77 [0.42; 1.44] 0.417
Female			
N' / N"	88 / 83	86 / 77	
Improved, n (%)	36 (40.9)	32 (37.2)	
Unchanged, n (%)	39 (44.3)	37 (43.0)	
Worsened, n (%)	13 (14.8)	17 (19.8)	1.36 [0.74; 2.52] 0.323

N: Number of patients
N': Number of patients in the analysis
N": Number of patients with non-missing value (not imputed)
n (%): Number and percentage of patients in this category, percentage based on the number of patients in the analysis
CI: Confidence interval
OR: Odds ratio
.....

Imputation method: Missing values after the first category-1-event (investigator reported or positively adjudicated) were set to the worst category.

Analysis method:
Interaction test and cumulative odds ratio from proportional cumulative odds model for ordinal response: logit(cumulative proportion) = treatment + gender + treatment * gender + baseline value + age group + NYHA/Ross class

Not considering cutoff date: Nominal week 52 assessments that were performed later than 58 weeks after baseline were included in the analysis.

Table 15.6 PGI-S change not considering cutoff by COVID-19 period (FAS), proportional odds model analysis

	Treatment Groups		Comparison
PGI-S change not considering cutoff by COVID-19 period (FAS)	**LCZ696 (N=182)**	**Enalapril (N=184)**	**Cumulative OR [95% CI] p-value**
Pre-pandemic, N	79	83	
Pre- and during-pandemic, N	62	59	
During-pandemic, N	41	42	
PGI-S score			
Week 52			
Interaction test	**p = 0.992**		
Pre-pandemic			
N' / N''	73 / 63	74 / 61	
Improved, n (%)	23 (31.5)	24 (32.4)	
Unchanged, n (%)	34 (46.6)	34 (45.9)	
Worsened, n (%)	16 (21.9)	16 (21.6)	1.06 [0.55; 2.03] 0.871
Pre- and during-pandemic			
N' / N''	58 / 57	55 / 53	
Improved, n (%)	20 (34.5)	19 (34.5)	
Unchanged, n (%)	31 (53.4)	29 (52.7)	
Worsened, n (%)	7 (12.1)	7 (12.7)	0.99 [0.46; 2.11] 0.976
During-pandemic			
N' / N''	38 / 37	41 / 40	
Improved, n (%)	15 (39.5)	16 (39.0)	
Unchanged, n (%)	18 (47.4)	21 (51.2)	
Worsened, n (%)	5 (13.2)	4 (9.8)	1.03 [0.42; 2.53] 0.952

	Treatment Groups		Comparison
PGI-S change not considering cutoff by COVID-19 period (FAS)	**LCZ696 (N=182)**	**Enalapril (N=184)**	**Cumulative OR [95% CI] p-value**

N: Number of patients
N': Number of patients in the analysis
N'': Number of patients with non-missing value (not imputed)
n (%): Number and percentage of patients in this category, percentage based on the number of patients in the analysis
CI: Confidence interval
OR: Odds ratio
.....

Imputation method: Missing values after the first category-1-event (investigator reported or positively adjudicated) were set to the worst category.

Analysis method:
Interaction test and cumulative odds ratio from proportional cumulative odds model for ordinal response: logit(cumulative proportion) = treatment + COVID-19 period + treatment * COVID-19 period + baseline value + age group + NYHA/Ross class

Not considering cutoff date: Nominal week 52 assessments that were performed later than 58 weeks after baseline were included in the analysis.

Table 15.7 PGI-S change not considering cutoff by race (FAS), proportional odds model analysis

	Treatment Groups		Comparison
PGI-S change not considering cutoff by race (FAS)	**LCZ696 (N=182)**	**Enalapril (N=184)**	**Cumulative OR [95% CI] p-value**
Caucasian, N	86	90	
Black, N	23	25	
Asian, N	55	45	
Unknown or other, N	18	24	
PGI-S score			
Week 52			
Interaction test	**p = 0.192**		
Caucasian			
N' / N"	81 / 76	84 / 77	
Improved, n (%)	30 (37.0)	25 (29.8)	
Unchanged, n (%)	39 (48.1)	46 (54.8)	
Worsened, n (%)	12 (14.8)	13 (15.5)	1.34 [0.72; 2.49] 0.361
Black			
N' / N"	20 / 20	23 / 19	
Improved, n (%)	10 (50.0)	8 (34.8)	
Unchanged, n (%)	8 (40.0)	10 (43.5)	
Worsened, n (%)	2 (10.0)	5 (21.7)	2.14 [0.60; 7.59] 0.239
Asian			
N' / N"	51 / 45	42 / 39	
Improved, n (%)	17 (33.3)	19 (45.2)	
Unchanged, n (%)	24 (47.1)	18 (42.9)	
Worsened, n (%)	10 (19.6)	5 (11.9)	0.59 [0.26; 1.36] 0.218
Unknown or other			
N' / N"	17 / 16	21 / 19	
Improved, n (%)	1 (5.9)	7 (33.3)	
Unchanged, n (%)	12 (70.6)	10 (47.6)	
Worsened, n (%)	4 (23.5)	4 (19.0)	0.51 [0.14; 1.86] 0.309

	Treatment Groups		Comparison
PGI-S change not considering cutoff by race (FAS)	**LCZ696 (N=182)**	**Enalapril (N=184)**	**Cumulative OR [95% CI] p-value**

N: Number of patients
N': Number of patients in the analysis
N'': Number of patients with non-missing value (not imputed)
n (%): Number and percentage of patients in this category, percentage based on the number of patients in the analysis
CI: Confidence interval
OR: Odds ratio
.....

Imputation method: Missing values after the first category-1-event (investigator reported or positively adjudicated) were set to the worst category.

Analysis method:
Interaction test and cumulative odds ratio from proportional cumulative odds model for ordinal response: logit(cumulative proportion) = treatment + race + treatment * race + baseline value + age group + NYHA/Ross class

Not considering cutoff date: Nominal week 52 assessments that were performed later than 58 weeks after baseline were included in the analysis.

16 PGI-C score, considering cutoff date for the last visit

Table 16.1 PGI-C score considering cutoff (FAS), proportional odds model analysis

	Treatment Groups		Comparison
PGI-C score considering cutoff (FAS)	**LCZ696 (N=182)**	**Enalapril (N=184)**	**Cumulative OR [95% CI] p-value**
PGI-C score			
Week 52			
N' / N''	148 / 137	154 / 139	
Much Better, n (%)	47 (31.8)	40 (26.0)	
Better, n (%)	58 (39.2)	60 (39.0)	
No Change, n (%)	28 (18.9)	38 (24.7)	
Worse, n (%)	3 (2.0)	1 (0.6)	
Much Worse, n (%)	12 (8.1)	15 (9.7)	1.35 [0.89; 2.04] 0.159

N: Number of patients
N': Number of patients in the analysis
N'': Number of patients with non-missing value (not imputed)
n (%): Number and percentage of patients in this category, percentage based on the number of patients in the analysis
CI: Confidence interval
OR: Odds ratio
.....

Imputation method: Missing values after the first category-1-event (investigator reported or positively adjudicated) were set to the worst category.

Analysis method:
Cumulative odds ratio from proportional cumulative odds model for ordinal response: logit(cumulative proportion) = treatment + age group + NYHA/Ross class

Considering cutoff date: Nominal week 52 assessments that were performed later than 58 weeks after baseline were excluded from the analysis.

Table 16.2 PGI-C score considering cutoff by age group (FAS), proportional odds model analysis

	Treatment Groups		Comparison
PGI-C score considering cutoff by age group (FAS)	**LCZ696 (N=182)**	**Enalapril (N=184)**	**Cumulative OR [95% CI] p-value**
6 years to < 18 years, N	109	111	
1 year to < 6 years, N	73	73	
PGI-C score			
Week 52			
Interaction test	**p = 0.190**		
6 years to < 18 years			
N' / N"	91 / 82	92 / 81	
Much Better, n (%)	22 (24.2)	23 (25.0)	
Better, n (%)	37 (40.7)	34 (37.0)	
No Change, n (%)	21 (23.1)	23 (25.0)	
Worse, n (%)	1 (1.1)	1 (1.1)	
Much Worse, n (%)	10 (11.0)	11 (12.0)	1.08 [0.64; 1.83] 0.777
1 year to < 6 years			
N' / N"	57 / 55	62 / 58	
Much Better, n (%)	25 (43.9)	17 (27.4)	
Better, n (%)	21 (36.8)	26 (41.9)	
No Change, n (%)	7 (12.3)	15 (24.2)	
Worse, n (%)	2 (3.5)	0 (0.0)	
Much Worse, n (%)	2 (3.5)	4 (6.5)	1.91 [0.98; 3.72] 0.059

N: Number of patients
N': Number of patients in the analysis
N": Number of patients with non-missing value (not imputed)
n (%): Number and percentage of patients in this category, percentage based on the number of patients in the analysis
CI: Confidence interval
OR: Odds ratio
.....

Imputation method: Missing values after the first category-1-event (investigator reported or positively adjudicated) were set to the worst category.

Analysis method:
Interaction test and cumulative odds ratio from proportional cumulative odds model for ordinal response: logit(cumulative proportion) = treatment + age group + treatment * age group + NYHA/Ross class

Considering cutoff date: Nominal week 52 assessments that were performed later than 58 weeks after baseline were excluded from the analysis.

Table 16.3 PGI-C score considering cutoff by NYHA/Ross class (FAS), proportional odds model analysis

	Treatment Groups		Comparison
PGI-C score considering cutoff by NYHA/Ross class (FAS)	**LCZ696 (N=182)**	**Enalapril (N=184)**	**Cumulative OR [95% CI] p-value**
Class I/II, N	157	157	
Class III/IV, N	25	27	
PGI-C score			
Week 52			
Interaction test	**p = 0.697**		
Class I/II			
N' / N"	127 / 119	130 / 118	
Much Better, n (%)	37 (29.1)	30 (23.1)	
Better, n (%)	52 (40.9)	51 (39.2)	
No Change, n (%)	26 (20.5)	36 (27.7)	
Worse, n (%)	3 (2.4)	1 (0.8)	
Much Worse, n (%)	9 (7.1)	12 (9.2)	1.39 [0.89; 2.17] 0.150
Class III/IV			
N' / N"	21 / 18	24 / 21	
Much Better, n (%)	10 (47.6)	10 (41.7)	
Better, n (%)	6 (28.6)	9 (37.5)	
No Change, n (%)	2 (9.5)	2 (8.3)	
Worse, n (%)	0 (0.0)	0 (0.0)	
Much Worse, n (%)	3 (14.3)	3 (12.5)	1.10 [0.37; 3.28] 0.865

N: Number of patients
N': Number of patients in the analysis
N": Number of patients with non-missing value (not imputed)
n (%): Number and percentage of patients in this category, percentage based on the number of patients in the analysis
CI: Confidence interval
OR: Odds ratio
.....

Imputation method: Missing values after the first category-1-event (investigator reported or positively adjudicated) were set to the worst category.

Analysis method:
Interaction test and cumulative odds ratio from proportional cumulative odds model for ordinal response: logit(cumulative proportion) = treatment + NYHA/Ross class + treatment * NYHA/Ross class + age group

Considering cutoff date: Nominal week 52 assessments that were performed later than 58 weeks after baseline were excluded from the analysis.

Table 16.4 PGI-C score considering cutoff by region (FAS), proportional odds model analysis

	Treatment Groups		Comparison
PGI-C score considering cutoff by region (FAS)	**LCZ696 (N=182)**	**Enalapril (N=184)**	**Cumulative OR [95% CI] p-value**
America, N	58	69	
Europe, N	58	55	
Asia/Pacific and other, N	66	60	
PGI-C score			
Week 52			
Interaction test	**p = 0.835**		
America			
N' / N''	42 / 41	53 / 45	
Much Better, n (%)	12 (28.6)	13 (24.5)	
Better, n (%)	15 (35.7)	16 (30.2)	
No Change, n (%)	12 (28.6)	16 (30.2)	
Worse, n (%)	2 (4.8)	0 (0.0)	
Much Worse, n (%)	1 (2.4)	8 (15.1)	1.60 [0.77; 3.36] 0.211
Europe			
N' / N''	50 / 47	51 / 49	
Much Better, n (%)	17 (34.0)	12 (23.5)	
Better, n (%)	18 (36.0)	24 (47.1)	
No Change, n (%)	11 (22.0)	12 (23.5)	
Worse, n (%)	0 (0.0)	1 (2.0)	
Much Worse, n (%)	4 (8.0)	2 (3.9)	1.29 [0.63; 2.65] 0.481
Asia/Pacific and other			
N' / N''	56 / 49	50 / 45	
Much Better, n (%)	18 (32.1)	15 (30.0)	
Better, n (%)	25 (44.6)	20 (40.0)	
No Change, n (%)	5 (8.9)	10 (20.0)	
Worse, n (%)	1 (1.8)	0 (0.0)	
Much Worse, n (%)	7 (12.5)	5 (10.0)	1.18 [0.59; 2.38] 0.644

	Treatment Groups		Comparison
PGI-C score considering cutoff by region (FAS)	**LCZ696 (N=182)**	**Enalapril (N=184)**	**Cumulative OR [95% CI] p-value**

N: Number of patients
N': Number of patients in the analysis
N'': Number of patients with non-missing value (not imputed)
n (%): Number and percentage of patients in this category, percentage based on the number of patients in the analysis
CI: Confidence interval
OR: Odds ratio
.....

Imputation method: Missing values after the first category-1-event (investigator reported or positively adjudicated) were set to the worst category.

Analysis method:
Interaction test and cumulative odds ratio from proportional cumulative odds model for ordinal response: logit(cumulative proportion) = treatment + region + treatment * region + age group + NYHA/Ross class

Considering cutoff date: Nominal week 52 assessments that were performed later than 58 weeks after baseline were excluded from the analysis.

Table 16.5 PGI-C score considering cutoff by gender (FAS), proportional odds model analysis

	Treatment Groups		Comparison
PGI-C score considering cutoff by gender (FAS)	**LCZ696 (N=182)**	**Enalapril (N=184)**	**Cumulative OR [95% CI] p-value**
Male, N	88	91	
Female, N	94	93	
PGI-C score			
Week 52			
Interaction test	**p = 0.366**		
Male			
N' / N"	74 / 67	74 / 68	
Much Better, n (%)	21 (28.4)	19 (25.7)	
Better, n (%)	26 (35.1)	28 (37.8)	
No Change, n (%)	18 (24.3)	21 (28.4)	
Worse, n (%)	2 (2.7)	0 (0.0)	
Much Worse, n (%)	7 (9.5)	6 (8.1)	1.11 [0.61; 2.00] 0.736
Female			
N' / N"	74 / 70	80 / 71	
Much Better, n (%)	26 (35.1)	21 (26.3)	
Better, n (%)	32 (43.2)	32 (40.0)	
No Change, n (%)	10 (13.5)	17 (21.3)	
Worse, n (%)	1 (1.4)	1 (1.3)	
Much Worse, n (%)	5 (6.8)	9 (11.3)	1.62 [0.91; 2.91] 0.104

N: Number of patients
N': Number of patients in the analysis
N": Number of patients with non-missing value (not imputed)
n (%): Number and percentage of patients in this category, percentage based on the number of patients in the analysis
CI: Confidence interval
OR: Odds ratio
.....

Imputation method: Missing values after the first category-1-event (investigator reported or positively adjudicated) were set to the worst category.

Analysis method:
Interaction test and cumulative odds ratio from proportional cumulative odds model for ordinal response: logit(cumulative proportion) = treatment + gender + treatment * gender + age group + NYHA/Ross class

Considering cutoff date: Nominal week 52 assessments that were performed later than 58 weeks after baseline were excluded from the analysis.

Table 16.6 PGI-C score considering cutoff by COVID-19 period (FAS), proportional odds model analysis

	Treatment Groups		Comparison
PGI-C score considering cutoff by COVID-19 period (FAS)	**LCZ696 (N=182)**	**Enalapril (N=184)**	**Cumulative OR [95% CI] p-value**
Pre-pandemic, N	79	83	
Pre- and during-pandemic, N	62	59	
During-pandemic, N	41	42	
PGI-C score			
Week 52			
Interaction test	**p = 0.996**		
Pre-pandemic			
N' / N''	68 / 59	65 / 54	
Much Better, n (%)	19 (27.9)	16 (24.6)	
Better, n (%)	24 (35.3)	21 (32.3)	
No Change, n (%)	15 (22.1)	16 (24.6)	
Worse, n (%)	1 (1.5)	1 (1.5)	
Much Worse, n (%)	9 (13.2)	11 (16.9)	1.36 [0.73; 2.52] 0.332
Pre- and during-pandemic			
N' / N''	43 / 42	48 / 45	
Much Better, n (%)	14 (32.6)	12 (25.0)	
Better, n (%)	20 (46.5)	24 (50.0)	
No Change, n (%)	7 (16.3)	9 (18.8)	
Worse, n (%)	1 (2.3)	0 (0.0)	
Much Worse, n (%)	1 (2.3)	3 (6.3)	1.36 [0.64; 2.91] 0.426
During-pandemic			
N' / N''	37 / 36	41 / 40	
Much Better, n (%)	14 (37.8)	12 (29.3)	
Better, n (%)	14 (37.8)	15 (36.6)	
No Change, n (%)	6 (16.2)	13 (31.7)	
Worse, n (%)	1 (2.7)	0 (0.0)	
Much Worse, n (%)	2 (5.4)	1 (2.4)	1.42 [0.62; 3.21] 0.406

	Treatment Groups		Comparison
PGI-C score considering cutoff by COVID-19 period (FAS)	**LCZ696 (N=182)**	**Enalapril (N=184)**	**Cumulative OR [95% CI] p-value**

N: Number of patients
N': Number of patients in the analysis
N'': Number of patients with non-missing value (not imputed)
n (%): Number and percentage of patients in this category, percentage based on the number of patients in the analysis
CI: Confidence interval
OR: Odds ratio
.....

Imputation method: Missing values after the first category-1-event (investigator reported or positively adjudicated) were set to the worst category.

Analysis method:
Interaction test and cumulative odds ratio from proportional cumulative odds model for ordinal response: logit(cumulative proportion) = treatment + COVID-19 period + treatment * COVID-19 period + age group + NYHA/Ross class

Considering cutoff date: Nominal week 52 assessments that were performed later than 58 weeks after baseline were excluded from the analysis.

Table 16.7 PGI-C score considering cutoff by race (FAS), proportional odds model analysis

	Treatment Groups		Comparison
PGI-C score considering cutoff by race (FAS)	**LCZ696 (N=182)**	**Enalapril (N=184)**	**Cumulative OR [95% CI] p-value**
Caucasian, N	86	90	
Black, N	23	25	
Asian, N	55	45	
Unknown or other, N	18	24	
PGI-C score			
Week 52			
Interaction test	**p = 0.426**		
Caucasian			
N' / N"	73 / 69	78 / 72	
Much Better, n (%)	23 (31.5)	17 (21.8)	
Better, n (%)	28 (38.4)	36 (46.2)	
No Change, n (%)	16 (21.9)	18 (23.1)	
Worse, n (%)	1 (1.4)	1 (1.3)	
Much Worse, n (%)	5 (6.8)	6 (7.7)	1.32 [0.73; 2.37] 0.353
Black			
N' / N"	17 / 17	20 / 16	
Much Better, n (%)	8 (47.1)	5 (25.0)	
Better, n (%)	3 (17.6)	6 (30.0)	
No Change, n (%)	5 (29.4)	5 (25.0)	
Worse, n (%)	1 (5.9)	0 (0.0)	
Much Worse, n (%)	0 (0.0)	4 (20.0)	2.47 [0.75; 8.12] 0.136
Asian			
N' / N"	45 / 39	37 / 34	
Much Better, n (%)	12 (26.7)	14 (37.8)	
Better, n (%)	22 (48.9)	12 (32.4)	
No Change, n (%)	4 (8.9)	8 (21.6)	
Worse, n (%)	1 (2.2)	0 (0.0)	
Much Worse, n (%)	6 (13.3)	3 (8.1)	0.86 [0.39; 1.92] 0.713

	Treatment Groups		Comparison
PGI-C score considering cutoff by race (FAS)	**LCZ696 (N=182)**	**Enalapril (N=184)**	**Cumulative OR [95% CI] p-value**
Unknown or other			
N' / N''	13 / 12	19 / 17	
Much Better, n (%)	4 (30.8)	4 (21.1)	
Better, n (%)	5 (38.5)	6 (31.6)	
No Change, n (%)	3 (23.1)	7 (36.8)	
Worse, n (%)	0 (0.0)	0 (0.0)	
Much Worse, n (%)	1 (7.7)	2 (10.5)	2.24 [0.61; 8.19] 0.223

N: Number of patients
N': Number of patients in the analysis
N'': Number of patients with non-missing value (not imputed)
n (%): Number and percentage of patients in this category, percentage based on the number of patients in the analysis
CI: Confidence interval
OR: Odds ratio
.....

Imputation method: Missing values after the first category-1-event (investigator reported or positively adjudicated) were set to the worst category.

Analysis method:
Interaction test and cumulative odds ratio from proportional cumulative odds model for ordinal response: logit(cumulative proportion) = treatment + race + treatment * race + age group + NYHA/Ross class

Considering cutoff date: Nominal week 52 assessments that were performed later than 58 weeks after baseline were excluded from the analysis.

17 PGI-C score, not considering cutoff date for the last visit

Table 17.1 PGI-C score not considering cutoff (FAS), proportional odds model analysis

	Treatment Groups		Comparison
PGI-C score not considering cutoff (FAS)	**LCZ696 (N=182)**	**Enalapril (N=184)**	**Cumulative OR [95% CI] p-value**
PGI-C score			
Week 52			
N' / N"	168 / 157	168 / 154	
Much Better, n (%)	54 (32.1)	47 (28.0)	
Better, n (%)	69 (41.1)	63 (37.5)	
No Change, n (%)	30 (17.9)	43 (25.6)	
Worse, n (%)	3 (1.8)	1 (0.6)	
Much Worse, n (%)	12 (7.1)	14 (8.3)	1.33 [0.90; 1.98] 0.151

N: Number of patients
N': Number of patients in the analysis
N": Number of patients with non-missing value (not imputed)
n (%): Number and percentage of patients in this category, percentage based on the number of patients in the analysis
CI: Confidence interval
OR: Odds ratio
.....

Imputation method: Missing values after the first category-1-event (investigator reported or positively adjudicated) were set to the worst category.

Analysis method:
Cumulative odds ratio from proportional cumulative odds model for ordinal response: logit(cumulative proportion) = treatment + age group + NYHA/Ross class

Not considering cutoff date: Nominal week 52 assessments that were performed later than 58 weeks after baseline were included in the analysis.

Table 17.2 PGI-C score not considering cutoff by age group (FAS), proportional odds model analysis

	Treatment Groups		Comparison
PGI-C score not considering cutoff by age group (FAS)	**LCZ696 (N=182)**	**Enalapril (N=184)**	**Cumulative OR [95% CI] p-value**
6 years to < 18 years, N	109	111	
1 year to < 6 years, N	73	73	
PGI-C score			
Week 52			
Interaction test	**p = 0.424**		
6 years to < 18 years			
N' / N"	101 / 92	99 / 89	
Much Better, n (%)	26 (25.7)	25 (25.3)	
Better, n (%)	42 (41.6)	36 (36.4)	
No Change, n (%)	22 (21.8)	27 (27.3)	
Worse, n (%)	1 (1.0)	1 (1.0)	
Much Worse, n (%)	10 (9.9)	10 (10.1)	1.17 [0.71; 1.94] 0.543
1 year to < 6 years			
N' / N"	67 / 65	69 / 65	
Much Better, n (%)	28 (41.8)	22 (31.9)	
Better, n (%)	27 (40.3)	27 (39.1)	
No Change, n (%)	8 (11.9)	16 (23.2)	
Worse, n (%)	2 (3.0)	0 (0.0)	
Much Worse, n (%)	2 (3.0)	4 (5.8)	1.62 [0.87; 3.03] 0.128

N: Number of patients
N': Number of patients in the analysis
N": Number of patients with non-missing value (not imputed)
n (%): Number and percentage of patients in this category, percentage based on the number of patients in the analysis
CI: Confidence interval
OR: Odds ratio
.....

Imputation method: Missing values after the first category-1-event (investigator reported or positively adjudicated) were set to the worst category.

Analysis method:
Interaction test and cumulative odds ratio from proportional cumulative odds model for ordinal response: logit(cumulative proportion) = treatment + age group + treatment * age group + NYHA/Ross class

Not considering cutoff date: Nominal week 52 assessments that were performed later than 58 weeks after baseline were included in the analysis.

Table 17.3 PGI-C score not considering cutoff by NYHA/Ross class (FAS), proportional odds model analysis

	Treatment Groups		Comparison
PGI-C score not considering cutoff by NYHA/Ross class (FAS)	**LCZ696 (N=182)**	**Enalapril (N=184)**	**Cumulative OR [95% CI] p-value**
Class I/II, N	157	157	
Class III/IV, N	25	27	
PGI-C score			
Week 52			
Interaction test	**p = 0.973**		
Class I/II			
N' / N"	146 / 138	143 / 132	
Much Better, n (%)	43 (29.5)	37 (25.9)	
Better, n (%)	63 (43.2)	54 (37.8)	
No Change, n (%)	28 (19.2)	40 (28.0)	
Worse, n (%)	3 (2.1)	1 (0.7)	
Much Worse, n (%)	9 (6.2)	11 (7.7)	1.33 [0.87; 2.03] 0.185
Class III/IV			
N' / N"	22 / 19	25 / 22	
Much Better, n (%)	11 (50.0)	10 (40.0)	
Better, n (%)	6 (27.3)	9 (36.0)	
No Change, n (%)	2 (9.1)	3 (12.0)	
Worse, n (%)	0 (0.0)	0 (0.0)	
Much Worse, n (%)	3 (13.6)	3 (12.0)	1.36 [0.47; 3.96] 0.575

N: Number of patients
N': Number of patients in the analysis
N": Number of patients with non-missing value (not imputed)
n (%): Number and percentage of patients in this category, percentage based on the number of patients in the analysis
CI: Confidence interval
OR: Odds ratio
.....

Imputation method: Missing values after the first category-1-event (investigator reported or positively adjudicated) were set to the worst category.

Analysis method:
Interaction test and cumulative odds ratio from proportional cumulative odds model for ordinal response: logit(cumulative proportion) = treatment + NYHA/Ross class + treatment * NYHA/Ross class + age group

Not considering cutoff date: Nominal week 52 assessments that were performed later than 58 weeks after baseline were included in the analysis.

Table 17.4 PGI-C score not considering cutoff by region (FAS), proportional odds model analysis

	Treatment Groups		Comparison
PGI-C score not considering cutoff by region (FAS)	**LCZ696 (N=182)**	**Enalapril (N=184)**	**Cumulative OR [95% CI] p-value**
America, N	58	69	
Europe, N	58	55	
Asia/Pacific and other, N	66	60	
PGI-C score			
Week 52			
Interaction test	**p = 0.574**		
America			
N' / N''	51 / 50	61 / 54	
Much Better, n (%)	17 (33.3)	16 (26.2)	
Better, n (%)	18 (35.3)	18 (29.5)	
No Change, n (%)	13 (25.5)	20 (32.8)	
Worse, n (%)	2 (3.9)	0 (0.0)	
Much Worse, n (%)	1 (2.0)	7 (11.5)	1.79 [0.90; 3.55] 0.094
Europe			
N' / N''	55 / 52	52 / 50	
Much Better, n (%)	17 (30.9)	13 (25.0)	
Better, n (%)	22 (40.0)	24 (46.2)	
No Change, n (%)	12 (21.8)	12 (23.1)	
Worse, n (%)	0 (0.0)	1 (1.9)	
Much Worse, n (%)	4 (7.3)	2 (3.8)	1.17 [0.59; 2.36] 0.651
Asia/Pacific and other			
N' / N''	62 / 55	55 / 50	
Much Better, n (%)	20 (32.3)	18 (32.7)	
Better, n (%)	29 (46.8)	21 (38.2)	
No Change, n (%)	5 (8.1)	11 (20.0)	
Worse, n (%)	1 (1.6)	0 (0.0)	
Much Worse, n (%)	7 (11.3)	5 (9.1)	1.12 [0.57; 2.18] 0.743

	Treatment Groups		Comparison
PGI-C score not considering cutoff by region (FAS)	**LCZ696 (N=182)**	**Enalapril (N=184)**	**Cumulative OR [95% CI] p-value**

N: Number of patients
N': Number of patients in the analysis
N'': Number of patients with non-missing value (not imputed)
n (%): Number and percentage of patients in this category, percentage based on the number of patients in the analysis
CI: Confidence interval
OR: Odds ratio
.....

Imputation method: Missing values after the first category-1-event (investigator reported or positively adjudicated) were set to the worst category.

Analysis method:
Interaction test and cumulative odds ratio from proportional cumulative odds model for ordinal response: logit(cumulative proportion) = treatment + region + treatment * region + age group + NYHA/Ross class

Not considering cutoff date: Nominal week 52 assessments that were performed later than 58 weeks after baseline were included in the analysis.

Table 17.5 PGI-C score not considering cutoff by gender (FAS), proportional odds model analysis

	Treatment Groups		Comparison
PGI-C score not considering cutoff by gender (FAS)	**LCZ696 (N=182)**	**Enalapril (N=184)**	**Cumulative OR [95% CI] p-value**
Male, N	88	91	
Female, N	94	93	
PGI-C score			
Week 52			
Interaction test	**p = 0.794**		
Male			
N' / N"	81 / 74	83 / 77	
Much Better, n (%)	24 (29.6)	22 (26.5)	
Better, n (%)	30 (37.0)	29 (34.9)	
No Change, n (%)	18 (22.2)	26 (31.3)	
Worse, n (%)	2 (2.5)	0 (0.0)	
Much Worse, n (%)	7 (8.6)	6 (7.2)	1.25 [0.72; 2.20] 0.429
Female			
N' / N"	87 / 83	85 / 77	
Much Better, n (%)	30 (34.5)	25 (29.4)	
Better, n (%)	39 (44.8)	34 (40.0)	
No Change, n (%)	12 (13.8)	17 (20.0)	
Worse, n (%)	1 (1.1)	1 (1.2)	
Much Worse, n (%)	5 (5.7)	8 (9.4)	1.39 [0.80; 2.42] 0.239

N: Number of patients
N': Number of patients in the analysis
N": Number of patients with non-missing value (not imputed)
n (%): Number and percentage of patients in this category, percentage based on the number of patients in the analysis
CI: Confidence interval
OR: Odds ratio
.....

Imputation method: Missing values after the first category-1-event (investigator reported or positively adjudicated) were set to the worst category.

Analysis method:
Interaction test and cumulative odds ratio from proportional cumulative odds model for ordinal response: logit(cumulative proportion) = treatment + gender + treatment * gender + age group + NYHA/Ross class

Not considering cutoff date: Nominal week 52 assessments that were performed later than 58 weeks after baseline were included in the analysis.

Table 17.6 PGI-C score not considering cutoff by COVID-19 period (FAS), proportional odds model analysis

	Treatment Groups		Comparison
PGI-C score not considering cutoff by COVID-19 period (FAS)	**LCZ696 (N=182)**	**Enalapril (N=184)**	**Cumulative OR [95% CI] p-value**
Pre-pandemic, N	79	83	
Pre- and during-pandemic, N	62	59	
During-pandemic, N	41	42	
PGI-C score			
Week 52			
Interaction test	**p = 0.941**		
Pre-pandemic			
N' / N''	72 / 63	72 / 61	
Much Better, n (%)	20 (27.8)	19 (26.4)	
Better, n (%)	27 (37.5)	21 (29.2)	
No Change, n (%)	15 (20.8)	20 (27.8)	
Worse, n (%)	1 (1.4)	1 (1.4)	
Much Worse, n (%)	9 (12.5)	11 (15.3)	1.42 [0.78; 2.57] 0.251
Pre- and during-pandemic			
N' / N''	58 / 57	55 / 53	
Much Better, n (%)	20 (34.5)	16 (29.1)	
Better, n (%)	27 (46.6)	27 (49.1)	
No Change, n (%)	9 (15.5)	10 (18.2)	
Worse, n (%)	1 (1.7)	0 (0.0)	
Much Worse, n (%)	1 (1.7)	2 (3.6)	1.22 [0.62; 2.41] 0.572
During-pandemic			
N' / N''	38 / 37	41 / 40	
Much Better, n (%)	14 (36.8)	12 (29.3)	
Better, n (%)	15 (39.5)	15 (36.6)	
No Change, n (%)	6 (15.8)	13 (31.7)	
Worse, n (%)	1 (2.6)	0 (0.0)	
Much Worse, n (%)	2 (5.3)	1 (2.4)	1.40 [0.62; 3.15] 0.420

	Treatment Groups		Comparison
PGI-C score not considering cutoff by COVID-19 period (FAS)	**LCZ696 (N=182)**	**Enalapril (N=184)**	**Cumulative OR [95% CI] p-value**

N: Number of patients
N': Number of patients in the analysis
N'': Number of patients with non-missing value (not imputed)
n (%): Number and percentage of patients in this category, percentage based on the number of patients in the analysis
CI: Confidence interval
OR: Odds ratio
.....

Imputation method: Missing values after the first category-1-event (investigator reported or positively adjudicated) were set to the worst category.

Analysis method:
Interaction test and cumulative odds ratio from proportional cumulative odds model for ordinal response: logit(cumulative proportion) = treatment + COVID-19 period + treatment * COVID-19 period + age group + NYHA/Ross class

Not considering cutoff date: Nominal week 52 assessments that were performed later than 58 weeks after baseline were included in the analysis.

Table 17.7 PGI-C score not considering cutoff by race (FAS), proportional odds model analysis

	Treatment Groups		Comparison
PGI-C score not considering cutoff by race (FAS)	**LCZ696 (N=182)**	**Enalapril (N=184)**	**Cumulative OR [95% CI] p-value**
Caucasian, N	86	90	
Black, N	23	25	
Asian, N	55	45	
Unknown or other, N	18	24	
PGI-C score			
Week 52			
Interaction test	**p = 0.440**		
Caucasian			
N' / N"	80 / 76	83 / 77	
Much Better, n (%)	26 (32.5)	19 (22.9)	
Better, n (%)	31 (38.8)	36 (43.4)	
No Change, n (%)	17 (21.3)	21 (25.3)	
Worse, n (%)	1 (1.3)	1 (1.2)	
Much Worse, n (%)	5 (6.3)	6 (7.2)	1.41 [0.80; 2.47] 0.235
Black			
N' / N"	20 / 20	22 / 19	
Much Better, n (%)	9 (45.0)	6 (27.3)	
Better, n (%)	5 (25.0)	7 (31.8)	
No Change, n (%)	5 (25.0)	6 (27.3)	
Worse, n (%)	1 (5.0)	0 (0.0)	
Much Worse, n (%)	0 (0.0)	3 (13.6)	2.14 [0.70; 6.54] 0.181
Asian			
N' / N"	51 / 45	42 / 39	
Much Better, n (%)	14 (27.5)	17 (40.5)	
Better, n (%)	26 (51.0)	13 (31.0)	
No Change, n (%)	4 (7.8)	9 (21.4)	
Worse, n (%)	1 (2.0)	0 (0.0)	
Much Worse, n (%)	6 (11.8)	3 (7.1)	0.82 [0.38; 1.74] 0.604

	Treatment Groups		Comparison
PGI-C score not considering cutoff by race (FAS)	**LCZ696 (N=182)**	**Enalapril (N=184)**	**Cumulative OR [95% CI] p-value**
Unknown or other			
N' / N''	17 / 16	21 / 19	
Much Better, n (%)	5 (29.4)	5 (23.8)	
Better, n (%)	7 (41.2)	7 (33.3)	
No Change, n (%)	4 (23.5)	7 (33.3)	
Worse, n (%)	0 (0.0)	0 (0.0)	
Much Worse, n (%)	1 (5.9)	2 (9.5)	1.94 [0.60; 6.30] 0.269

N: Number of patients
N': Number of patients in the analysis
N'': Number of patients with non-missing value (not imputed)
n (%): Number and percentage of patients in this category, percentage based on the number of patients in the analysis
CI: Confidence interval
OR: Odds ratio
.....

Imputation method: Missing values after the first category-1-event (investigator reported or positively adjudicated) were set to the worst category.

Analysis method:
Interaction test and cumulative odds ratio from proportional cumulative odds model for ordinal response: logit(cumulative proportion) = treatment + race + treatment * race + age group + NYHA/Ross class

Not considering cutoff date: Nominal week 52 assessments that were performed later than 58 weeks after baseline were included in the analysis.

18 PedsQL patient reported total score in the age group 5 to < 18 years, considering cutoff date for the last visit

Table 18.0 PedsQL patient reported total score in the age group 5 to < 18 years considering cutoff (FAS), return rates

	Treatment Groups		
PedsQL patient reported total score in the age group 5 to < 18 years considering cutoff (FAS)	**LCZ696 (N=114)**	**Enalapril (N=116)**	**Total (N=230)**
PedsQL patient reported total summary score			
Baseline returns, n (%)	107 (93.9)	110 (94.8)	217 (94.3)
Week 12 returns, n (%)	100 (87.7)	107 (92.2)	207 (90.0)
Week 24 returns, n (%)	99 (86.8)	105 (90.5)	204 (88.7)
Week 36 returns, n (%)	96 (84.2)	102 (87.9)	198 (86.1)
Week 52 returns, n (%)	92 (80.7)	97 (83.6)	189 (82.2)

N: Number of patients
n (%): Number and percentage of patients with available value
.....

The return rate is the proportion of patients with available value at the given visit based on the whole analysis population.

The PedsQL for the patient was applied in children from 5 years to < 18 years. The analysis is based on this age group.
Considering
cutoff date: Nominal week 52 assessments that were performed later than 58 weeks after baseline were excluded from the analysis.

Table 18.1 PedsQL patient reported total score in the age group 5 to < 18 years considering cutoff (FAS), change from baseline analysis

	Treatment Groups		Comparison	
PedsQL patient reported total score in the age group 5 to < 18 years considering cutoff (FAS)	**LCZ696 (N=114)**	**Enalapril (N=116)**	**Mean Difference [95% CI] p-value**	**Hedges G [95% CI]**
PedsQL patient reported total summary score				
N' / N''	105 / 101	108 / 103		
Baseline: mean (SD)	72.51 (15.06)	69.90 (18.91)		
Week 52: mean (SD)	67.58 (28.28)	61.92 (29.88)		
Week 12: adjusted mean change (SE)	0.58 (1.78)	-1.47 (1.75)		
Week 24: adjusted mean change (SE)	-1.97 (2.22)	-1.43 (2.19)		
Week 36: adjusted mean change (SE)	-2.69 (2.49)	-5.07 (2.47)		
Week 52: adjusted mean change (SE)	-3.24 (2.66)	-6.23 (2.65)	2.99 [-4.42; 10.40] 0.427	0.116 [-0.170; 0.401]

N: Number of patients
N': Number of patients in the analysis
N'': Number of patients with non-missing value (not imputed)
CI: Confidence interval
SD: Standard deviation
SE: Standard error
MMRM: Mixed model for repeated measures
.....

Imputation method: Missing values after the first category-1-event (investigator reported or positively adjudicated) were set to the worst value.

Analysis method:
Adjusted mean change and mean difference obtained from MMRM with unstructured covariance matrix: change from baseline = treatment + visit + treatment * visit + baseline value + baseline value * visit + NYHA/Ross class + region

The PedsQL for the patient was applied in children from 5 years to < 18 years. The analysis is based on this age group.
Subgroup analysis by age is not performed as there are less than 10 patients < 6 years with non-missing PedsQL patient score.
The PedsQL is on scale 0 to 100, higher scores indicate better health-related quality of life.
Considering cutoff date: Nominal week 52 assessments
that were performed later than 58 weeks after baseline were excluded from the analysis.

Table 18.2 PedsQL patient reported total score in the age group 5 to < 18 years considering cutoff by NYHA/Ross class (FAS), change from baseline analysis

	Treatment Groups		Comparison	
PedsQL patient reported total score in the age group 5 to < 18 years considering cutoff by NYHA/Ross class (FAS)	**LCZ696 (N=114)**	**Enalapril (N=116)**	**Mean Difference [95% CI] p-value**	**Hedges G [95% CI]**
Class I/II, N	98	99		
Class III/IV, N	16	17		
PedsQL patient reported total summary score				
Interaction test	**p = 0.311**			
Class I/II				
N' / N"	91 / 88	91 / 88		
Baseline: mean (SD)	73.27 (14.76)	72.00 (18.49)		
Week 52: mean (SD)	69.34 (26.52)	63.17 (29.88)		
Week 12: adjusted mean change (SE)	0.89 (1.91)	-0.75 (1.89)		
Week 24: adjusted mean change (SE)	-0.51 (2.38)	-1.34 (2.38)		
Week 36: adjusted mean change (SE)	-0.66 (2.66)	-5.41 (2.67)		
Week 52: adjusted mean change (SE)	-2.07 (2.87)	-6.14 (2.90)	4.07 [-3.95; 12.10] 0.318	0.158 [-0.152; 0.467]
Class III/IV				
N' / N"	14 / 13	17 / 15		
Baseline: mean (SD)	67.85 (16.59)	58.43 (17.51)		
Week 52: mean (SD)	56.86 (36.71)	55.11 (29.99)		
Week 12: adjusted mean change (SE)	-0.64 (5.01)	-6.30 (4.69)		
Week 24: adjusted mean change (SE)	-11.65 (6.10)	-2.28 (5.74)		
Week 36: adjusted mean change (SE)	-17.07 (6.92)	-3.43 (6.45)		
Week 52: adjusted mean change (SE)	-10.70 (7.19)	-6.91 (6.84)	-3.78 [-23.19; 15.63] 0.701	-0.146 [-0.889; 0.598]

	Treatment Groups		Comparison	
PedsQL patient reported total score in the age group 5 to < 18 years considering cutoff by NYHA/Ross class (FAS)	**LCZ696 (N=114)**	**Enalapril (N=116)**	**Mean Difference [95% CI] p-value**	**Hedges G [95% CI]**

N: Number of patients
N': Number of patients in the analysis
N'': Number of patients with non-missing value (not imputed)
CI: Confidence interval
SD: Standard deviation
SE: Standard error
MMRM: Mixed model for repeated measures
.....

Imputation method: Missing values after the first category-1-event (investigator reported or positively adjudicated) were set to the worst value.

Analysis method:
Interaction test, adjusted mean change and mean difference obtained from MMRM with unstructured covariance matrix: change from baseline = treatment + visit + treatment * visit + NYHA/Ross class + treatment * NYHA/Ross class + NYHA/Ross class * visit + treatment * NYHA/Ross class * visit + baseline value + baseline value * visit + region

The PedsQL for the patient was applied in children from 5 years to < 18 years. The analysis is based on this age group.
The PedsQL is on scale 0 to 100, higher scores indicate better health-related quality of life.
Considering cutoff date: Nominal week 52
assessments that were performed later than 58 weeks after baseline were excluded from the analysis.

Table 18.3 PedsQL patient reported total score in the age group 5 to < 18 years considering cutoff by region (FAS), change from baseline analysis

	Treatment Groups		Comparison	
PedsQL patient reported total score in the age group 5 to < 18 years considering cutoff by region (FAS)	**LCZ696 (N=114)**	**Enalapril (N=116)**	**Mean Difference [95% CI] p-value**	**Hedges G [95% CI]**
America, N	43	46		
Europe, N	39	36		
Asia/Pacific and other, N	32	34		
PedsQL patient reported total summary score				
Interaction test	**p = 0.889**			
America				
N' / N''	38 / 36	43 / 41		
Baseline: mean (SD)	73.21 (12.72)	68.63 (19.56)		
Week 52: mean (SD)	68.75 (24.06)	57.43 (31.14)		
Week 12: adjusted mean change (SE)	-0.77 (2.95)	-2.31 (2.77)		
Week 24: adjusted mean change (SE)	-4.14 (3.67)	-1.53 (3.44)		
Week 36: adjusted mean change (SE)	-2.53 (4.09)	-7.06 (3.92)		
Week 52: adjusted mean change (SE)	-0.44 (4.50)	-7.56 (4.32)	7.12 [-5.19; 19.44] 0.256	0.279 [-0.203; 0.762]
Europe				
N' / N''	36 / 36	33 / 32		
Baseline: mean (SD)	73.31 (16.97)	71.07 (17.88)		
Week 52: mean (SD)	69.04 (27.06)	68.97 (21.02)		
Week 12: adjusted mean change (SE)	1.01 (3.09)	0.28 (3.18)		
Week 24: adjusted mean change (SE)	1.61 (3.88)	-0.35 (4.02)		
Week 36: adjusted mean change (SE)	-0.59 (4.32)	1.19 (4.46)		
Week 52: adjusted mean change (SE)	-3.61 (4.53)	-2.00 (4.77)	-1.61 [-14.58; 11.37] 0.807	-0.061 [-0.551; 0.429]
Asia/Pacific and other				
N' / N''	31 / 29	32 / 30		
Baseline: mean (SD)	70.74 (15.60)	70.35 (19.57)		
Week 52: mean (SD)	64.56 (34.21)	60.03 (35.32)		
Week 12: adjusted mean change (SE)	1.80 (3.26)	-2.21 (3.23)		
Week 24: adjusted mean change (SE)	-2.89 (4.04)	-2.71 (4.08)		
Week 36: adjusted mean change (SE)	-4.85 (4.54)	-9.20 (4.53)		
Week 52: adjusted mean change (SE)	-5.64 (4.86)	-8.76 (4.82)	3.12 [-10.38; 16.62] 0.649	0.120 [-0.396; 0.635]

	Treatment Groups		Comparison	
PedsQL patient reported total score in the age group 5 to < 18 years considering cutoff by region (FAS)	**LCZ696 (N=114)**	**Enalapril (N=116)**	**Mean Difference [95% CI] p-value**	**Hedges G [95% CI]**

N: Number of patients
N': Number of patients in the analysis
N'': Number of patients with non-missing value (not imputed)
CI: Confidence interval
SD: Standard deviation
SE: Standard error
MMRM: Mixed model for repeated measures
.....

Imputation method: Missing values after the first category-1-event (investigator reported or positively adjudicated) were set to the worst value.

Analysis method:
Interaction test, adjusted mean change and mean difference obtained from MMRM with unstructured covariance matrix: change from baseline = treatment + visit + treatment * visit + region + treatment * region + region * visit + treatment * region * visit + baseline value + baseline value * visit + NYHA/Ross class

The PedsQL for the patient was applied in children from 5 years to < 18 years. The analysis is based on this age group.
The PedsQL is on scale 0 to 100, higher scores indicate better health-related quality of life.
Considering cutoff date: Nominal week 52
assessments that were performed later than 58 weeks after baseline were excluded from the analysis.

Table 18.4 PedsQL patient reported total score in the age group 5 to < 18 years considering cutoff by gender (FAS), change from baseline analysis

	Treatment Groups		Comparison	
PedsQL patient reported total score in the age group 5 to < 18 years considering cutoff by gender (FAS)	**LCZ696 (N=114)**	**Enalapril (N=116)**	**Mean Difference [95% CI] p-value**	**Hedges G [95% CI]**
Male, N	59	56		
Female, N	55	60		
PedsQL patient reported total summary score				
Interaction test	**p = 0.638**			
Male				
N' / N"	54 / 53	53 / 50		
Baseline: mean (SD)	76.62 (13.13)	69.85 (17.89)		
Week 52: mean (SD)	70.87 (28.00)	63.24 (29.22)		
Week 12: adjusted mean change (SE)	1.43 (2.53)	-1.70 (2.49)		
Week 24: adjusted mean change (SE)	1.49 (3.14)	-1.16 (3.13)		
Week 36: adjusted mean change (SE)	-0.12 (3.53)	-4.03 (3.54)		
Week 52: adjusted mean change (SE)	-2.06 (3.75)	-4.38 (3.88)	2.33 [-8.33; 12.99] 0.667	0.090 [-0.319; 0.499]
Female				
N' / N"	51 / 48	55 / 53		
Baseline: mean (SD)	68.32 (15.85)	69.94 (19.98)		
Week 52: mean (SD)	63.98 (28.45)	60.83 (30.66)		
Week 12: adjusted mean change (SE)	-0.27 (2.58)	-1.25 (2.47)		
Week 24: adjusted mean change (SE)	-5.49 (3.18)	-1.74 (3.07)		
Week 36: adjusted mean change (SE)	-5.32 (3.58)	-6.10 (3.46)		
Week 52: adjusted mean change (SE)	-4.47 (3.85)	-7.86 (3.66)	3.40 [-7.06; 13.85] 0.523	0.131 [-0.270; 0.531]

	Treatment Groups		Comparison	
PedsQL patient reported total score in the age group 5 to < 18 years considering cutoff by gender (FAS)	**LCZ696 (N=114)**	**Enalapril (N=116)**	**Mean Difference [95% CI] p-value**	**Hedges G [95% CI]**

N: Number of patients
N': Number of patients in the analysis
N'': Number of patients with non-missing value (not imputed)
CI: Confidence interval
SD: Standard deviation
SE: Standard error
MMRM: Mixed model for repeated measures
.....

Imputation method: Missing values after the first category-1-event (investigator reported or positively adjudicated) were set to the worst value.

Analysis method:
Interaction test, adjusted mean change and mean difference obtained from MMRM with unstructured covariance matrix: change from baseline = treatment + visit + treatment * visit + gender + treatment * gender + gender * visit + treatment * gender * visit + baseline value + baseline value * visit + NYHA/Ross class + region

The PedsQL for the patient was applied in children from 5 years to < 18 years. The analysis is based on this age group.
The PedsQL is on scale 0 to 100, higher scores indicate better health-related quality of life.
Considering cutoff date: Nominal week 52
assessments that were performed later than 58 weeks after baseline were excluded from the analysis.

Table 18.5 PedsQL patient reported total score in the age group 5 to < 18 years considering cutoff by COVID-19 period (FAS), change from baseline analysis

	Treatment Groups		Comparison	
PedsQL patient reported total score in the age group 5 to < 18 years considering cutoff by COVID-19 period (FAS)	**LCZ696 (N=114)**	**Enalapril (N=116)**	**Mean Difference [95% CI] p-value**	**Hedges G [95% CI]**
Pre-pandemic, N	59	60		
Pre- and during-pandemic, N	33	33		
During-pandemic, N	22	23		
PedsQL patient reported total summary score				
Interaction test	**p = 0.039 ***			
Pre-pandemic				
N' / N''	55 / 52	55 / 50		
Baseline: mean (SD)	73.79 (13.37)	67.06 (19.28)		
Week 52: mean (SD)	62.79 (32.66)	50.19 (32.54)		
Week 12: adjusted mean change (SE)	0.43 (2.46)	-4.02 (2.45)		
Week 24: adjusted mean change (SE)	-4.08 (2.96)	-7.17 (2.99)		
Week 36: adjusted mean change (SE)	-4.16 (3.31)	-13.80 (3.37)		
Week 52: adjusted mean change (SE)	-7.95 (3.56)	-14.55 (3.67)	6.60 [-3.50; 16.71] 0.199	0.264 [-0.140; 0.668]
Pre- and during-pandemic				
N' / N''	28 / 28	32 / 32		
Baseline: mean (SD)	70.66 (17.83)	71.51 (19.43)		
Week 52: mean (SD)	72.67 (21.86)	70.38 (21.64)		
Week 12: adjusted mean change (SE)	6.01 (3.46)	-0.61 (3.17)		
Week 24: adjusted mean change (SE)	8.16 (4.20)	3.06 (3.96)		
Week 36: adjusted mean change (SE)	4.40 (4.67)	1.83 (4.41)		
Week 52: adjusted mean change (SE)	2.67 (5.04)	-1.25 (4.70)	3.93 [-9.67; 17.52] 0.570	0.160 [-0.392; 0.713]
During-pandemic				
N' / N''	22 / 21	21 / 21		
Baseline: mean (SD)	71.81 (15.39)	74.94 (16.43)		
Week 52: mean (SD)	72.95 (22.15)	76.21 (23.32)		
Week 12: adjusted mean change (SE)	-5.61 (3.84)	3.73 (3.99)		
Week 24: adjusted mean change (SE)	-9.54 (4.84)	6.71 (4.84)		
Week 36: adjusted mean change (SE)	-8.13 (5.37)	7.05 (5.38)		
Week 52: adjusted mean change (SE)	0.53 (5.58)	7.14 (5.71)	-6.61 [-22.31; 9.09] 0.407	-0.253 [-0.854; 0.347]

	Treatment Groups		Comparison	
PedsQL patient reported total score in the age group 5 to < 18 years considering cutoff by COVID-19 period (FAS)	**LCZ696 (N=114)**	**Enalapril (N=116)**	**Mean Difference [95% CI] p-value**	**Hedges G [95% CI]**

N: Number of patients
N': Number of patients in the analysis
N'': Number of patients with non-missing value (not imputed)
CI: Confidence interval
SD: Standard deviation
SE: Standard error
MMRM: Mixed model for repeated measures
*: $p < 0.05$
.....

Imputation method: Missing values after the first category-1-event (investigator reported or positively adjudicated) were set to the worst value.

Analysis method:
Interaction test, adjusted mean change and mean difference obtained from MMRM with unstructured covariance matrix: change from baseline = treatment + visit + treatment * visit + COVID-19 period + treatment * COVID-19 period + COVID-19 period * visit + treatment * COVID-19 period * visit + baseline value + baseline value * visit + NYHA/Ross class + region

The PedsQL for the patient was applied in children from 5 years to < 18 years. The analysis is based on this age group.
The PedsQL is on scale 0 to 100, higher scores indicate better health-related quality of life.
Considering cutoff date: Nominal week 52
assessments that were performed later than 58 weeks after baseline were excluded from the analysis.

Table 18.6 PedsQL patient reported total score in the age group 5 to < 18 years considering cutoff by race (FAS), change from baseline analysis

	Treatment Groups		Comparison	
PedsQL patient reported total score in the age group 5 to < 18 years considering cutoff by race (FAS)	**LCZ696 (N=114)**	**Enalapril (N=116)**	**Mean Difference [95% CI] p-value**	**Hedges G [95% CI]**
Caucasian, N	62	63		
Black, N	15	21		
Asian, N	26	23		
Unknown or other, N	11	9		
PedsQL patient reported total summary score				
Interaction test	**p = 0.649**			
Caucasian				
N' / N"	56 / 53	60 / 57		
Baseline: mean (SD)	71.28 (16.28)	70.22 (19.24)		
Week 52: mean (SD)	66.49 (26.98)	65.34 (26.68)		
Week 12: adjusted mean change (SE)	1.58 (2.75)	0.14 (2.62)		
Week 24: adjusted mean change (SE)	-0.73 (3.31)	-1.54 (3.17)		
Week 36: adjusted mean change (SE)	0.52 (3.63)	-3.12 (3.49)		
Week 52: adjusted mean change (SE)	-3.85 (3.79)	-4.02 (3.69)	0.17 [-9.77; 10.11] 0.973	0.007 [-0.376; 0.389]
Black				
N' / N"	15 / 15	19 / 18		
Baseline: mean (SD)	74.76 (16.31)	70.27 (21.19)		
Week 52: mean (SD)	80.24 (16.53)	48.64 (35.85)		
Week 12: adjusted mean change (SE)	-2.42 (4.81)	-5.92 (4.25)		
Week 24: adjusted mean change (SE)	-3.58 (6.02)	-2.44 (5.25)		
Week 36: adjusted mean change (SE)	-4.32 (6.71)	-13.75 (5.91)		
Week 52: adjusted mean change (SE)	10.10 (7.37)	-16.30 (6.25)	26.40 [7.41; 45.39] 0.007 *	1.049 [0.252; 1.846]

	Treatment Groups		Comparison	
PedsQL patient reported total score in the age group 5 to < 18 years considering cutoff by race (FAS)	**LCZ696 (N=114)**	**Enalapril (N=116)**	**Mean Difference [95% CI] p-value**	**Hedges G [95% CI]**
Asian				
N' / N''	25 / 24	22 / 21		
Baseline: mean (SD)	70.60 (12.42)	69.86 (17.02)		
Week 52: mean (SD)	63.78 (34.11)	63.45 (33.20)		
Week 12: adjusted mean change (SE)	-1.18 (4.78)	-2.98 (5.11)		
Week 24: adjusted mean change (SE)	-5.26 (5.52)	-1.12 (5.97)		
Week 36: adjusted mean change (SE)	-6.57 (5.98)	-4.06 (6.41)		
Week 52: adjusted mean change (SE)	-7.16 (6.24)	-5.73 (6.74)	-1.43 [-17.14; 14.28] 0.858	-0.055 [-0.661; 0.550]
Unknown or other				
N' / N''	9 / 9	7 / 7		
Baseline: mean (SD)	82.06 (8.24)	66.71 (18.72)		
Week 52: mean (SD)	67.70 (32.48)	66.49 (19.83)		
Week 12: adjusted mean change (SE)	4.84 (6.54)	1.71 (7.02)		
Week 24: adjusted mean change (SE)	3.09 (8.06)	0.58 (9.11)		
Week 36: adjusted mean change (SE)	-7.95 (8.81)	-0.84 (10.54)		
Week 52: adjusted mean change (SE)	-4.67 (9.45)	2.48 (11.39)	-7.15 [-36.31; 22.01] 0.629	-0.269 [-1.364; 0.826]

N: Number of patients
N': Number of patients in the analysis
N'': Number of patients with non-missing value (not imputed)
CI: Confidence interval
SD: Standard deviation
SE: Standard error
MMRM: Mixed model for repeated measures
*: $p < 0.05$
.....

Imputation method: Missing values after the first category-1-event (investigator reported or positively adjudicated) were set to the worst value.

Analysis method:
Interaction test, adjusted mean change and mean difference obtained from MMRM with unstructured covariance matrix: change from baseline = treatment + visit + treatment * visit + race + treatment * race + race * visit + treatment * race * visit + baseline value + baseline value * visit + NYHA/Ross class + region

The PedsQL for the patient was applied in children from 5 years to < 18 years. The analysis is based on this age group.
The PedsQL is on scale 0 to 100, higher scores indicate better health-related quality of life.
Considering cutoff date: Nominal week 52
assessments that were performed later than 58 weeks after baseline were excluded from the analysis.

19 PedsQL patient reported total score in the age group 5 to < 18 years, not considering cutoff date for the last visit

Table 19.0 PedsQL patient reported total score in the age group 5 to < 18 years not considering cutoff (FAS), return rates

	Treatment Groups		
PedsQL patient reported total score in the age group 5 to < 18 years not considering cutoff (FAS)	**LCZ696 (N=114)**	**Enalapril (N=116)**	**Total (N=230)**
PedsQL patient reported total summary score			
Baseline returns, n (%)	107 (93.9)	110 (94.8)	217 (94.3)
Week 12 returns, n (%)	100 (87.7)	107 (92.2)	207 (90.0)
Week 24 returns, n (%)	99 (86.8)	105 (90.5)	204 (88.7)
Week 36 returns, n (%)	96 (84.2)	102 (87.9)	198 (86.1)
Week 52 returns, n (%)	100 (87.7)	105 (90.5)	205 (89.1)

N: Number of patients
n (%): Number and percentage of patients with available value
.....

The return rate is the proportion of patients with available value at the given visit based on the whole analysis population.

The PedsQL for the patient was applied in children from 5 years to < 18 years. The analysis is based on this age group.
Not considering
cutoff date: Nominal week 52 assessments that were performed later than 58 weeks after baseline were included in the analysis.

Table 19.1 PedsQL patient reported total score in the age group 5 to < 18 years not considering cutoff (FAS), change from baseline analysis

	Treatment Groups		Comparison	
PedsQL patient reported total score in the age group 5 to < 18 years not considering cutoff (FAS)	**LCZ696 (N=114)**	**Enalapril (N=116)**	**Mean Difference [95% CI] p-value**	**Hedges G [95% CI]**
PedsQL patient reported total summary score				
N' / N''	105 / 101	108 / 103		
Baseline: mean (SD)	72.51 (15.06)	69.90 (18.91)		
Week 52: mean (SD)	69.12 (27.80)	63.93 (28.61)		
Week 12: adjusted mean change (SE)	0.58 (1.78)	-1.48 (1.75)		
Week 24: adjusted mean change (SE)	-1.96 (2.22)	-1.44 (2.19)		
Week 36: adjusted mean change (SE)	-2.82 (2.49)	-5.10 (2.47)		
Week 52: adjusted mean change (SE)	-2.71 (2.56)	-5.00 (2.56)	2.29 [-4.86; 9.44] 0.529	0.088 [-0.186; 0.362]

N: Number of patients
N': Number of patients in the analysis
N'': Number of patients with non-missing value (not imputed)
CI: Confidence interval
SD: Standard deviation
SE: Standard error
MMRM: Mixed model for repeated measures
.....

Imputation method: Missing values after the first category-1-event (investigator reported or positively adjudicated) were set to the worst value.

Analysis method:
Adjusted mean change and mean difference obtained from MMRM with unstructured covariance matrix: change from baseline = treatment + visit + treatment * visit + baseline value + baseline value * visit + NYHA/Ross class + region

The PedsQL for the patient was applied in children from 5 years to < 18 years. The analysis is based on this age group.
Subgroup analysis by age is not performed as there are less than 10 patients < 6 years with non-missing PedsQL patient score.
The PedsQL is on scale 0 to 100, higher scores indicate better health-related quality of life.
Not considering cutoff date: Nominal week 52
assessments that were performed later than 58 weeks after baseline were included in the analysis.

Table 19.2 PedsQL patient reported total score in the age group 5 to < 18 years not considering cutoff by NYHA/Ross class (FAS), change from baseline analysis

	Treatment Groups		Comparison	
PedsQL patient reported total score in the age group 5 to < 18 years not considering cutoff by NYHA/Ross class (FAS)	**LCZ696 (N=114)**	**Enalapril (N=116)**	**Mean Difference [95% CI] p-value**	**Hedges G [95% CI]**
Class I/II, N	98	99		
Class III/IV, N	16	17		
PedsQL patient reported total summary score				
Interaction test	**p = 0.306**			
Class I/II				
N' / N"	91 / 88	91 / 88		
Baseline: mean (SD)	73.27 (14.76)	72.00 (18.49)		
Week 52: mean (SD)	70.95 (25.99)	65.21 (28.38)		
Week 12: adjusted mean change (SE)	0.89 (1.91)	-0.76 (1.89)		
Week 24: adjusted mean change (SE)	-0.51 (2.39)	-1.35 (2.38)		
Week 36: adjusted mean change (SE)	-0.71 (2.67)	-5.44 (2.68)		
Week 52: adjusted mean change (SE)	-1.42 (2.76)	-4.78 (2.79)	3.36 [-4.37; 11.09] 0.393	0.129 [-0.167; 0.425]
Class III/IV				
N' / N"	14 / 13	17 / 15		
Baseline: mean (SD)	67.85 (16.59)	58.43 (17.51)		
Week 52: mean (SD)	56.86 (36.71)	56.83 (29.78)		
Week 12: adjusted mean change (SE)	-0.67 (5.01)	-6.32 (4.69)		
Week 24: adjusted mean change (SE)	-11.64 (6.10)	-2.26 (5.74)		
Week 36: adjusted mean change (SE)	-17.85 (6.92)	-3.49 (6.46)		
Week 52: adjusted mean change (SE)	-10.60 (7.04)	-6.56 (6.61)	-4.04 [-22.95; 14.87] 0.674	-0.157 [-0.890; 0.576]

	Treatment Groups		Comparison	
PedsQL patient reported total score in the age group 5 to < 18 years not considering cutoff by NYHA/Ross class (FAS)	**LCZ696 (N=114)**	**Enalapril (N=116)**	**Mean Difference [95% CI] p-value**	**Hedges G [95% CI]**

N: Number of patients
N': Number of patients in the analysis
N'': Number of patients with non-missing value (not imputed)
CI: Confidence interval
SD: Standard deviation
SE: Standard error
MMRM: Mixed model for repeated measures
.....

Imputation method: Missing values after the first category-1-event (investigator reported or positively adjudicated) were set to the worst value.

Analysis method:
Interaction test, adjusted mean change and mean difference obtained from MMRM with unstructured covariance matrix: change from baseline = treatment + visit + treatment * visit + NYHA/Ross class + treatment * NYHA/Ross class + NYHA/Ross class * visit + treatment * NYHA/Ross class * visit + baseline value + baseline value * visit + region

The PedsQL for the patient was applied in children from 5 years to < 18 years. The analysis is based on this age group.
The PedsQL is on scale 0 to 100, higher scores indicate better health-related quality of life.
Not considering cutoff date: Nominal week 52
assessments that were performed later than 58 weeks after baseline were included in the analysis.

Table 19.3 PedsQL patient reported total score in the age group 5 to < 18 years not considering cutoff by region (FAS), change from baseline analysis

	Treatment Groups		Comparison	
PedsQL patient reported total score in the age group 5 to < 18 years not considering cutoff by region (FAS)	**LCZ696 (N=114)**	**Enalapril (N=116)**	**Mean Difference [95% CI] p-value**	**Hedges G [95% CI]**
America, N	43	46		
Europe, N	39	36		
Asia/Pacific and other, N	32	34		
PedsQL patient reported total summary score				
Interaction test	**p = 0.899**			
America				
N' / N''	38 / 36	43 / 41		
Baseline: mean (SD)	73.21 (12.72)	68.63 (19.56)		
Week 52: mean (SD)	72.13 (24.08)	62.61 (29.20)		
Week 12: adjusted mean change (SE)	-0.76 (2.95)	-2.30 (2.77)		
Week 24: adjusted mean change (SE)	-4.12 (3.67)	-1.52 (3.44)		
Week 36: adjusted mean change (SE)	-2.50 (4.11)	-7.13 (3.93)		
Week 52: adjusted mean change (SE)	0.51 (4.27)	-4.77 (4.11)	5.28 [-6.43; 16.98] 0.375	0.203 [-0.246; 0.652]
Europe				
N' / N''	36 / 36	33 / 32		
Baseline: mean (SD)	73.31 (16.97)	71.07 (17.88)		
Week 52: mean (SD)	69.56 (26.40)	69.26 (20.74)		
Week 12: adjusted mean change (SE)	1.01 (3.09)	0.28 (3.19)		
Week 24: adjusted mean change (SE)	1.61 (3.88)	-0.34 (4.02)		
Week 36: adjusted mean change (SE)	-0.74 (4.32)	1.21 (4.47)		
Week 52: adjusted mean change (SE)	-3.46 (4.38)	-1.69 (4.63)	-1.77 [-14.35; 10.81] 0.782	-0.068 [-0.547; 0.412]
Asia/Pacific and other				
N' / N''	31 / 29	32 / 30		
Baseline: mean (SD)	70.74 (15.60)	70.35 (19.57)		
Week 52: mean (SD)	64.84 (33.63)	60.29 (34.21)		
Week 12: adjusted mean change (SE)	1.81 (3.26)	-2.19 (3.23)		
Week 24: adjusted mean change (SE)	-2.88 (4.04)	-2.70 (4.08)		
Week 36: adjusted mean change (SE)	-5.09 (4.55)	-9.19 (4.54)		
Week 52: adjusted mean change (SE)	-5.50 (4.72)	-8.62 (4.66)	3.12 [-9.94; 16.19] 0.638	0.121 [-0.382; 0.624]

	Treatment Groups		Comparison	
PedsQL patient reported total score in the age group 5 to < 18 years not considering cutoff by region (FAS)	**LCZ696 (N=114)**	**Enalapril (N=116)**	**Mean Difference [95% CI] p-value**	**Hedges G [95% CI]**

N: Number of patients
N': Number of patients in the analysis
N'': Number of patients with non-missing value (not imputed)
CI: Confidence interval
SD: Standard deviation
SE: Standard error
MMRM: Mixed model for repeated measures
.....

Imputation method: Missing values after the first category-1-event (investigator reported or positively adjudicated) were set to the worst value.

Analysis method:
Interaction test, adjusted mean change and mean difference obtained from MMRM with unstructured covariance matrix: change from baseline = treatment + visit + treatment * visit + region + treatment * region + region * visit + treatment * region * visit + baseline value + baseline value * visit + NYHA/Ross class

The PedsQL for the patient was applied in children from 5 years to < 18 years. The analysis is based on this age group.
The PedsQL is on scale 0 to 100, higher scores indicate better health-related quality of life.
Not considering cutoff date: Nominal week 52
assessments that were performed later than 58 weeks after baseline were included in the analysis.

Table 19.4 PedsQL patient reported total score in the age group 5 to < 18 years not considering cutoff by gender (FAS), change from baseline analysis

	Treatment Groups		Comparison	
PedsQL patient reported total score in the age group 5 to < 18 years not considering cutoff by gender (FAS)	**LCZ696 (N=114)**	**Enalapril (N=116)**	**Mean Difference [95% CI] p-value**	**Hedges G [95% CI]**
Male, N	59	56		
Female, N	55	60		
PedsQL patient reported total summary score				
Interaction test	**p = 0.612**			
Male				
N' / N"	54 / 53	53 / 50		
Baseline: mean (SD)	76.62 (13.13)	69.85 (17.89)		
Week 52: mean (SD)	72.09 (27.61)	65.15 (27.82)		
Week 12: adjusted mean change (SE)	1.46 (2.53)	-1.70 (2.49)		
Week 24: adjusted mean change (SE)	1.52 (3.14)	-1.17 (3.13)		
Week 36: adjusted mean change (SE)	-0.27 (3.54)	-4.05 (3.55)		
Week 52: adjusted mean change (SE)	-1.95 (3.64)	-4.03 (3.68)	2.09 [-8.15; 12.32] 0.688	0.080 [-0.309; 0.468]
Female				
N' / N"	51 / 48	55 / 53		
Baseline: mean (SD)	68.32 (15.85)	69.94 (19.98)		
Week 52: mean (SD)	66.02 (27.94)	62.78 (29.55)		
Week 12: adjusted mean change (SE)	-0.29 (2.58)	-1.26 (2.47)		
Week 24: adjusted mean change (SE)	-5.50 (3.18)	-1.75 (3.07)		
Week 36: adjusted mean change (SE)	-5.42 (3.58)	-6.13 (3.47)		
Week 52: adjusted mean change (SE)	-3.56 (3.70)	-5.92 (3.58)	2.36 [-7.76; 12.49] 0.646	0.091 [-0.296; 0.478]

	Treatment Groups		Comparison	
PedsQL patient reported total score in the age group 5 to < 18 years not considering cutoff by gender (FAS)	**LCZ696 (N=114)**	**Enalapril (N=116)**	**Mean Difference [95% CI] p-value**	**Hedges G [95% CI]**

N: Number of patients
N': Number of patients in the analysis
N'': Number of patients with non-missing value (not imputed)
CI: Confidence interval
SD: Standard deviation
SE: Standard error
MMRM: Mixed model for repeated measures
.....

Imputation method: Missing values after the first category-1-event (investigator reported or positively adjudicated) were set to the worst value.

Analysis method:
Interaction test, adjusted mean change and mean difference obtained from MMRM with unstructured covariance matrix: change from baseline = treatment + visit + treatment * visit + gender + treatment * gender + gender * visit + treatment * gender * visit + baseline value + baseline value * visit + NYHA/Ross class + region

The PedsQL for the patient was applied in children from 5 years to < 18 years. The analysis is based on this age group.
The PedsQL is on scale 0 to 100, higher scores indicate better health-related quality of life.
Not considering cutoff date: Nominal week 52
assessments that were performed later than 58 weeks after baseline were included in the analysis.

Table 19.5 PedsQL patient reported total score in the age group 5 to < 18 years not considering cutoff by COVID-19 period (FAS), change from baseline analysis

	Treatment Groups		Comparison	
PedsQL patient reported total score in the age group 5 to < 18 years not considering cutoff by COVID-19 period (FAS)	**LCZ696 (N=114)**	**Enalapril (N=116)**	**Mean Difference [95% CI] p-value**	**Hedges G [95% CI]**
Pre-pandemic, N	59	60		
Pre- and during-pandemic, N	33	33		
During-pandemic, N	22	23		
PedsQL patient reported total summary score				
Interaction test	**p = 0.041 ***			
Pre-pandemic				
N' / N''	55 / 52	55 / 50		
Baseline: mean (SD)	73.79 (13.37)	67.06 (19.28)		
Week 52: mean (SD)	64.79 (32.22)	53.61 (32.21)		
Week 12: adjusted mean change (SE)	0.37 (2.46)	-4.05 (2.45)		
Week 24: adjusted mean change (SE)	-4.11 (2.96)	-7.19 (2.99)		
Week 36: adjusted mean change (SE)	-4.34 (3.32)	-13.85 (3.37)		
Week 52: adjusted mean change (SE)	-7.17 (3.43)	-13.98 (3.49)	6.81 [-2.86; 16.48] 0.166	0.271 [-0.113; 0.655]
Pre- and during-pandemic				
N' / N''	28 / 28	32 / 32		
Baseline: mean (SD)	70.66 (17.83)	71.51 (19.43)		
Week 52: mean (SD)	74.47 (21.22)	73.15 (16.87)		
Week 12: adjusted mean change (SE)	6.04 (3.46)	-0.62 (3.18)		
Week 24: adjusted mean change (SE)	8.20 (4.20)	3.08 (3.96)		
Week 36: adjusted mean change (SE)	4.22 (4.68)	1.71 (4.43)		
Week 52: adjusted mean change (SE)	3.57 (4.76)	2.18 (4.53)	1.39 [-11.58; 14.36] 0.833	0.056 [-0.464; 0.576]
During-pandemic				
N' / N''	22 / 21	21 / 21		
Baseline: mean (SD)	71.81 (15.39)	74.94 (16.43)		
Week 52: mean (SD)	72.95 (22.15)	76.21 (23.32)		
Week 12: adjusted mean change (SE)	-5.49 (3.85)	3.83 (3.99)		
Week 24: adjusted mean change (SE)	-9.45 (4.84)	6.78 (4.84)		
Week 36: adjusted mean change (SE)	-8.10 (5.38)	7.15 (5.40)		
Week 52: adjusted mean change (SE)	0.63 (5.46)	7.21 (5.58)	-6.57 [-21.92; 8.77] 0.399	-0.258 [-0.858; 0.343]

	Treatment Groups		Comparison	
PedsQL patient reported total score in the age group 5 to < 18 years not considering cutoff by COVID-19 period (FAS)	**LCZ696 (N=114)**	**Enalapril (N=116)**	**Mean Difference [95% CI] p-value**	**Hedges G [95% CI]**

N: Number of patients
N': Number of patients in the analysis
N'': Number of patients with non-missing value (not imputed)
CI: Confidence interval
SD: Standard deviation
SE: Standard error
MMRM: Mixed model for repeated measures
*: $p < 0.05$
.....

Imputation method: Missing values after the first category-1-event (investigator reported or positively adjudicated) were set to the worst value.

Analysis method:
Interaction test, adjusted mean change and mean difference obtained from MMRM with unstructured covariance matrix: change from baseline = treatment + visit + treatment * visit + COVID-19 period + treatment * COVID-19 period + COVID-19 period * visit + treatment * COVID-19 period * visit + baseline value + baseline value * visit + NYHA/Ross class + region

The PedsQL for the patient was applied in children from 5 years to < 18 years. The analysis is based on this age group.
The PedsQL is on scale 0 to 100, higher scores indicate better health-related quality of life.
Not considering cutoff date: Nominal week 52
assessments that were performed later than 58 weeks after baseline were included in the analysis.

Table 19.6 PedsQL patient reported total score in the age group 5 to < 18 years not considering cutoff by race (FAS), change from baseline analysis

	Treatment Groups		Comparison	
PedsQL patient reported total score in the age group 5 to < 18 years not considering cutoff by race (FAS)	**LCZ696 (N=114)**	**Enalapril (N=116)**	**Mean Difference [95% CI] p-value**	**Hedges G [95% CI]**
Caucasian, N	62	63		
Black, N	15	21		
Asian, N	26	23		
Unknown or other, N	11	9		
PedsQL patient reported total summary score				
Interaction test	**p = 0.728**			
Caucasian				
N' / N"	56 / 53	60 / 57		
Baseline: mean (SD)	71.28 (16.28)	70.22 (19.24)		
Week 52: mean (SD)	67.23 (26.50)	66.41 (25.78)		
Week 12: adjusted mean change (SE)	1.48 (2.75)	0.05 (2.62)		
Week 24: adjusted mean change (SE)	-0.82 (3.31)	-1.64 (3.17)		
Week 36: adjusted mean change (SE)	0.33 (3.63)	-3.23 (3.49)		
Week 52: adjusted mean change (SE)	-3.74 (3.70)	-3.87 (3.58)	0.13 [-9.51; 9.77] 0.979	0.005 [-0.364; 0.374]
Black				
N' / N"	15 / 15	19 / 18		
Baseline: mean (SD)	74.76 (16.31)	70.27 (21.19)		
Week 52: mean (SD)	82.94 (16.49)	56.03 (35.48)		
Week 12: adjusted mean change (SE)	-2.54 (4.82)	-6.04 (4.25)		
Week 24: adjusted mean change (SE)	-3.64 (6.01)	-2.50 (5.24)		
Week 36: adjusted mean change (SE)	-4.36 (6.72)	-13.96 (5.92)		
Week 52: adjusted mean change (SE)	10.57 (7.00)	-10.64 (6.08)	21.21 [2.99; 39.44] 0.023 *	0.826 [0.092; 1.560]

	Treatment Groups		Comparison	
PedsQL patient reported total score in the age group 5 to < 18 years not considering cutoff by race (FAS)	**LCZ696 (N=114)**	**Enalapril (N=116)**	**Mean Difference [95% CI] p-value**	**Hedges G [95% CI]**
Asian				
N' / N''	25 / 24	22 / 21		
Baseline: mean (SD)	70.60 (12.42)	69.86 (17.02)		
Week 52: mean (SD)	64.18 (33.38)	63.52 (31.64)		
Week 12: adjusted mean change (SE)	-0.87 (4.79)	-2.65 (5.12)		
Week 24: adjusted mean change (SE)	-4.96 (5.52)	-0.79 (5.97)		
Week 36: adjusted mean change (SE)	-6.64 (5.99)	-3.72 (6.43)		
Week 52: adjusted mean change (SE)	-6.67 (6.13)	-5.11 (6.57)	-1.57 [-16.79; 13.66] 0.840	-0.060 [-0.645; 0.524]
Unknown or other				
N' / N''	9 / 9	7 / 7		
Baseline: mean (SD)	82.06 (8.24)	66.71 (18.72)		
Week 52: mean (SD)	73.31 (30.45)	66.49 (19.83)		
Week 12: adjusted mean change (SE)	4.66 (6.54)	1.56 (7.02)		
Week 24: adjusted mean change (SE)	2.91 (8.05)	0.42 (9.10)		
Week 36: adjusted mean change (SE)	-8.09 (8.80)	-1.06 (10.57)		
Week 52: adjusted mean change (SE)	-4.07 (8.87)	2.19 (11.17)	-6.26 [-34.36; 21.83] 0.661	-0.232 [-1.268; 0.805]

N: Number of patients
N': Number of patients in the analysis
N'': Number of patients with non-missing value (not imputed)
CI: Confidence interval
SD: Standard deviation
SE: Standard error
MMRM: Mixed model for repeated measures
*: $p < 0.05$
.....

Imputation method: Missing values after the first category-1-event (investigator reported or positively adjudicated) were set to the worst value.

Analysis method:
Interaction test, adjusted mean change and mean difference obtained from MMRM with unstructured covariance matrix: change from baseline = treatment + visit + treatment * visit + race + treatment * race + race * visit + treatment * race * visit + baseline value + baseline value * visit + NYHA/Ross class + region

The PedsQL for the patient was applied in children from 5 years to < 18 years. The analysis is based on this age group.
The PedsQL is on scale 0 to 100, higher scores indicate better health-related quality of life.
Not considering cutoff date: Nominal week 52
assessments that were performed later than 58 weeks after baseline were included in the analysis.

20 PedsQL parent reported total score, considering cutoff date for the last visit

Table 20.0 PedsQL parent reported total score considering cutoff (FAS), return rates

	Treatment Groups		
PedsQL parent reported total score considering cutoff (FAS)	**LCZ696 (N=182)**	**Enalapril (N=184)**	**Total (N=366)**
PedsQL parent reported total summary score			
Baseline returns, n (%)	176 (96.7)	177 (96.2)	353 (96.4)
Week 12 returns, n (%)	165 (90.7)	170 (92.4)	335 (91.5)
Week 24 returns, n (%)	165 (90.7)	163 (88.6)	328 (89.6)
Week 36 returns, n (%)	156 (85.7)	159 (86.4)	315 (86.1)
Week 52 returns, n (%)	147 (80.8)	153 (83.2)	300 (82.0)

N: Number of patients
n (%): Number and percentage of patients with available value
.....

The return rate is the proportion of patients with available value at the given visit based on the whole analysis population.

Considering cutoff date: Nominal week 52 assessments that were performed later than 58 weeks after baseline were excluded from the analysis.

Table 20.1 PedsQL parent reported total score considering cutoff (FAS), change from baseline analysis

	Treatment Groups		Comparison	
PedsQL parent reported total score considering cutoff (FAS)	**LCZ696 (N=182)**	**Enalapril (N=184)**	**Mean Difference [95% CI] p-value**	**Hedges G [95% CI]**
PedsQL parent reported total summary score				
N' / N''	172 / 169	173 / 166		
Baseline: mean (SD)	70.41 (17.83)	72.04 (18.78)		
Week 52: mean (SD)	70.32 (27.13)	67.14 (30.78)		
Week 12: adjusted mean change (SE)	1.90 (1.38)	0.99 (1.37)		
Week 24: adjusted mean change (SE)	1.05 (1.58)	-1.18 (1.58)		
Week 36: adjusted mean change (SE)	0.00 (1.86)	-2.04 (1.86)		
Week 52: adjusted mean change (SE)	0.03 (2.02)	-3.34 (2.00)	3.38 [-2.21; 8.97] 0.236	0.137 [-0.089; 0.364]

N: Number of patients
N': Number of patients in the analysis
N'': Number of patients with non-missing value (not imputed)
CI: Confidence interval
SD: Standard deviation
SE: Standard error
MMRM: Mixed model for repeated measures
.....

Imputation method: Missing values after the first category-1-event (investigator reported or positively adjudicated) were set to the worst value.

Analysis method:
Adjusted mean change and mean difference obtained from MMRM with unstructured covariance matrix: change from baseline = treatment + visit + treatment * visit + baseline value + baseline value * visit + age group + NYHA/Ross class + region

The PedsQL is on scale 0 to 100, higher scores indicate better health-related quality of life.
Considering cutoff date: Nominal week
52 assessments that were performed later than 58 weeks after baseline were excluded from the analysis.

Table 20.2 PedsQL parent reported total score considering cutoff by age group (FAS), change from baseline analysis

	Treatment Groups		Comparison	
PedsQL parent reported total score considering cutoff by age group (FAS)	**LCZ696 (N=182)**	**Enalapril (N=184)**	**Mean Difference [95% CI] p-value**	**Hedges G [95% CI]**
6 years to < 18 years, N	109	111		
1 year to < 6 years, N	73	73		
PedsQL parent reported total summary score				
Interaction test	**p = 0.136**			
6 years to < 18 years				
N' / N"	103 / 102	106 / 100		
Baseline: mean (SD)	66.93 (17.48)	67.53 (18.21)		
Week 52: mean (SD)	65.44 (27.41)	58.72 (30.70)		
Week 12: adjusted mean change (SE)	1.14 (1.82)	-1.91 (1.77)		
Week 24: adjusted mean change (SE)	-0.35 (2.06)	-5.48 (2.03)		
Week 36: adjusted mean change (SE)	-2.71 (2.42)	-7.00 (2.39)		
Week 52: adjusted mean change (SE)	-2.64 (2.61)	-8.63 (2.58)	6.00 [-1.15; 13.15] 0.100	0.245 [-0.047; 0.538]
1 year to < 6 years				
N' / N"	69 / 67	67 / 66		
Baseline: mean (SD)	75.55 (17.20)	78.94 (17.61)		
Week 52: mean (SD)	78.04 (25.00)	79.49 (26.65)		
Week 12: adjusted mean change (SE)	3.19 (2.20)	5.46 (2.24)		
Week 24: adjusted mean change (SE)	3.21 (2.51)	5.52 (2.57)		
Week 36: adjusted mean change (SE)	4.09 (2.98)	5.74 (3.04)		
Week 52: adjusted mean change (SE)	4.11 (3.24)	4.87 (3.25)	-0.77 [-9.66; 8.13] 0.866	-0.031 [-0.391; 0.329]

	Treatment Groups		Comparison	
PedsQL parent reported total score considering cutoff by age group (FAS)	**LCZ696 (N=182)**	**Enalapril (N=184)**	**Mean Difference [95% CI] p-value**	**Hedges G [95% CI]**

N: Number of patients
N': Number of patients in the analysis
N'': Number of patients with non-missing value (not imputed)
CI: Confidence interval
SD: Standard deviation
SE: Standard error
MMRM: Mixed model for repeated measures
.....

Imputation method: Missing values after the first category-1-event (investigator reported or positively adjudicated) were set to the worst value.

Analysis method:
Interaction test, adjusted mean change and mean difference obtained from MMRM with unstructured covariance matrix: change from baseline = treatment + visit + treatment * visit + age group + treatment * age group + age group * visit + treatment * age group * visit + baseline value + baseline value * visit + NYHA/Ross class + region

The PedsQL is on scale 0 to 100, higher scores indicate better health-related quality of life.
Considering cutoff date: Nominal week
52 assessments that were performed later than 58 weeks after baseline were excluded from the analysis.

Table 20.3 PedsQL parent reported total score considering cutoff by NYHA/Ross class (FAS), change from baseline analysis

	Treatment Groups		Comparison	
PedsQL parent reported total score considering cutoff by NYHA/Ross class (FAS)	**LCZ696 (N=182)**	**Enalapril (N=184)**	**Mean Difference [95% CI] p-value**	**Hedges G [95% CI]**
Class I/II, N	157	157		
Class III/IV, N	25	27		
PedsQL parent reported total summary score				
Interaction test	**p = 0.900**			
Class I/II				
N' / N"	151 / 148	149 / 144		
Baseline: mean (SD)	71.07 (17.40)	73.98 (18.10)		
Week 52: mean (SD)	71.15 (26.00)	68.27 (30.40)		
Week 12: adjusted mean change (SE)	1.97 (1.48)	1.46 (1.48)		
Week 24: adjusted mean change (SE)	1.47 (1.68)	-1.14 (1.71)		
Week 36: adjusted mean change (SE)	0.78 (1.99)	-1.96 (2.01)		
Week 52: adjusted mean change (SE)	-0.01 (2.16)	-2.90 (2.17)	2.89 [-3.14; 8.92] 0.347	0.117 [-0.127; 0.362]
Class III/IV				
N' / N"	21 / 21	24 / 22		
Baseline: mean (SD)	66.04 (20.34)	60.27 (18.86)		
Week 52: mean (SD)	64.76 (34.06)	60.75 (32.82)		
Week 12: adjusted mean change (SE)	1.43 (3.96)	-2.20 (3.76)		
Week 24: adjusted mean change (SE)	-1.92 (4.55)	-1.46 (4.37)		
Week 36: adjusted mean change (SE)	-6.56 (5.46)	-2.59 (5.09)		
Week 52: adjusted mean change (SE)	0.33 (5.75)	-6.09 (5.36)	6.42 [-8.99; 21.83] 0.413	0.254 [-0.356; 0.864]

	Treatment Groups		Comparison	
PedsQL parent reported total score considering cutoff by NYHA/Ross class (FAS)	**LCZ696 (N=182)**	**Enalapril (N=184)**	**Mean Difference [95% CI] p-value**	**Hedges G [95% CI]**

N: Number of patients
N': Number of patients in the analysis
N'': Number of patients with non-missing value (not imputed)
CI: Confidence interval
SD: Standard deviation
SE: Standard error
MMRM: Mixed model for repeated measures
.....

Imputation method: Missing values after the first category-1-event (investigator reported or positively adjudicated) were set to the worst value.

Analysis method:
Interaction test, adjusted mean change and mean difference obtained from MMRM with unstructured covariance matrix: change from baseline = treatment + visit + treatment * visit + NYHA/Ross class + treatment * NYHA/Ross class + NYHA/Ross class * visit + treatment * NYHA/Ross class * visit + baseline value + baseline value * visit + age group + region

The PedsQL is on scale 0 to 100, higher scores indicate better health-related quality of life.
Considering cutoff date: Nominal week
52 assessments that were performed later than 58 weeks after baseline were excluded from the analysis.

Table 20.4 PedsQL parent reported total score considering cutoff by region (FAS), change from baseline analysis

	Treatment Groups		Comparison	
PedsQL parent reported total score considering cutoff by region (FAS)	**LCZ696 (N=182)**	**Enalapril (N=184)**	**Mean Difference [95% CI] p-value**	**Hedges G [95% CI]**
America, N	58	69		
Europe, N	58	55		
Asia/Pacific and other, N	66	60		
PedsQL parent reported total summary score				
Interaction test	**p = 0.177**			
America				
N' / N''	55 / 54	66 / 63		
Baseline: mean (SD)	69.71 (18.14)	72.28 (18.35)		
Week 52: mean (SD)	72.36 (22.59)	60.52 (33.63)		
Week 12: adjusted mean change (SE)	3.31 (2.43)	-1.30 (2.22)		
Week 24: adjusted mean change (SE)	3.13 (2.78)	-3.29 (2.54)		
Week 36: adjusted mean change (SE)	3.02 (3.29)	-4.68 (3.01)		
Week 52: adjusted mean change (SE)	4.14 (3.67)	-6.64 (3.32)	10.78 [1.06; 20.50] 0.030 *	0.453 [0.041; 0.864]
Europe				
N' / N''	53 / 53	52 / 51		
Baseline: mean (SD)	71.74 (15.35)	72.32 (16.31)		
Week 52: mean (SD)	71.35 (24.88)	72.61 (23.90)		
Week 12: adjusted mean change (SE)	3.82 (2.54)	1.82 (2.51)		
Week 24: adjusted mean change (SE)	3.08 (2.87)	1.52 (2.93)		
Week 36: adjusted mean change (SE)	2.67 (3.36)	2.73 (3.38)		
Week 52: adjusted mean change (SE)	-0.35 (3.58)	0.04 (3.60)	-0.39 [-10.37; 9.60] 0.939	-0.015 [-0.409; 0.379]
Asia/Pacific and other				
N' / N''	64 / 62	55 / 52		
Baseline: mean (SD)	69.89 (19.64)	71.54 (21.40)		
Week 52: mean (SD)	67.90 (31.97)	68.53 (33.02)		
Week 12: adjusted mean change (SE)	-0.86 (2.27)	2.91 (2.42)		
Week 24: adjusted mean change (SE)	-2.36 (2.59)	-1.09 (2.78)		
Week 36: adjusted mean change (SE)	-4.68 (3.05)	-3.17 (3.25)		
Week 52: adjusted mean change (SE)	-2.84 (3.29)	-2.64 (3.50)	-0.21 [-9.63; 9.22] 0.966	-0.008 [-0.388; 0.371]

	Treatment Groups		Comparison	
PedsQL parent reported total score considering cutoff by region (FAS)	**LCZ696 (N=182)**	**Enalapril (N=184)**	**Mean Difference [95% CI] p-value**	**Hedges G [95% CI]**

N: Number of patients
N': Number of patients in the analysis
N'': Number of patients with non-missing value (not imputed)
CI: Confidence interval
SD: Standard deviation
SE: Standard error
MMRM: Mixed model for repeated measures
*: $p < 0.05$
.....

Imputation method: Missing values after the first category-1-event (investigator reported or positively adjudicated) were set to the worst value.

Analysis method:
Interaction test, adjusted mean change and mean difference obtained from MMRM with unstructured covariance matrix: change from baseline = treatment + visit + treatment * visit + region + treatment * region + region * visit + treatment * region * visit + baseline value + baseline value * visit + age group + NYHA/Ross class

The PedsQL is on scale 0 to 100, higher scores indicate better health-related quality of life.
Considering cutoff date: Nominal week
52 assessments that were performed later than 58 weeks after baseline were excluded from the analysis.

Table 20.5 PedsQL parent reported total score considering cutoff by gender (FAS), change from baseline analysis

	Treatment Groups		Comparison	
PedsQL parent reported total score considering cutoff by gender (FAS)	**LCZ696 (N=182)**	**Enalapril (N=184)**	**Mean Difference [95% CI] p-value**	**Hedges G [95% CI]**
Male, N	88	91		
Female, N	94	93		
PedsQL parent reported total summary score				
Interaction test	**p = 0.835**			
Male				
N' / N"	83 / 82	86 / 82		
Baseline: mean (SD)	70.94 (16.13)	74.48 (17.98)		
Week 52: mean (SD)	67.99 (27.72)	70.41 (30.36)		
Week 12: adjusted mean change (SE)	3.00 (2.00)	0.25 (1.95)		
Week 24: adjusted mean change (SE)	1.98 (2.28)	-1.84 (2.26)		
Week 36: adjusted mean change (SE)	-1.32 (2.69)	-1.44 (2.66)		
Week 52: adjusted mean change (SE)	-2.39 (2.89)	-2.49 (2.87)	0.10 [-7.92; 8.12] 0.981	0.004 [-0.318; 0.326]
Female				
N' / N"	89 / 87	87 / 84		
Baseline: mean (SD)	69.92 (19.36)	69.69 (19.32)		
Week 52: mean (SD)	72.63 (26.51)	63.99 (31.06)		
Week 12: adjusted mean change (SE)	0.86 (1.94)	1.74 (1.95)		
Week 24: adjusted mean change (SE)	0.21 (2.20)	-0.53 (2.22)		
Week 36: adjusted mean change (SE)	1.29 (2.60)	-2.59 (2.61)		
Week 52: adjusted mean change (SE)	2.39 (2.83)	-4.14 (2.81)	6.53 [-1.30; 14.36] 0.102	0.266 [-0.053; 0.586]

	Treatment Groups		Comparison	
PedsQL parent reported total score considering cutoff by gender (FAS)	**LCZ696 (N=182)**	**Enalapril (N=184)**	**Mean Difference [95% CI] p-value**	**Hedges G [95% CI]**

N: Number of patients
N': Number of patients in the analysis
N'': Number of patients with non-missing value (not imputed)
CI: Confidence interval
SD: Standard deviation
SE: Standard error
MMRM: Mixed model for repeated measures
.....

Imputation method: Missing values after the first category-1-event (investigator reported or positively adjudicated) were set to the worst value.

Analysis method:
Interaction test, adjusted mean change and mean difference obtained from MMRM with unstructured covariance matrix: change from baseline = treatment + visit + treatment * visit + gender + treatment * gender + gender * visit + treatment * gender * visit + baseline value + baseline value * visit + age group + NYHA/Ross class + region

The PedsQL is on scale 0 to 100, higher scores indicate better health-related quality of life.
Considering cutoff date: Nominal week
52 assessments that were performed later than 58 weeks after baseline were excluded from the analysis.

Table 20.6 PedsQL parent reported total score considering cutoff by COVID-19 period (FAS), change from baseline analysis

	Treatment Groups		Comparison	
PedsQL parent reported total score considering cutoff by COVID-19 period (FAS)	**LCZ696 (N=182)**	**Enalapril (N=184)**	**Mean Difference [95% CI] p-value**	**Hedges G [95% CI]**
Pre-pandemic, N	79	83		
Pre- and during-pandemic, N	62	59		
During-pandemic, N	41	42		
PedsQL parent reported total summary score				
Interaction test	**p = 0.096**			
Pre-pandemic				
N' / N''	72 / 70	77 / 71		
Baseline: mean (SD)	71.23 (15.36)	71.28 (20.21)		
Week 52: mean (SD)	64.54 (31.77)	57.39 (35.14)		
Week 12: adjusted mean change (SE)	2.64 (2.16)	-1.84 (2.08)		
Week 24: adjusted mean change (SE)	0.49 (2.39)	-8.16 (2.31)		
Week 36: adjusted mean change (SE)	-2.91 (2.79)	-10.44 (2.72)		
Week 52: adjusted mean change (SE)	-5.53 (3.00)	-11.54 (2.97)	6.01 [-2.24; 14.26] 0.153	0.250 [-0.093; 0.592]
Pre- and during-pandemic				
N' / N''	59 / 59	55 / 55		
Baseline: mean (SD)	69.61 (22.08)	71.36 (19.03)		
Week 52: mean (SD)	73.25 (22.39)	72.78 (26.78)		
Week 12: adjusted mean change (SE)	2.95 (2.40)	3.44 (2.43)		
Week 24: adjusted mean change (SE)	4.51 (2.64)	3.50 (2.76)		
Week 36: adjusted mean change (SE)	5.18 (3.17)	4.81 (3.26)		
Week 52: adjusted mean change (SE)	1.77 (3.50)	2.59 (3.49)	-0.82 [-10.55; 8.90] 0.868	-0.035 [-0.449; 0.379]
During-pandemic				
N' / N''	41 / 40	41 / 40		
Baseline: mean (SD)	70.13 (15.05)	74.46 (15.49)		
Week 52: mean (SD)	77.40 (20.61)	76.14 (22.93)		
Week 12: adjusted mean change (SE)	-0.81 (2.84)	2.95 (2.82)		
Week 24: adjusted mean change (SE)	-3.17 (3.25)	5.99 (3.21)		
Week 36: adjusted mean change (SE)	-2.02 (3.77)	4.70 (3.73)		
Week 52: adjusted mean change (SE)	6.80 (3.99)	3.69 (3.91)	3.10 [-7.86; 14.07] 0.578	0.126 [-0.319; 0.571]

	Treatment Groups		Comparison	
PedsQL parent reported total score considering cutoff by COVID-19 period (FAS)	**LCZ696 (N=182)**	**Enalapril (N=184)**	**Mean Difference [95% CI] p-value**	**Hedges G [95% CI]**

N: Number of patients
N': Number of patients in the analysis
N'': Number of patients with non-missing value (not imputed)
CI: Confidence interval
SD: Standard deviation
SE: Standard error
MMRM: Mixed model for repeated measures
.....

Imputation method: Missing values after the first category-1-event (investigator reported or positively adjudicated) were set to the worst value.

Analysis method:
Interaction test, adjusted mean change and mean difference obtained from MMRM with unstructured covariance matrix: change from baseline = treatment + visit + treatment * visit + COVID-19 period + treatment * COVID-19 period + COVID-19 period * visit + treatment * COVID-19 period * visit + baseline value + baseline value * visit + age group + NYHA/Ross class + region

The PedsQL is on scale 0 to 100, higher scores indicate better health-related quality of life.
Considering cutoff date: Nominal week
52 assessments that were performed later than 58 weeks after baseline were excluded from the analysis.

Table 20.7 PedsQL parent reported total score considering cutoff by race (FAS), change from baseline analysis

	Treatment Groups		Comparison	
PedsQL parent reported total score considering cutoff by race (FAS)	**LCZ696 (N=182)**	**Enalapril (N=184)**	**Mean Difference [95% CI] p-value**	**Hedges G [95% CI]**
Caucasian, N	86	90		
Black, N	23	25		
Asian, N	55	45		
Unknown or other, N	18	24		
PedsQL parent reported total summary score				
Interaction test	**p = 0.374**			
Caucasian				
N' / N"	79 / 78	88 / 84		
Baseline: mean (SD)	69.18 (17.62)	71.98 (18.05)		
Week 52: mean (SD)	68.86 (26.08)	68.01 (28.81)		
Week 12: adjusted mean change (SE)	1.68 (2.25)	0.32 (2.16)		
Week 24: adjusted mean change (SE)	1.46 (2.53)	-2.69 (2.43)		
Week 36: adjusted mean change (SE)	2.18 (2.88)	-0.48 (2.76)		
Week 52: adjusted mean change (SE)	-0.94 (3.08)	-3.31 (2.94)	2.37 [-5.58; 10.33] 0.558	0.096 [-0.225; 0.418]
Black				
N' / N"	21 / 21	22 / 21		
Baseline: mean (SD)	70.16 (18.38)	73.19 (19.70)		
Week 52: mean (SD)	72.10 (17.80)	48.79 (35.69)		
Week 12: adjusted mean change (SE)	2.99 (4.11)	-5.87 (3.95)		
Week 24: adjusted mean change (SE)	1.01 (4.62)	-2.02 (4.45)		
Week 36: adjusted mean change (SE)	-3.56 (5.37)	-14.41 (5.17)		
Week 52: adjusted mean change (SE)	2.16 (5.93)	-18.48 (5.58)	20.64 [4.72; 36.55] 0.011 *	0.841 [0.167; 1.516]

	Treatment Groups		Comparison	
PedsQL parent reported total score considering cutoff by race (FAS)	**LCZ696 (N=182)**	**Enalapril (N=184)**	**Mean Difference [95% CI] p-value**	**Hedges G [95% CI]**
Asian				
N' / N''	54 / 52	42 / 40		
Baseline: mean (SD)	70.05 (18.23)	70.55 (19.66)		
Week 52: mean (SD)	70.07 (31.97)	72.16 (28.76)		
Week 12: adjusted mean change (SE)	1.21 (3.27)	4.18 (3.45)		
Week 24: adjusted mean change (SE)	-0.56 (3.55)	0.26 (3.82)		
Week 36: adjusted mean change (SE)	-2.16 (3.95)	-1.92 (4.26)		
Week 52: adjusted mean change (SE)	0.43 (4.18)	1.84 (4.51)	-1.41 [-11.98; 9.16] 0.794	-0.058 [-0.493; 0.377]
Unknown or other				
N' / N''	18 / 18	21 / 21		
Baseline: mean (SD)	77.35 (16.76)	74.24 (19.93)		
Week 52: mean (SD)	76.40 (26.36)	73.45 (32.28)		
Week 12: adjusted mean change (SE)	4.03 (4.55)	4.02 (4.05)		
Week 24: adjusted mean change (SE)	4.17 (5.09)	2.57 (4.67)		
Week 36: adjusted mean change (SE)	1.35 (5.88)	4.34 (5.50)		
Week 52: adjusted mean change (SE)	1.41 (6.42)	1.62 (5.92)	-0.21 [-17.14; 16.73] 0.981	-0.009 [-0.707; 0.690]

N: Number of patients
N': Number of patients in the analysis
N'': Number of patients with non-missing value (not imputed)
CI: Confidence interval
SD: Standard deviation
SE: Standard error
MMRM: Mixed model for repeated measures
*: $p < 0.05$
.....

Imputation method: Missing values after the first category-1-event (investigator reported or positively adjudicated) were set to the worst value.

Analysis method:
Interaction test, adjusted mean change and mean difference obtained from MMRM with unstructured covariance matrix: change from baseline = treatment + visit + treatment * visit + race + treatment * race + race * visit + treatment * race * visit + baseline value + baseline value * visit + age group + NYHA/Ross class + region

The PedsQL is on scale 0 to 100, higher scores indicate better health-related quality of life.
Considering cutoff date: Nominal week
52 assessments that were performed later than 58 weeks after baseline were excluded from the analysis.

21 PedsQL parent reported total score, not considering cutoff date for the last visit

Table 21.0 PedsQL parent reported total score not considering cutoff (FAS), return rates

	Treatment Groups		
PedsQL parent reported total score not considering cutoff (FAS)	**LCZ696 (N=182)**	**Enalapril (N=184)**	**Total (N=366)**
PedsQL parent reported total summary score			
Baseline returns, n (%)	176 (96.7)	177 (96.2)	353 (96.4)
Week 12 returns, n (%)	165 (90.7)	170 (92.4)	335 (91.5)
Week 24 returns, n (%)	165 (90.7)	163 (88.6)	328 (89.6)
Week 36 returns, n (%)	156 (85.7)	159 (86.4)	315 (86.1)
Week 52 returns, n (%)	167 (91.8)	166 (90.2)	333 (91.0)

N: Number of patients
n (%): Number and percentage of patients with available value
.....

The return rate is the proportion of patients with available value at the given visit based on the whole analysis population.

Not considering cutoff date: Nominal week 52 assessments that were performed later than 58 weeks after baseline were included in the analysis.

Table 21.1 PedsQL parent reported total score not considering cutoff (FAS), change from baseline analysis

	Treatment Groups		Comparison	
PedsQL parent reported total score not considering cutoff (FAS)	**LCZ696 (N=182)**	**Enalapril (N=184)**	**Mean Difference [95% CI] p-value**	**Hedges G [95% CI]**
PedsQL parent reported total summary score				
N' / N''	173 / 170	174 / 167		
Baseline: mean (SD)	70.41 (17.83)	72.04 (18.78)		
Week 52: mean (SD)	71.16 (26.20)	68.80 (29.61)		
Week 12: adjusted mean change (SE)	1.92 (1.38)	1.08 (1.37)		
Week 24: adjusted mean change (SE)	1.07 (1.57)	-1.07 (1.58)		
Week 36: adjusted mean change (SE)	0.04 (1.85)	-1.83 (1.85)		
Week 52: adjusted mean change (SE)	0.71 (1.92)	-2.10 (1.92)	2.81 [-2.53; 8.15] 0.302	0.113 [-0.102; 0.328]

N: Number of patients
N': Number of patients in the analysis
N'': Number of patients with non-missing value (not imputed)
CI: Confidence interval
SD: Standard deviation
SE: Standard error
MMRM: Mixed model for repeated measures
.....

Imputation method: Missing values after the first category-1-event (investigator reported or positively adjudicated) were set to the worst value.

Analysis method:
Adjusted mean change and mean difference obtained from MMRM with unstructured covariance matrix: change from baseline = treatment + visit + treatment * visit + baseline value + baseline value * visit + age group + NYHA/Ross class + region

The PedsQL is on scale 0 to 100, higher scores indicate better health-related quality of life.
Not considering cutoff date: Nominal
week 52 assessments that were performed later than 58 weeks after baseline were included in the analysis.

Table 21.2 PedsQL parent reported total score not considering cutoff by age group (FAS), change from baseline analysis

	Treatment Groups		Comparison	
PedsQL parent reported total score not considering cutoff by age group (FAS)	**LCZ696 (N=182)**	**Enalapril (N=184)**	**Mean Difference [95% CI] p-value**	**Hedges G [95% CI]**
6 years to < 18 years, N	109	111		
1 year to < 6 years, N	73	73		
PedsQL parent reported total summary score				
Interaction test	**p = 0.148**			
6 years to < 18 years				
N' / N"	104 / 103	106 / 100		
Baseline: mean (SD)	66.93 (17.48)	67.53 (18.21)		
Week 52: mean (SD)	65.95 (26.87)	60.87 (29.76)		
Week 12: adjusted mean change (SE)	1.11 (1.82)	-1.91 (1.77)		
Week 24: adjusted mean change (SE)	-0.39 (2.05)	-5.47 (2.03)		
Week 36: adjusted mean change (SE)	-2.79 (2.41)	-6.96 (2.38)		
Week 52: adjusted mean change (SE)	-2.22 (2.50)	-7.14 (2.49)	4.92 [-1.95; 11.80] 0.160	0.201 [-0.080; 0.482]
1 year to < 6 years				
N' / N"	69 / 67	68 / 67		
Baseline: mean (SD)	75.55 (17.20)	78.94 (17.61)		
Week 52: mean (SD)	78.74 (23.38)	79.94 (25.71)		
Week 12: adjusted mean change (SE)	3.23 (2.20)	5.61 (2.23)		
Week 24: adjusted mean change (SE)	3.27 (2.51)	5.70 (2.56)		
Week 36: adjusted mean change (SE)	4.20 (2.95)	6.10 (3.01)		
Week 52: adjusted mean change (SE)	4.99 (3.04)	5.57 (3.09)	-0.58 [-9.00; 7.84] 0.892	-0.023 [-0.358; 0.312]

	Treatment Groups		Comparison	
PedsQL parent reported total score not considering cutoff by age group (FAS)	**LCZ696 (N=182)**	**Enalapril (N=184)**	**Mean Difference [95% CI] p-value**	**Hedges G [95% CI]**

N: Number of patients
N': Number of patients in the analysis
N'': Number of patients with non-missing value (not imputed)
CI: Confidence interval
SD: Standard deviation
SE: Standard error
MMRM: Mixed model for repeated measures
.....

Imputation method: Missing values after the first category-1-event (investigator reported or positively adjudicated) were set to the worst value.

Analysis method:
Interaction test, adjusted mean change and mean difference obtained from MMRM with unstructured covariance matrix: change from baseline = treatment + visit + treatment * visit + age group + treatment * age group + age group * visit + treatment * age group * visit + baseline value + baseline value * visit + NYHA/Ross class + region

The PedsQL is on scale 0 to 100, higher scores indicate better health-related quality of life.
Not considering cutoff date: Nominal
week 52 assessments that were performed later than 58 weeks after baseline were included in the analysis.

Table 21.3 PedsQL parent reported total score not considering cutoff by NYHA/Ross class (FAS), change from baseline analysis

	Treatment Groups		Comparison	
PedsQL parent reported total score not considering cutoff by NYHA/Ross class (FAS)	**LCZ696 (N=182)**	**Enalapril (N=184)**	**Mean Difference [95% CI] p-value**	**Hedges G [95% CI]**
Class I/II, N	157	157		
Class III/IV, N	25	27		
PedsQL parent reported total summary score				
Interaction test	**p = 0.956**			
Class I/II				
N' / N"	152 / 149	150 / 145		
Baseline: mean (SD)	71.07 (17.40)	73.98 (18.10)		
Week 52: mean (SD)	72.16 (25.04)	70.00 (29.06)		
Week 12: adjusted mean change (SE)	1.98 (1.48)	1.56 (1.48)		
Week 24: adjusted mean change (SE)	1.49 (1.68)	-1.01 (1.70)		
Week 36: adjusted mean change (SE)	0.81 (1.97)	-1.69 (2.00)		
Week 52: adjusted mean change (SE)	0.72 (2.05)	-1.51 (2.08)	2.24 [-3.51; 7.99] 0.445	0.090 [-0.141; 0.321]
Class III/IV				
N' / N"	21 / 21	24 / 22		
Baseline: mean (SD)	66.04 (20.34)	60.27 (18.86)		
Week 52: mean (SD)	63.81 (33.42)	61.66 (32.41)		
Week 12: adjusted mean change (SE)	1.46 (3.96)	-2.16 (3.76)		
Week 24: adjusted mean change (SE)	-1.89 (4.55)	-1.46 (4.37)		
Week 36: adjusted mean change (SE)	-6.50 (5.43)	-2.79 (5.08)		
Week 52: adjusted mean change (SE)	1.03 (5.55)	-5.79 (5.21)	6.82 [-8.08; 21.72] 0.369	0.272 [-0.324; 0.869]

	Treatment Groups		Comparison	
PedsQL parent reported total score not considering cutoff by NYHA/Ross class (FAS)	**LCZ696 (N=182)**	**Enalapril (N=184)**	**Mean Difference [95% CI] p-value**	**Hedges G [95% CI]**

N: Number of patients
N': Number of patients in the analysis
N'': Number of patients with non-missing value (not imputed)
CI: Confidence interval
SD: Standard deviation
SE: Standard error
MMRM: Mixed model for repeated measures
.....

Imputation method: Missing values after the first category-1-event (investigator reported or positively adjudicated) were set to the worst value.

Analysis method:
Interaction test, adjusted mean change and mean difference obtained from MMRM with unstructured covariance matrix: change from baseline = treatment + visit + treatment * visit + NYHA/Ross class + treatment * NYHA/Ross class + NYHA/Ross class * visit + treatment * NYHA/Ross class * visit + baseline value + baseline value * visit + age group + region

The PedsQL is on scale 0 to 100, higher scores indicate better health-related quality of life.
Not considering cutoff date: Nominal
week 52 assessments that were performed later than 58 weeks after baseline were included in the analysis.

Table 21.4 PedsQL parent reported total score not considering cutoff by region (FAS), change from baseline analysis

	Treatment Groups		Comparison	
PedsQL parent reported total score not considering cutoff by region (FAS)	**LCZ696 (N=182)**	**Enalapril (N=184)**	**Mean Difference [95% CI] p-value**	**Hedges G [95% CI]**
America, N	58	69		
Europe, N	58	55		
Asia/Pacific and other, N	66	60		
PedsQL parent reported total summary score				
Interaction test	**p = 0.179**			
America				
N' / N''	56 / 55	66 / 63		
Baseline: mean (SD)	69.71 (18.14)	72.28 (18.35)		
Week 52: mean (SD)	73.38 (22.32)	64.82 (31.83)		
Week 12: adjusted mean change (SE)	3.26 (2.42)	-1.25 (2.22)		
Week 24: adjusted mean change (SE)	3.04 (2.77)	-3.23 (2.53)		
Week 36: adjusted mean change (SE)	3.06 (3.24)	-4.64 (3.00)		
Week 52: adjusted mean change (SE)	5.43 (3.39)	-3.96 (3.16)	9.39 [0.30; 18.49] 0.043 *	0.386 [0.010; 0.763]
Europe				
N' / N''	53 / 53	52 / 51		
Baseline: mean (SD)	71.74 (15.35)	72.32 (16.31)		
Week 52: mean (SD)	71.57 (24.24)	72.83 (23.71)		
Week 12: adjusted mean change (SE)	3.89 (2.54)	1.87 (2.51)		
Week 24: adjusted mean change (SE)	3.14 (2.87)	1.55 (2.93)		
Week 36: adjusted mean change (SE)	2.68 (3.35)	2.86 (3.37)		
Week 52: adjusted mean change (SE)	0.03 (3.46)	0.34 (3.50)	-0.31 [-9.99; 9.36] 0.949	-0.013 [-0.397; 0.372]
Asia/Pacific and other				
N' / N''	64 / 62	56 / 53		
Baseline: mean (SD)	69.89 (19.64)	71.54 (21.40)		
Week 52: mean (SD)	68.94 (30.69)	69.32 (31.91)		
Week 12: adjusted mean change (SE)	-0.83 (2.27)	3.13 (2.41)		
Week 24: adjusted mean change (SE)	-2.32 (2.59)	-0.81 (2.77)		
Week 36: adjusted mean change (SE)	-4.77 (3.04)	-2.71 (3.22)		
Week 52: adjusted mean change (SE)	-2.71 (3.15)	-2.04 (3.34)	-0.66 [-9.68; 8.35] 0.885	-0.027 [-0.388; 0.335]

	Treatment Groups		Comparison	
PedsQL parent reported total score not considering cutoff by region (FAS)	**LCZ696 (N=182)**	**Enalapril (N=184)**	**Mean Difference [95% CI] p-value**	**Hedges G [95% CI]**

N: Number of patients
N': Number of patients in the analysis
N'': Number of patients with non-missing value (not imputed)
CI: Confidence interval
SD: Standard deviation
SE: Standard error
MMRM: Mixed model for repeated measures
*: $p < 0.05$
.....

Imputation method: Missing values after the first category-1-event (investigator reported or positively adjudicated) were set to the worst value.

Analysis method:
Interaction test, adjusted mean change and mean difference obtained from MMRM with unstructured covariance matrix: change from baseline = treatment + visit + treatment * visit + region + treatment * region + region * visit + treatment * region * visit + baseline value + baseline value * visit + age group + NYHA/Ross class

The PedsQL is on scale 0 to 100, higher scores indicate better health-related quality of life.
Not considering cutoff date: Nominal
week 52 assessments that were performed later than 58 weeks after baseline were included in the analysis.

Table 21.5 PedsQL parent reported total score not considering cutoff by gender (FAS), change from baseline analysis

	Treatment Groups		Comparison	
PedsQL parent reported total score not considering cutoff by gender (FAS)	**LCZ696 (N=182)**	**Enalapril (N=184)**	**Mean Difference [95% CI] p-value**	**Hedges G [95% CI]**
Male, N	88	91		
Female, N	94	93		
PedsQL parent reported total summary score				
Interaction test	**p = 0.821**			
Male				
N' / N"	84 / 83	87 / 83		
Baseline: mean (SD)	70.94 (16.13)	74.48 (17.98)		
Week 52: mean (SD)	68.24 (27.13)	71.24 (29.22)		
Week 12: adjusted mean change (SE)	3.02 (2.00)	0.41 (1.94)		
Week 24: adjusted mean change (SE)	1.98 (2.28)	-1.65 (2.25)		
Week 36: adjusted mean change (SE)	-1.29 (2.67)	-1.10 (2.64)		
Week 52: adjusted mean change (SE)	-1.64 (2.77)	-1.26 (2.73)	-0.38 [-8.04; 7.29] 0.923	-0.015 [-0.323; 0.293]
Female				
N' / N"	89 / 87	87 / 84		
Baseline: mean (SD)	69.92 (19.36)	69.69 (19.32)		
Week 52: mean (SD)	73.78 (25.21)	66.36 (29.97)		
Week 12: adjusted mean change (SE)	0.90 (1.94)	1.77 (1.95)		
Week 24: adjusted mean change (SE)	0.25 (2.20)	-0.50 (2.22)		
Week 36: adjusted mean change (SE)	1.30 (2.59)	-2.53 (2.60)		
Week 52: adjusted mean change (SE)	2.82 (2.66)	-2.92 (2.71)	5.74 [-1.72; 13.20] 0.131	0.231 [-0.070; 0.532]

	Treatment Groups		Comparison	
PedsQL parent reported total score not considering cutoff by gender (FAS)	**LCZ696 (N=182)**	**Enalapril (N=184)**	**Mean Difference [95% CI] p-value**	**Hedges G [95% CI]**

N: Number of patients
N': Number of patients in the analysis
N'': Number of patients with non-missing value (not imputed)
CI: Confidence interval
SD: Standard deviation
SE: Standard error
MMRM: Mixed model for repeated measures
.....

Imputation method: Missing values after the first category-1-event (investigator reported or positively adjudicated) were set to the worst value.

Analysis method:
Interaction test, adjusted mean change and mean difference obtained from MMRM with unstructured covariance matrix: change from baseline = treatment + visit + treatment * visit + gender + treatment * gender + gender * visit + treatment * gender * visit + baseline value + baseline value * visit + age group + NYHA/Ross class + region

The PedsQL is on scale 0 to 100, higher scores indicate better health-related quality of life.
Not considering cutoff date: Nominal
week 52 assessments that were performed later than 58 weeks after baseline were included in the analysis.

Table 21.6 PedsQL parent reported total score not considering cutoff by COVID-19 period (FAS), change from baseline analysis

	Treatment Groups		Comparison	
PedsQL parent reported total score not considering cutoff by COVID-19 period (FAS)	**LCZ696 (N=182)**	**Enalapril (N=184)**	**Mean Difference [95% CI] p-value**	**Hedges G [95% CI]**
Pre-pandemic, N	79	83		
Pre- and during-pandemic, N	62	59		
During-pandemic, N	41	42		
PedsQL parent reported total summary score				
Interaction test	**p = 0.098**			
Pre-pandemic				
N' / N''	73 / 71	77 / 71		
Baseline: mean (SD)	71.23 (15.36)	71.28 (20.21)		
Week 52: mean (SD)	65.04 (31.15)	59.78 (34.60)		
Week 12: adjusted mean change (SE)	2.62 (2.15)	-1.83 (2.08)		
Week 24: adjusted mean change (SE)	0.48 (2.38)	-8.13 (2.31)		
Week 36: adjusted mean change (SE)	-3.00 (2.77)	-10.32 (2.71)		
Week 52: adjusted mean change (SE)	-5.12 (2.88)	-10.57 (2.85)	5.45 [-2.47; 13.36] 0.177	0.226 [-0.102; 0.555]
Pre- and during-pandemic				
N' / N''	59 / 59	56 / 56		
Baseline: mean (SD)	69.61 (22.08)	71.36 (19.03)		
Week 52: mean (SD)	74.50 (20.97)	75.09 (23.67)		
Week 12: adjusted mean change (SE)	2.98 (2.40)	3.62 (2.43)		
Week 24: adjusted mean change (SE)	4.55 (2.63)	3.69 (2.75)		
Week 36: adjusted mean change (SE)	5.31 (3.14)	5.08 (3.22)		
Week 52: adjusted mean change (SE)	4.03 (3.19)	4.92 (3.29)	-0.89 [-9.90; 8.12] 0.846	-0.037 [-0.409; 0.335]
During-pandemic				
N' / N''	41 / 40	41 / 40		
Baseline: mean (SD)	70.13 (15.05)	74.46 (15.49)		
Week 52: mean (SD)	77.75 (20.44)	76.14 (22.93)		
Week 12: adjusted mean change (SE)	-0.71 (2.84)	3.03 (2.82)		
Week 24: adjusted mean change (SE)	-3.06 (3.25)	6.08 (3.21)		
Week 36: adjusted mean change (SE)	-1.89 (3.77)	4.78 (3.72)		
Week 52: adjusted mean change (SE)	6.53 (3.89)	3.89 (3.83)	2.64 [-8.06; 13.33] 0.628	0.109 [-0.332; 0.551]

	Treatment Groups		Comparison	
PedsQL parent reported total score not considering cutoff by COVID-19 period (FAS)	**LCZ696 (N=182)**	**Enalapril (N=184)**	**Mean Difference [95% CI] p-value**	**Hedges G [95% CI]**

N: Number of patients
N': Number of patients in the analysis
N'': Number of patients with non-missing value (not imputed)
CI: Confidence interval
SD: Standard deviation
SE: Standard error
MMRM: Mixed model for repeated measures
.....

Imputation method: Missing values after the first category-1-event (investigator reported or positively adjudicated) were set to the worst value.

Analysis method:
Interaction test, adjusted mean change and mean difference obtained from MMRM with unstructured covariance matrix: change from baseline = treatment + visit + treatment * visit + COVID-19 period + treatment * COVID-19 period + COVID-19 period * visit + treatment * COVID-19 period * visit + baseline value + baseline value * visit + age group + NYHA/Ross class + region

The PedsQL is on scale 0 to 100, higher scores indicate better health-related quality of life.
Not considering cutoff date: Nominal
week 52 assessments that were performed later than 58 weeks after baseline were included in the analysis.

Table 21.7 PedsQL parent reported total score not considering cutoff by race (FAS), change from baseline analysis

	Treatment Groups		Comparison	
PedsQL parent reported total score not considering cutoff by race (FAS)	**LCZ696 (N=182)**	**Enalapril (N=184)**	**Mean Difference [95% CI] p-value**	**Hedges G [95% CI]**
Caucasian, N	86	90		
Black, N	23	25		
Asian, N	55	45		
Unknown or other, N	18	24		
PedsQL parent reported total summary score				
Interaction test	**p = 0.402**			
Caucasian				
N' / N''	80 / 79	88 / 84		
Baseline: mean (SD)	69.18 (17.62)	71.98 (18.05)		
Week 52: mean (SD)	68.83 (25.39)	68.87 (28.41)		
Week 12: adjusted mean change (SE)	1.62 (2.24)	0.30 (2.16)		
Week 24: adjusted mean change (SE)	1.36 (2.52)	-2.71 (2.43)		
Week 36: adjusted mean change (SE)	2.15 (2.86)	-0.47 (2.75)		
Week 52: adjusted mean change (SE)	-0.20 (2.96)	-2.66 (2.87)	2.46 [-5.22; 10.13] 0.529	0.099 [-0.210; 0.409]
Black				
N' / N''	21 / 21	22 / 21		
Baseline: mean (SD)	70.16 (18.38)	73.19 (19.70)		
Week 52: mean (SD)	74.54 (18.37)	56.06 (34.41)		
Week 12: adjusted mean change (SE)	2.88 (4.11)	-5.93 (3.95)		
Week 24: adjusted mean change (SE)	1.03 (4.61)	-2.06 (4.44)		
Week 36: adjusted mean change (SE)	-3.50 (5.32)	-14.54 (5.16)		
Week 52: adjusted mean change (SE)	3.70 (5.64)	-13.48 (5.39)	17.17 [1.92; 32.43] 0.027 *	0.694 [0.062; 1.326]

	Treatment Groups		Comparison	
PedsQL parent reported total score not considering cutoff by race (FAS)	**LCZ696 (N=182)**	**Enalapril (N=184)**	**Mean Difference [95% CI] p-value**	**Hedges G [95% CI]**
Asian				
N' / N"	54 / 52	43 / 41		
Baseline: mean (SD)	70.05 (18.23)	70.55 (19.66)		
Week 52: mean (SD)	71.09 (30.32)	72.79 (27.51)		
Week 12: adjusted mean change (SE)	1.42 (3.27)	4.60 (3.45)		
Week 24: adjusted mean change (SE)	-0.35 (3.55)	0.76 (3.81)		
Week 36: adjusted mean change (SE)	-2.12 (3.94)	-1.25 (4.22)		
Week 52: adjusted mean change (SE)	0.61 (4.05)	2.38 (4.35)	-1.77 [-11.86; 8.32] 0.730	-0.072 [-0.481; 0.337]
Unknown or other				
N' / N"	18 / 18	21 / 21		
Baseline: mean (SD)	77.35 (16.76)	74.24 (19.93)		
Week 52: mean (SD)	78.02 (24.44)	74.16 (31.25)		
Week 12: adjusted mean change (SE)	3.98 (4.55)	3.97 (4.05)		
Week 24: adjusted mean change (SE)	4.12 (5.08)	2.52 (4.66)		
Week 36: adjusted mean change (SE)	1.68 (5.84)	4.47 (5.46)		
Week 52: adjusted mean change (SE)	2.29 (6.00)	2.20 (5.67)	0.10 [-15.89; 16.08] 0.990	0.004 [-0.633; 0.641]

N: Number of patients
N': Number of patients in the analysis
N": Number of patients with non-missing value (not imputed)
CI: Confidence interval
SD: Standard deviation
SE: Standard error
MMRM: Mixed model for repeated measures
*: $p < 0.05$
.....

Imputation method: Missing values after the first category-1-event (investigator reported or positively adjudicated) were set to the worst value.

Analysis method:
Interaction test, adjusted mean change and mean difference obtained from MMRM with unstructured covariance matrix: change from baseline = treatment + visit + treatment * visit + race + treatment * race + race * visit + treatment * race * visit + baseline value + baseline value * visit + age group + NYHA/Ross class + region

The PedsQL is on scale 0 to 100, higher scores indicate better health-related quality of life.
Not considering cutoff date: Nominal
week 52 assessments that were performed later than 58 weeks after baseline were included in the analysis.

22 PedsQL patient reported clinically relevant response in the age group 5 to < 18 years, considering cutoff date for the last visit

Table 22.1 PedsQL patient reported clinically relevant response in the age group 5 to < 18 years considering cutoff (FAS), binary analysis

	Treatment Groups		Comparison		
PedsQL patient reported clinically relevant response in the age group 5 to < 18 years considering cutoff (FAS)	**LCZ696 (N=114)**	**Enalapril (N=116)**	**OR [95% CI] p-value**	**RR [95% CI] p-value**	**RD [95% CI] p-value**
PedsQL patient reported 15 points response					
Week 52					
N' / N"	114 / 82	116 / 81			
n (%)	18 (15.8)	16 (13.8)	1.79 [0.77; 4.20] 0.178	1.14 [0.61; 2.13] 0.670	0.02 [-0.07; 0.11] 0.670

N: Number of patients
N': Number of patients in the analysis
N": Number of patients with non-missing value (not imputed)
n (%): Number and percentage of patients with event
CI: Confidence interval
OR: Odds ratio
RR: Relative risk
RD: Risk difference
.....

Imputation method: Missing values after the first category-1-event (investigator reported or positively adjudicated) were set to the worst value. Other missing values were replaced by non-response imputation (NRI).

Analysis method:
OR with Wald CI and p-value obtained from logistic regression model: logit(proportion) = treatment + baseline score + NYHA/Ross class
RR and RD with Wald CI and p-value calculated directly

The PedsQL for the patient was applied in children from 5 years to < 18 years. The analysis is based on this age group.
Subgroup analysis by age is not performed as there are less than 10 patients < 6 years with non-missing PedsQL patient score.
Clinically relevant response on the PedsQL scale is defined by an improvement by more than 15 points.
Considering cutoff date: Nominal week
52 assessments that were performed later than 58 weeks after baseline were excluded from the analysis.

Table 22.2 PedsQL patient reported clinically relevant response in the age group 5 to < 18 years considering cutoff by NYHA/Ross class (FAS), binary analysis

	Treatment Groups		Comparison		
PedsQL patient reported clinically relevant response in the age group 5 to < 18 years considering cutoff by NYHA/Ross class (FAS)	**LCZ696 (N=114)**	**Enalapril (N=116)**	**OR [95% CI] p-value**	**RR [95% CI] p-value**	**RD [95% CI] p-value**
Class I/II, N	98	99			
Class III/IV, N	16	17			
PedsQL patient reported 15 points response					
Week 52					
Interaction test	**p = 0.421**				
Class I/II					
N' / N''	98 / 72	99 / 68			
n (%)	14 (14.3)	13 (13.1)	1.53 [0.60; 3.88] 0.375	1.09 [0.54; 2.19] 0.814	0.01 [-0.08; 0.11] 0.814
Class III/IV					
N' / N''	16 / 10	17 / 13			
n (%)	4 (25.0)	3 (17.6)	3.59 [0.54; 23.98] 0.187	1.42 [0.37; 5.37] 0.608	0.07 [-0.21; 0.35] 0.606

N: Number of patients
N': Number of patients in the analysis
N'': Number of patients with non-missing value (not imputed)
n (%): Number and percentage of patients with event
CI: Confidence interval
OR: Odds ratio
RR: Relative risk
RD: Risk difference
.....

Imputation method: Missing values after the first category-1-event (investigator reported or positively adjudicated) were set to the worst value. Other missing values were replaced by non-response imputation (NRI).

Analysis method:
Interaction test and OR with Wald CI and p-value obtained from logistic regression model: logit(proportion) = treatment + NYHA/Ross class + treatment * NYHA/Ross class + baseline score
RR and RD with Wald CI and p-value calculated directly

The PedsQL for the patient was applied in children from 5 years to < 18 years. The analysis is based on this age group.
Clinically relevant response on the PedsQL scale is defined by an improvement by more than 15 points.
Considering cutoff date: Nominal week
52 assessments that were performed later than 58 weeks after baseline were excluded from the analysis.

Table 22.3 PedsQL patient reported clinically relevant response in the age group 5 to < 18 years considering cutoff by region (FAS), binary analysis

	Treatment Groups		Comparison		
PedsQL patient reported clinically relevant response in the age group 5 to < 18 years considering cutoff by region (FAS)	**LCZ696 (N=114)**	**Enalapril (N=116)**	**OR [95% CI] p-value**	**RR [95% CI] p-value**	**RD [95% CI] p-value**
America, N	43	46			
Europe, N	39	36			
Asia/Pacific and other, N	32	34			
PedsQL patient reported 15 points response					
Week 52					
Interaction test	**p = 0.434**				
America					
N' / N"	43 / 29	46 / 28			
n (%)	5 (11.6)	5 (10.9)	2.25 [0.51; 9.85] 0.282	1.07 [0.33; 3.44] 0.910	0.01 [-0.12; 0.14] 0.910
Europe					
N' / N"	39 / 30	36 / 29			
n (%)	5 (12.8)	6 (16.7)	0.81 [0.19; 3.51] 0.779	0.77 [0.26; 2.30] 0.639	-0.04 [-0.20; 0.12] 0.639
Asia/Pacific and other					
N' / N"	32 / 23	34 / 24			
n (%)	8 (25.0)	5 (14.7)	3.01 [0.69; 13.19] 0.145	1.70 [0.62; 4.66] 0.302	0.10 [-0.09; 0.29] 0.292

N: Number of patients
N': Number of patients in the analysis
N": Number of patients with non-missing value (not imputed)
n (%): Number and percentage of patients with event
CI: Confidence interval
OR: Odds ratio
RR: Relative risk
RD: Risk difference
.....

Imputation method: Missing values after the first category-1-event (investigator reported or positively adjudicated) were set to the worst value. Other missing values were replaced by non-response imputation (NRI).

Analysis method:
Interaction test and OR with Wald CI and p-value obtained from logistic regression model: logit(proportion) = treatment + region + treatment * region + baseline score + NYHA/Ross class
RR and RD with Wald CI and p-value calculated directly

The PedsQL for the patient was applied in children from 5 years to < 18 years. The analysis is based on this age group.
Clinically relevant response on the PedsQL scale is defined by an improvement by more than 15 points.
Considering cutoff date: Nominal week
52 assessments that were performed later than 58 weeks after baseline were excluded from the analysis.

Table 22.4 PedsQL patient reported clinically relevant response in the age group 5 to < 18 years considering cutoff by gender (FAS), binary analysis

	Treatment Groups		Comparison		
PedsQL patient reported clinically relevant response in the age group 5 to < 18 years considering cutoff by gender (FAS)	**LCZ696 (N=114)**	**Enalapril (N=116)**	**OR [95% CI] p-value**	**RR [95% CI] p-value**	**RD [95% CI] p-value**
Male, N	59	56			
Female, N	55	60			
PedsQL patient reported 15 points response					
Week 52					
Interaction test	**p = 0.027 ***				
Male					
N' / N''	59 / 43	56 / 37			
n (%)	9 (15.3)	4 (7.1)	5.92 [1.42; 24.71] 0.015 *	2.14 [0.70; 6.54] 0.184	0.08 [-0.03; 0.19] 0.163
Female					
N' / N''	55 / 39	60 / 44			
n (%)	9 (16.4)	12 (20.0)	0.78 [0.25; 2.36] 0.654	0.82 [0.37; 1.79] 0.615	-0.04 [-0.18; 0.10] 0.613

N: Number of patients
N': Number of patients in the analysis
N'': Number of patients with non-missing value (not imputed)
n (%): Number and percentage of patients with event
CI: Confidence interval
OR: Odds ratio
RR: Relative risk
RD: Risk difference
*: $p < 0.05$
.....

Imputation method: Missing values after the first category-1-event (investigator reported or positively adjudicated) were set to the worst value. Other missing values were replaced by non-response imputation (NRI).

Analysis method:
Interaction test and OR with Wald CI and p-value obtained from logistic regression model: logit(proportion) = treatment + gender + treatment * gender + baseline score + NYHA/Ross class
RR and RD with Wald CI and p-value calculated directly

The PedsQL for the patient was applied in children from 5 years to < 18 years. The analysis is based on this age group.
Clinically relevant response on the PedsQL scale is defined by an improvement by more than 15 points.
Considering cutoff date: Nominal week
52 assessments that were performed later than 58 weeks after baseline were excluded from the analysis.

Table 22.5 PedsQL patient reported clinically relevant response in the age group 5 to < 18 years considering cutoff by COVID-19 period (FAS), binary analysis

	Treatment Groups		Comparison		
PedsQL patient reported clinically relevant response in the age group 5 to < 18 years considering cutoff by COVID-19 period (FAS)	**LCZ696 (N=114)**	**Enalapril (N=116)**	**OR [95% CI] p-value**	**RR [95% CI] p-value**	**RD [95% CI] p-value**
Pre-pandemic, N	59	60			
Pre- and during-pandemic, N	33	33			
During-pandemic, N	22	23			
PedsQL patient reported 15 points response					
Week 52					
Interaction test	**p = 0.317**				
Pre-pandemic					
N' / N''	59 / 40	60 / 34			
n (%)	9 (15.3)	7 (11.7)	3.54 [0.98; 12.85] 0.054	1.31 [0.52; 3.28] 0.568	0.04 [-0.09; 0.16] 0.566
Pre- and during-pandemic					
N' / N''	33 / 22	33 / 27			
n (%)	5 (15.2)	6 (18.2)	0.80 [0.17; 3.64] 0.768	0.83 [0.28; 2.46] 0.742	-0.03 [-0.21; 0.15] 0.741
During-pandemic					
N' / N''	22 / 20	23 / 20			
n (%)	4 (18.2)	3 (13.0)	1.27 [0.21; 7.59] 0.796	1.39 [0.35; 5.53] 0.637	0.05 [-0.16; 0.26] 0.635

N: Number of patients
N': Number of patients in the analysis
N'': Number of patients with non-missing value (not imputed)
n (%): Number and percentage of patients with event
CI: Confidence interval
OR: Odds ratio
RR: Relative risk
RD: Risk difference
.....

Imputation method: Missing values after the first category-1-event (investigator reported or positively adjudicated) were set to the worst value. Other missing values were replaced by non-response imputation (NRI).

Analysis method:
Interaction test and OR with Wald CI and p-value obtained from logistic regression model: logit(proportion) = treatment + COVID-19 period + treatment * COVID-19 period + baseline score + NYHA/Ross class
RR and RD with Wald CI and p-value calculated directly

The PedsQL for the patient was applied in children from 5 years to < 18 years. The analysis is based on this age group.
Clinically relevant response on the PedsQL scale is defined by an improvement by more than 15 points.
Considering cutoff date: Nominal week
52 assessments that were performed later than 58 weeks after baseline were excluded from the analysis.

Table 22.6 PedsQL patient reported clinically relevant response in the age group 5 to < 18 years considering cutoff by race (FAS), binary analysis

	Treatment Groups		Comparison		
PedsQL patient reported clinically relevant response in the age group 5 to < 18 years considering cutoff by race (FAS)	**LCZ696 (N=114)**	**Enalapril (N=116)**	**OR [95% CI] p-value**	**RR [95% CI] p-value**	**RD [95% CI] p-value**
Caucasian, N	62	63			
Black, N	15	21			
Asian, N	26	23			
Unknown or other, N	11	9			
PedsQL patient reported 15 points response					
Week 52					
Interaction test	**N.E.**				
Caucasian					
N' / N''	62 / 47	63 / 46			
n (%)	8 (12.9)	9 (14.3)	1.11 [0.34; 3.59] 0.864	0.90 [0.37; 2.19] 0.822	-0.01 [-0.13; 0.11] 0.822
Black					
N' / N''	15 / 11	21 / 13			
n (%)	4 (26.7)	2 (9.5)	20.75 [0.84; 513.81] 0.064	2.80 [0.59; 13.36] 0.197	0.17 [-0.09; 0.43] 0.190
Asian					
N' / N''	26 / 18	23 / 17			
n (%)	6 (23.1)	3 (13.0)	2.39 [0.46; 12.40] 0.298	1.77 [0.50; 6.28] 0.378	0.10 [-0.11; 0.31] 0.355
Unknown or other					
N' / N''	11 / 6	9 / 5			
n (%)	0 (0.0)	2 (22.2)	N.E.	0.17 [<0.01; 3.08] 0.229	-0.22 [-0.49; 0.05] 0.109

	Treatment Groups		Comparison		
PedsQL patient reported clinically relevant response in the age group 5 to < 18 years considering cutoff by race (FAS)	**LCZ696 (N=114)**	**Enalapril (N=116)**	**OR [95% CI] p-value**	**RR [95% CI] p-value**	**RD [95% CI] p-value**

N: Number of patients
N': Number of patients in the analysis
N'': Number of patients with non-missing value (not imputed)
n (%): Number and percentage of patients with event
CI: Confidence interval
OR: Odds ratio
RR: Relative risk
RD: Risk difference
N.E.: Not estimable
.....

Imputation method: Missing values after the first category-1-event (investigator reported or positively adjudicated) were set to the worst value. Other missing values were replaced by non-response imputation (NRI).

Analysis method:
Interaction test and OR with Wald CI and p-value obtained from logistic regression model: logit(proportion) = treatment + race + treatment * race + baseline score + NYHA/Ross class
RR and RD with Wald CI and p-value calculated directly

Exceptionally applied model(s) due to non-convergence:
PedsQL patient reported 15 points response, Week 52: logit(proportion) = treatment + baseline score + NYHA/Ross class, by race

The PedsQL for the patient was applied in children from 5 years to < 18 years. The analysis is based on this age group.
Clinically relevant response on the PedsQL scale is defined by an improvement by more than 15 points.
Considering cutoff date: Nominal week
52 assessments that were performed later than 58 weeks after baseline were excluded from the analysis.

23 PedsQL patient reported clinically relevant response in the age group 5 to < 18 years, not considering cutoff date for the last visit

Table 23.1 PedsQL patient reported clinically relevant response in the age group 5 to < 18 years not considering cutoff (FAS), binary analysis

	Treatment Groups		Comparison		
PedsQL patient reported clinically relevant response in the age group 5 to < 18 years not considering cutoff (FAS)	**LCZ696 (N=114)**	**Enalapril (N=116)**	**OR [95% CI] p-value**	**RR [95% CI] p-value**	**RD [95% CI] p-value**
PedsQL patient reported 15 points response					
Week 52					
N' / N"	114 / 90	116 / 90			
n (%)	21 (18.4)	19 (16.4)	1.67 [0.76; 3.67] 0.201	1.12 [0.64; 1.98] 0.683	0.02 [-0.08; 0.12] 0.683

N: Number of patients
N': Number of patients in the analysis
N": Number of patients with non-missing value (not imputed)
n (%): Number and percentage of patients with event
CI: Confidence interval
OR: Odds ratio
RR: Relative risk
RD: Risk difference
.....

Imputation method: Missing values after the first category-1-event (investigator reported or positively adjudicated) were set to the worst value. Other missing values were replaced by non-response imputation (NRI).

Analysis method:
OR with Wald CI and p-value obtained from logistic regression model: logit(proportion) = treatment + baseline score + NYHA/Ross class
RR and RD with Wald CI and p-value calculated directly

The PedsQL for the patient was applied in children from 5 years to < 18 years. The analysis is based on this age group.
Subgroup analysis by age is not performed as there are less than 10 patients < 6 years with non-missing PedsQL patient score.
Clinically relevant response on the PedsQL scale is defined by an improvement by more than 15 points.
Not considering cutoff date: Nominal
week 52 assessments that were performed later than 58 weeks after baseline were included in the analysis.

Table 23.2 PedsQL patient reported clinically relevant response in the age group 5 to < 18 years not considering cutoff by NYHA/Ross class (FAS), binary analysis

	Treatment Groups		Comparison		
PedsQL patient reported clinically relevant response in the age group 5 to < 18 years not considering cutoff by NYHA/Ross class (FAS)	**LCZ696 (N=114)**	**Enalapril (N=116)**	**OR [95% CI] p-value**	**RR [95% CI] p-value**	**RD [95% CI] p-value**
Class I/II, N	98	99			
Class III/IV, N	16	17			
PedsQL patient reported 15 points response					
Week 52					
Interaction test	**p = 0.402**				
Class I/II					
N' / N''	98 / 80	99 / 76			
n (%)	17 (17.3)	16 (16.2)	1.45 [0.62; 3.40] 0.398	1.07 [0.58; 2.00] 0.824	0.01 [-0.09; 0.12] 0.824
Class III/IV					
N' / N''	16 / 10	17 / 14			
n (%)	4 (25.0)	3 (17.6)	3.46 [0.53; 22.73] 0.196	1.42 [0.37; 5.37] 0.608	0.07 [-0.21; 0.35] 0.606

N: Number of patients
N': Number of patients in the analysis
N'': Number of patients with non-missing value (not imputed)
n (%): Number and percentage of patients with event
CI: Confidence interval
OR: Odds ratio
RR: Relative risk
RD: Risk difference
.....

Imputation method: Missing values after the first category-1-event (investigator reported or positively adjudicated) were set to the worst value. Other missing values were replaced by non-response imputation (NRI).

Analysis method:
Interaction test and OR with Wald CI and p-value obtained from logistic regression model: logit(proportion) = treatment + NYHA/Ross class + treatment * NYHA/Ross class + baseline score
RR and RD with Wald CI and p-value calculated directly

The PedsQL for the patient was applied in children from 5 years to < 18 years. The analysis is based on this age group.
Clinically relevant response on the PedsQL scale is defined by an improvement by more than 15 points.
Not considering cutoff date: Nominal
week 52 assessments that were performed later than 58 weeks after baseline were included in the analysis.

Table 23.3 PedsQL patient reported clinically relevant response in the age group 5 to < 18 years not considering cutoff by region (FAS), binary analysis

	Treatment Groups		Comparison		
PedsQL patient reported clinically relevant response in the age group 5 to < 18 years not considering cutoff by region (FAS)	**LCZ696 (N=114)**	**Enalapril (N=116)**	**OR [95% CI] p-value**	**RR [95% CI] p-value**	**RD [95% CI] p-value**
America, N	43	46			
Europe, N	39	36			
Asia/Pacific and other, N	32	34			
PedsQL patient reported 15 points response					
Week 52					
Interaction test	**p = 0.377**				
America					
N' / N"	43 / 34	46 / 34			
n (%)	7 (16.3)	8 (17.4)	1.67 [0.48; 5.85] 0.420	0.94 [0.37; 2.36] 0.889	-0.01 [-0.17; 0.14] 0.888
Europe					
N' / N"	39 / 32	36 / 30			
n (%)	5 (12.8)	6 (16.7)	0.80 [0.19; 3.37] 0.757	0.77 [0.26; 2.30] 0.639	-0.04 [-0.20; 0.12] 0.639
Asia/Pacific and other					
N' / N"	32 / 24	34 / 26			
n (%)	9 (28.1)	5 (14.7)	3.37 [0.81; 14.05] 0.095	1.91 [0.72; 5.10] 0.195	0.13 [-0.06; 0.33] 0.180

N: Number of patients
N': Number of patients in the analysis
N": Number of patients with non-missing value (not imputed)
n (%): Number and percentage of patients with event
CI: Confidence interval
OR: Odds ratio
RR: Relative risk
RD: Risk difference
.....

Imputation method: Missing values after the first category-1-event (investigator reported or positively adjudicated) were set to the worst value. Other missing values were replaced by non-response imputation (NRI).

Analysis method:
Interaction test and OR with Wald CI and p-value obtained from logistic regression model: logit(proportion) = treatment + region + treatment * region + baseline score + NYHA/Ross class
RR and RD with Wald CI and p-value calculated directly

The PedsQL for the patient was applied in children from 5 years to < 18 years. The analysis is based on this age group.
Clinically relevant response on the PedsQL scale is defined by an improvement by more than 15 points.
Not considering cutoff date: Nominal
week 52 assessments that were performed later than 58 weeks after baseline were included in the analysis.

Table 23.4 PedsQL patient reported clinically relevant response in the age group 5 to < 18 years not considering cutoff by gender (FAS), binary analysis

	Treatment Groups		Comparison		
PedsQL patient reported clinically relevant response in the age group 5 to < 18 years not considering cutoff by gender (FAS)	**LCZ696 (N=114)**	**Enalapril (N=116)**	**OR [95% CI] p-value**	**RR [95% CI] p-value**	**RD [95% CI] p-value**
Male, N	59	56			
Female, N	55	60			
PedsQL patient reported 15 points response					
Week 52					
Interaction test	**p = 0.170**				
Male					
N' / N''	59 / 46	56 / 44			
n (%)	9 (15.3)	6 (10.7)	3.17 [0.91; 11.11] 0.071	1.42 [0.54; 3.74] 0.474	0.05 [-0.08; 0.17] 0.467
Female					
N' / N''	55 / 44	60 / 46			
n (%)	12 (21.8)	13 (21.7)	1.03 [0.37; 2.86] 0.953	1.01 [0.50; 2.02] 0.984	0.00 [-0.15; 0.15] 0.984

N: Number of patients
N': Number of patients in the analysis
N'': Number of patients with non-missing value (not imputed)
n (%): Number and percentage of patients with event
CI: Confidence interval
OR: Odds ratio
RR: Relative risk
RD: Risk difference
.....

Imputation method: Missing values after the first category-1-event (investigator reported or positively adjudicated) were set to the worst value. Other missing values were replaced by non-response imputation (NRI).

Analysis method:
Interaction test and OR with Wald CI and p-value obtained from logistic regression model: logit(proportion) = treatment + gender + treatment * gender + baseline score + NYHA/Ross class
RR and RD with Wald CI and p-value calculated directly

The PedsQL for the patient was applied in children from 5 years to < 18 years. The analysis is based on this age group.
Clinically relevant response on the PedsQL scale is defined by an improvement by more than 15 points.
Not considering cutoff date: Nominal
week 52 assessments that were performed later than 58 weeks after baseline were included in the analysis.

Table 23.5 PedsQL patient reported clinically relevant response in the age group 5 to < 18 years not considering cutoff by COVID-19 period (FAS), binary analysis

	Treatment Groups		Comparison		
PedsQL patient reported clinically relevant response in the age group 5 to < 18 years not considering cutoff by COVID-19 period (FAS)	**LCZ696 (N=114)**	**Enalapril (N=116)**	**OR [95% CI] p-value**	**RR [95% CI] p-value**	**RD [95% CI] p-value**
Pre-pandemic, N	59	60			
Pre- and during-pandemic, N	33	33			
During-pandemic, N	22	23			
PedsQL patient reported 15 points response					
Week 52					
Interaction test	**p = 0.573**				
Pre-pandemic					
N' / N''	59 / 44	60 / 40			
n (%)	10 (16.9)	9 (15.0)	2.55 [0.80; 8.13] 0.113	1.13 [0.49; 2.58] 0.772	0.02 [-0.11; 0.15] 0.772
Pre- and during-pandemic					
N' / N''	33 / 26	33 / 30			
n (%)	7 (21.2)	7 (21.2)	1.02 [0.26; 3.99] 0.982	1.00 [0.39; 2.53] 1.000	0.00 [-0.20; 0.20] 1.000
During-pandemic					
N' / N''	22 / 20	23 / 20			
n (%)	4 (18.2)	3 (13.0)	1.27 [0.22; 7.39] 0.791	1.39 [0.35; 5.53] 0.637	0.05 [-0.16; 0.26] 0.635

N: Number of patients
N': Number of patients in the analysis
N'': Number of patients with non-missing value (not imputed)
n (%): Number and percentage of patients with event
CI: Confidence interval
OR: Odds ratio
RR: Relative risk
RD: Risk difference
.....

Imputation method: Missing values after the first category-1-event (investigator reported or positively adjudicated) were set to the worst value. Other missing values were replaced by non-response imputation (NRI).

Analysis method:
Interaction test and OR with Wald CI and p-value obtained from logistic regression model: logit(proportion) = treatment + COVID-19 period + treatment * COVID-19 period + baseline score + NYHA/Ross class
RR and RD with Wald CI and p-value calculated directly

The PedsQL for the patient was applied in children from 5 years to < 18 years. The analysis is based on this age group.
Clinically relevant response on the PedsQL scale is defined by an improvement by more than 15 points.
Not considering cutoff date: Nominal
week 52 assessments that were performed later than 58 weeks after baseline were included in the analysis.

Table 23.6 PedsQL patient reported clinically relevant response in the age group 5 to < 18 years not considering cutoff by race (FAS), binary analysis

	Treatment Groups		Comparison		
PedsQL patient reported clinically relevant response in the age group 5 to < 18 years not considering cutoff by race (FAS)	**LCZ696 (N=114)**	**Enalapril (N=116)**	**OR [95% CI] p-value**	**RR [95% CI] p-value**	**RD [95% CI] p-value**
Caucasian, N	62	63			
Black, N	15	21			
Asian, N	26	23			
Unknown or other, N	11	9			
PedsQL patient reported 15 points response					
Week 52					
Interaction test	**p = 0.408**				
Caucasian					
N' / N''	62 / 50	63 / 51			
n (%)	8 (12.9)	10 (15.9)	0.93 [0.30; 2.92] 0.903	0.81 [0.34; 1.92] 0.637	-0.03 [-0.15; 0.09] 0.636
Black					
N' / N''	15 / 13	21 / 15			
n (%)	5 (33.3)	4 (19.0)	4.24 [0.70; 25.87] 0.117	1.75 [0.56; 5.45] 0.334	0.14 [-0.15; 0.43] 0.337
Asian					
N' / N''	26 / 19	23 / 19			
n (%)	7 (26.9)	3 (13.0)	3.43 [0.66; 17.90] 0.144	2.06 [0.60; 7.07] 0.248	0.14 [-0.08; 0.36] 0.214
Unknown or other					
N' / N''	11 / 8	9 / 5			
n (%)	1 (9.1)	2 (22.2)	1.06 [0.07; 16.85] 0.967	0.41 [0.04; 3.82] 0.433	-0.13 [-0.45; 0.19] 0.422

	Treatment Groups		Comparison		
PedsQL patient reported clinically relevant response in the age group 5 to < 18 years not considering cutoff by race (FAS)	**LCZ696 (N=114)**	**Enalapril (N=116)**	**OR [95% CI] p-value**	**RR [95% CI] p-value**	**RD [95% CI] p-value**

N: Number of patients
N': Number of patients in the analysis
N'': Number of patients with non-missing value (not imputed)
n (%): Number and percentage of patients with event
CI: Confidence interval
OR: Odds ratio
RR: Relative risk
RD: Risk difference
.....

Imputation method: Missing values after the first category-1-event (investigator reported or positively adjudicated) were set to the worst value. Other missing values were replaced by non-response imputation (NRI).

Analysis method:
Interaction test and OR with Wald CI and p-value obtained from logistic regression model: logit(proportion) = treatment + race + treatment * race + baseline score + NYHA/Ross class
RR and RD with Wald CI and p-value calculated directly

The PedsQL for the patient was applied in children from 5 years to < 18 years. The analysis is based on this age group.
Clinically relevant response on the PedsQL scale is defined by an improvement by more than 15 points.
Not considering cutoff date: Nominal
week 52 assessments that were performed later than 58 weeks after baseline were included in the analysis.

24 PedsQL parent reported clinically relevant response, considering cutoff date for the last visit

Table 24.1 PedsQL parent reported clinically relevant response considering cutoff (FAS), binary analysis

	Treatment Groups		Comparison		
PedsQL parent reported clinically relevant response considering cutoff (FAS)	**LCZ696 (N=182)**	**Enalapril (N=184)**	**OR [95% CI] p-value**	**RR [95% CI] p-value**	**RD [95% CI] p-value**
PedsQL parent reported 15 points response					
Week 52					
N' / N"	182 / 132	184 / 133			
n (%)	35 (19.2)	28 (15.2)	1.31 [0.73; 2.32] 0.364	1.26 [0.80; 1.99] 0.311	0.04 [-0.04; 0.12] 0.309

N: Number of patients
N': Number of patients in the analysis
N": Number of patients with non-missing value (not imputed)
n (%): Number and percentage of patients with event
CI: Confidence interval
OR: Odds ratio
RR: Relative risk
RD: Risk difference
.....

Imputation method: Missing values after the first category-1-event (investigator reported or positively adjudicated) were set to the worst value. Other missing values were replaced by non-response imputation (NRI).

Analysis method:
OR with Wald CI and p-value obtained from logistic regression model: logit(proportion) = treatment + baseline score + age group + NYHA/Ross class
RR and RD with Wald CI and p-value calculated directly

Clinically relevant response on the PedsQL scale is defined by an improvement by more than 15 points.
Considering cutoff date:
Nominal week 52 assessments that were performed later than 58 weeks after baseline were excluded from the analysis.

Table 24.2 PedsQL parent reported clinically relevant response considering cutoff by age group (FAS), binary analysis

	Treatment Groups		Comparison		
PedsQL parent reported clinically relevant response considering cutoff by age group (FAS)	**LCZ696 (N=182)**	**Enalapril (N=184)**	**OR [95% CI] p-value**	**RR [95% CI] p-value**	**RD [95% CI] p-value**
6 years to < 18 years, N	109	111			
1 year to < 6 years, N	73	73			
PedsQL parent reported 15 points response					
Week 52					
Interaction test	**p = 0.925**				
6 years to < 18 years					
N' / N''	109 / 79	111 / 77			
n (%)	23 (21.1)	19 (17.1)	1.33 [0.65; 2.71] 0.430	1.23 [0.71; 2.13] 0.454	0.04 [-0.06; 0.14] 0.452
1 year to < 6 years					
N' / N''	73 / 53	73 / 56			
n (%)	12 (16.4)	9 (12.3)	1.26 [0.47; 3.35] 0.648	1.33 [0.60; 2.97] 0.482	0.04 [-0.07; 0.15] 0.478

N: Number of patients
N': Number of patients in the analysis
N'': Number of patients with non-missing value (not imputed)
n (%): Number and percentage of patients with event
CI: Confidence interval
OR: Odds ratio
RR: Relative risk
RD: Risk difference
.....

Imputation method: Missing values after the first category-1-event (investigator reported or positively adjudicated) were set to the worst value. Other missing values were replaced by non-response imputation (NRI).

Analysis method:
Interaction test and OR with Wald CI and p-value obtained from logistic regression model: logit(proportion) = treatment + age group + treatment * age group + baseline score + NYHA/Ross class
RR and RD with Wald CI and p-value calculated directly

Clinically relevant response on the PedsQL scale is defined by an improvement by more than 15 points.
Considering cutoff date:
Nominal week 52 assessments that were performed later than 58 weeks after baseline were excluded from the analysis.

Table 24.3 PedsQL parent reported clinically relevant response considering cutoff by NYHA/Ross class (FAS), binary analysis

	Treatment Groups		Comparison		
PedsQL parent reported clinically relevant response considering cutoff by NYHA/Ross class (FAS)	**LCZ696 (N=182)**	**Enalapril (N=184)**	**OR [95% CI] p-value**	**RR [95% CI] p-value**	**RD [95% CI] p-value**
Class I/II, N	157	157			
Class III/IV, N	25	27			
PedsQL parent reported 15 points response					
Week 52					
Interaction test	**p = 0.910**				
Class I/II					
N' / N"	157 / 116	157 / 114			
n (%)	29 (18.5)	22 (14.0)	1.29 [0.68; 2.42] 0.437	1.32 [0.79; 2.19] 0.287	0.04 [-0.04; 0.13] 0.283
Class III/IV					
N' / N"	25 / 16	27 / 19			
n (%)	6 (24.0)	6 (22.2)	1.40 [0.35; 5.57] 0.630	1.08 [0.40; 2.91] 0.879	0.02 [-0.21; 0.25] 0.879

N: Number of patients
N': Number of patients in the analysis
N": Number of patients with non-missing value (not imputed)
n (%): Number and percentage of patients with event
CI: Confidence interval
OR: Odds ratio
RR: Relative risk
RD: Risk difference
.....

Imputation method: Missing values after the first category-1-event (investigator reported or positively adjudicated) were set to the worst value. Other missing values were replaced by non-response imputation (NRI).

Analysis method:
Interaction test and OR with Wald CI and p-value obtained from logistic regression model: logit(proportion) = treatment + NYHA/Ross class + treatment * NYHA/Ross class + baseline score + age group
RR and RD with Wald CI and p-value calculated directly

Clinically relevant response on the PedsQL scale is defined by an improvement by more than 15 points.
Considering cutoff date:
Nominal week 52 assessments that were performed later than 58 weeks after baseline were excluded from the analysis.

Table 24.4 PedsQL parent reported clinically relevant response considering cutoff by region (FAS), binary analysis

	Treatment Groups		Comparison		
PedsQL parent reported clinically relevant response considering cutoff by region (FAS)	**LCZ696 (N=182)**	**Enalapril (N=184)**	**OR [95% CI] p-value**	**RR [95% CI] p-value**	**RD [95% CI] p-value**
America, N	58	69			
Europe, N	58	55			
Asia/Pacific and other, N	66	60			
PedsQL parent reported 15 points response					
Week 52					
Interaction test	**p = 0.365**				
America					
N' / N''	58 / 40	69 / 43			
n (%)	10 (17.2)	9 (13.0)	1.28 [0.46; 3.55] 0.638	1.32 [0.58; 3.03] 0.510	0.04 [-0.08; 0.17] 0.512
Europe					
N' / N''	58 / 44	55 / 46			
n (%)	11 (19.0)	5 (9.1)	2.47 [0.77; 7.91] 0.129	2.09 [0.77; 5.62] 0.146	0.10 [-0.03; 0.23] 0.125
Asia/Pacific and other					
N' / N''	66 / 48	60 / 44			
n (%)	14 (21.2)	14 (23.3)	0.85 [0.34; 2.11] 0.719	0.91 [0.47; 1.75] 0.775	-0.02 [-0.17; 0.12] 0.775

N: Number of patients
N': Number of patients in the analysis
N'': Number of patients with non-missing value (not imputed)
n (%): Number and percentage of patients with event
CI: Confidence interval
OR: Odds ratio
RR: Relative risk
RD: Risk difference
.....

Imputation method: Missing values after the first category-1-event (investigator reported or positively adjudicated) were set to the worst value. Other missing values were replaced by non-response imputation (NRI).

Analysis method:
Interaction test and OR with Wald CI and p-value obtained from logistic regression model: logit(proportion) = treatment + region + treatment * region + baseline score + age group + NYHA/Ross class
RR and RD with Wald CI and p-value calculated directly

Clinically relevant response on the PedsQL scale is defined by an improvement by more than 15 points.
Considering cutoff date:
Nominal week 52 assessments that were performed later than 58 weeks after baseline were excluded from the analysis.

Table 24.5 PedsQL parent reported clinically relevant response considering cutoff by gender (FAS), binary analysis

	Treatment Groups		Comparison		
PedsQL parent reported clinically relevant response considering cutoff by gender (FAS)	**LCZ696 (N=182)**	**Enalapril (N=184)**	**OR [95% CI] p-value**	**RR [95% CI] p-value**	**RD [95% CI] p-value**
Male, N	88	91			
Female, N	94	93			
PedsQL parent reported 15 points response					
Week 52					
Interaction test	**p = 0.027 ***				
Male					
N' / N''	88 / 65	91 / 65			
n (%)	18 (20.5)	7 (7.7)	2.97 [1.14; 7.75] 0.026 *	2.66 [1.17; 6.05] 0.020 *	0.13 [0.03; 0.23] 0.013 *
Female					
N' / N''	94 / 67	93 / 68			
n (%)	17 (18.1)	21 (22.6)	0.75 [0.35; 1.60] 0.453	0.80 [0.45; 1.42] 0.447	-0.04 [-0.16; 0.07] 0.444

N: Number of patients
N': Number of patients in the analysis
N'': Number of patients with non-missing value (not imputed)
n (%): Number and percentage of patients with event
CI: Confidence interval
OR: Odds ratio
RR: Relative risk
RD: Risk difference
*: $p < 0.05$
.....

Imputation method: Missing values after the first category-1-event (investigator reported or positively adjudicated) were set to the worst value. Other missing values were replaced by non-response imputation (NRI).

Analysis method:
Interaction test and OR with Wald CI and p-value obtained from logistic regression model: logit(proportion) = treatment + gender + treatment * gender + baseline score + age group + NYHA/Ross class
RR and RD with Wald CI and p-value calculated directly

Clinically relevant response on the PedsQL scale is defined by an improvement by more than 15 points.
Considering cutoff date:
Nominal week 52 assessments that were performed later than 58 weeks after baseline were excluded from the analysis.

Table 24.6 PedsQL parent reported clinically relevant response considering cutoff by COVID-19 period (FAS), binary analysis

	Treatment Groups		Comparison		
PedsQL parent reported clinically relevant response considering cutoff by COVID-19 period (FAS)	**LCZ696 (N=182)**	**Enalapril (N=184)**	**OR [95% CI] p-value**	**RR [95% CI] p-value**	**RD [95% CI] p-value**
Pre-pandemic, N	79	83			
Pre- and during-pandemic, N	62	59			
During-pandemic, N	41	42			
PedsQL parent reported 15 points response					
Week 52					
Interaction test	**p = 0.588**				
Pre-pandemic					
N' / N''	79 / 55	83 / 50			
n (%)	9 (11.4)	10 (12.0)	1.06 [0.39; 2.91] 0.903	0.95 [0.41; 2.20] 0.897	-0.01 [-0.11; 0.09] 0.897
Pre- and during-pandemic					
N' / N''	62 / 41	59 / 44			
n (%)	13 (21.0)	11 (18.6)	1.04 [0.39; 2.72] 0.942	1.12 [0.55; 2.31] 0.749	0.02 [-0.12; 0.17] 0.748
During-pandemic					
N' / N''	41 / 36	42 / 39			
n (%)	13 (31.7)	7 (16.7)	2.07 [0.70; 6.16] 0.191	1.90 [0.84; 4.28] 0.121	0.15 [-0.03; 0.33] 0.105

N: Number of patients
N': Number of patients in the analysis
N'': Number of patients with non-missing value (not imputed)
n (%): Number and percentage of patients with event
CI: Confidence interval
OR: Odds ratio
RR: Relative risk
RD: Risk difference
.....

Imputation method: Missing values after the first category-1-event (investigator reported or positively adjudicated) were set to the worst value. Other missing values were replaced by non-response imputation (NRI).

Analysis method:
Interaction test and OR with Wald CI and p-value obtained from logistic regression model: logit(proportion) = treatment + COVID-19 period + treatment * COVID-19 period + baseline score + age group + NYHA/Ross class
RR and RD with Wald CI and p-value calculated directly

Clinically relevant response on the PedsQL scale is defined by an improvement by more than 15 points.
Considering cutoff date:
Nominal week 52 assessments that were performed later than 58 weeks after baseline were excluded from the analysis.

Table 24.7 PedsQL parent reported clinically relevant response considering cutoff by race (FAS), binary analysis

	Treatment Groups		Comparison		
PedsQL parent reported clinically relevant response considering cutoff by race (FAS)	**LCZ696 (N=182)**	**Enalapril (N=184)**	**OR [95% CI] p-value**	**RR [95% CI] p-value**	**RD [95% CI] p-value**
Caucasian, N	86	90			
Black, N	23	25			
Asian, N	55	45			
Unknown or other, N	18	24			
PedsQL parent reported 15 points response					
Week 52					
Interaction test	**p = 0.541**				
Caucasian					
N' / N"	86 / 64	90 / 69			
n (%)	16 (18.6)	9 (10.0)	2.00 [0.80; 5.00] 0.140	1.86 [0.87; 3.98] 0.110	0.09 [-0.02; 0.19] 0.102
Black					
N' / N"	23 / 16	25 / 14			
n (%)	4 (17.4)	5 (20.0)	0.74 [0.16; 3.43] 0.702	0.87 [0.27; 2.85] 0.817	-0.03 [-0.25; 0.19] 0.817
Asian					
N' / N"	55 / 39	45 / 34			
n (%)	12 (21.8)	11 (24.4)	0.85 [0.31; 2.32] 0.751	0.89 [0.44; 1.83] 0.756	-0.03 [-0.19; 0.14] 0.757
Unknown or other					
N' / N"	18 / 13	24 / 16			
n (%)	3 (16.7)	3 (12.5)	1.79 [0.29; 11.09] 0.531	1.33 [0.30; 5.85] 0.703	0.04 [-0.18; 0.26] 0.707

	Treatment Groups		Comparison		
PedsQL parent reported clinically relevant response considering cutoff by race (FAS)	**LCZ696 (N=182)**	**Enalapril (N=184)**	**OR [95% CI] p-value**	**RR [95% CI] p-value**	**RD [95% CI] p-value**

N: Number of patients
N': Number of patients in the analysis
N'': Number of patients with non-missing value (not imputed)
n (%): Number and percentage of patients with event
CI: Confidence interval
OR: Odds ratio
RR: Relative risk
RD: Risk difference
.....

Imputation method: Missing values after the first category-1-event (investigator reported or positively adjudicated) were set to the worst value. Other missing values were replaced by non-response imputation (NRI).

Analysis method:
Interaction test and OR with Wald CI and p-value obtained from logistic regression model: logit(proportion) = treatment + race + treatment * race + baseline score + age group + NYHA/Ross class
RR and RD with Wald CI and p-value calculated directly

Clinically relevant response on the PedsQL scale is defined by an improvement by more than 15 points.
Considering cutoff date:
Nominal week 52 assessments that were performed later than 58 weeks after baseline were excluded from the analysis.

25 PedsQL parent reported clinically relevant response, not considering cutoff date for the last visit

Table 25.1 PedsQL parent reported clinically relevant response not considering cutoff (FAS), binary analysis

	Treatment Groups		Comparison		
PedsQL parent reported clinically relevant response not considering cutoff (FAS)	**LCZ696 (N=182)**	**Enalapril (N=184)**	**OR [95% CI] p-value**	**RR [95% CI] p-value**	**RD [95% CI] p-value**
PedsQL parent reported 15 points response					
Week 52					
N' / N"	182 / 152	184 / 147			
n (%)	42 (23.1)	33 (17.9)	1.36 [0.78; 2.38] 0.276	1.29 [0.86; 1.93] 0.225	0.05 [-0.03; 0.13] 0.222

N: Number of patients
N': Number of patients in the analysis
N": Number of patients with non-missing value (not imputed)
n (%): Number and percentage of patients with event
CI: Confidence interval
OR: Odds ratio
RR: Relative risk
RD: Risk difference
.....

Imputation method: Missing values after the first category-1-event (investigator reported or positively adjudicated) were set to the worst value. Other missing values were replaced by non-response imputation (NRI).

Analysis method:
OR with Wald CI and p-value obtained from logistic regression model: logit(proportion) = treatment + baseline score + age group + NYHA/Ross class
RR and RD with Wald CI and p-value calculated directly

Clinically relevant response on the PedsQL scale is defined by an improvement by more than 15 points.
Not considering cutoff date:
Nominal week 52 assessments that were performed later than 58 weeks after baseline were included in the analysis.

Table 25.2 PedsQL parent reported clinically relevant response not considering cutoff by age group (FAS), binary analysis

	Treatment Groups		Comparison		
PedsQL parent reported clinically relevant response not considering cutoff by age group (FAS)	**LCZ696 (N=182)**	**Enalapril (N=184)**	**OR [95% CI] p-value**	**RR [95% CI] p-value**	**RD [95% CI] p-value**
6 years to < 18 years, N	109	111			
1 year to < 6 years, N	73	73			
PedsQL parent reported 15 points response					
Week 52					
Interaction test	**p = 0.918**				
6 years to < 18 years					
N' / N"	109 / 88	111 / 84			
n (%)	26 (23.9)	22 (19.8)	1.33 [0.66; 2.68] 0.419	1.20 [0.73; 1.99] 0.470	0.04 [-0.07; 0.15] 0.469
1 year to < 6 years					
N' / N"	73 / 64	73 / 63			
n (%)	16 (21.9)	11 (15.1)	1.42 [0.56; 3.57] 0.460	1.45 [0.73; 2.92] 0.291	0.07 [-0.06; 0.19] 0.285

N: Number of patients
N': Number of patients in the analysis
N": Number of patients with non-missing value (not imputed)
n (%): Number and percentage of patients with event
CI: Confidence interval
OR: Odds ratio
RR: Relative risk
RD: Risk difference
.....

Imputation method: Missing values after the first category-1-event (investigator reported or positively adjudicated) were set to the worst value. Other missing values were replaced by non-response imputation (NRI).

Analysis method:
Interaction test and OR with Wald CI and p-value obtained from logistic regression model: logit(proportion) = treatment + age group + treatment * age group + baseline score + NYHA/Ross class
RR and RD with Wald CI and p-value calculated directly

Clinically relevant response on the PedsQL scale is defined by an improvement by more than 15 points.
Not considering cutoff date:
Nominal week 52 assessments that were performed later than 58 weeks after baseline were included in the analysis.

Table 25.3 PedsQL parent reported clinically relevant response not considering cutoff by NYHA/Ross class (FAS), binary analysis

	Treatment Groups		Comparison		
PedsQL parent reported clinically relevant response not considering cutoff by NYHA/Ross class (FAS)	**LCZ696 (N=182)**	**Enalapril (N=184)**	**OR [95% CI] p-value**	**RR [95% CI] p-value**	**RD [95% CI] p-value**
Class I/II, N	157	157			
Class III/IV, N	25	27			
PedsQL parent reported 15 points response					
Week 52					
Interaction test	**p = 0.869**				
Class I/II					
N' / N"	157 / 135	157 / 127			
n (%)	35 (22.3)	26 (16.6)	1.33 [0.73; 2.45] 0.354	1.35 [0.85; 2.13] 0.202	0.06 [-0.03; 0.14] 0.198
Class III/IV					
N' / N"	25 / 17	27 / 20			
n (%)	7 (28.0)	7 (25.9)	1.51 [0.39; 5.88] 0.551	1.08 [0.44; 2.64] 0.866	0.02 [-0.22; 0.26] 0.866

N: Number of patients
N': Number of patients in the analysis
N": Number of patients with non-missing value (not imputed)
n (%): Number and percentage of patients with event
CI: Confidence interval
OR: Odds ratio
RR: Relative risk
RD: Risk difference
.....

Imputation method: Missing values after the first category-1-event (investigator reported or positively adjudicated) were set to the worst value. Other missing values were replaced by non-response imputation (NRI).

Analysis method:
Interaction test and OR with Wald CI and p-value obtained from logistic regression model: logit(proportion) = treatment + NYHA/Ross class + treatment * NYHA/Ross class + baseline score + age group
RR and RD with Wald CI and p-value calculated directly

Clinically relevant response on the PedsQL scale is defined by an improvement by more than 15 points.
Not considering cutoff date:
Nominal week 52 assessments that were performed later than 58 weeks after baseline were included in the analysis.

Table 25.4 PedsQL parent reported clinically relevant response not considering cutoff by region (FAS), binary analysis

	Treatment Groups		Comparison		
PedsQL parent reported clinically relevant response not considering cutoff by region (FAS)	**LCZ696 (N=182)**	**Enalapril (N=184)**	**OR [95% CI] p-value**	**RR [95% CI] p-value**	**RD [95% CI] p-value**
America, N	58	69			
Europe, N	58	55			
Asia/Pacific and other, N	66	60			
PedsQL parent reported 15 points response					
Week 52					
Interaction test	**p = 0.444**				
America					
N' / N''	58 / 50	69 / 51			
n (%)	14 (24.1)	13 (18.8)	1.28 [0.51; 3.23] 0.594	1.28 [0.66; 2.50] 0.468	0.05 [-0.09; 0.20] 0.470
Europe					
N' / N''	58 / 48	55 / 47			
n (%)	11 (19.0)	5 (9.1)	2.55 [0.78; 8.31] 0.120	2.09 [0.77; 5.62] 0.146	0.10 [-0.03; 0.23] 0.125
Asia/Pacific and other					
N' / N''	66 / 54	60 / 49			
n (%)	17 (25.8)	15 (25.0)	0.97 [0.39; 2.42] 0.956	1.03 [0.57; 1.88] 0.922	0.01 [-0.14; 0.16] 0.922

N: Number of patients
N': Number of patients in the analysis
N'': Number of patients with non-missing value (not imputed)
n (%): Number and percentage of patients with event
CI: Confidence interval
OR: Odds ratio
RR: Relative risk
RD: Risk difference
.....

Imputation method: Missing values after the first category-1-event (investigator reported or positively adjudicated) were set to the worst value. Other missing values were replaced by non-response imputation (NRI).

Analysis method:
Interaction test and OR with Wald CI and p-value obtained from logistic regression model: logit(proportion) = treatment + region + treatment * region + baseline score + age group + NYHA/Ross class
RR and RD with Wald CI and p-value calculated directly

Clinically relevant response on the PedsQL scale is defined by an improvement by more than 15 points.
Not considering cutoff date:
Nominal week 52 assessments that were performed later than 58 weeks after baseline were included in the analysis.

Table 25.5 PedsQL parent reported clinically relevant response not considering cutoff by gender (FAS), binary analysis

	Treatment Groups		Comparison		
PedsQL parent reported clinically relevant response not considering cutoff by gender (FAS)	**LCZ696 (N=182)**	**Enalapril (N=184)**	**OR [95% CI] p-value**	**RR [95% CI] p-value**	**RD [95% CI] p-value**
Male, N	88	91			
Female, N	94	93			
PedsQL parent reported 15 points response					
Week 52					
Interaction test	**p = 0.141**				
Male					
N' / N''	88 / 71	91 / 73			
n (%)	21 (23.9)	11 (12.1)	2.18 [0.93; 5.11] 0.071	1.97 [1.01; 3.85] 0.046 *	0.12 [0.01; 0.23] 0.038 *
Female					
N' / N''	94 / 81	93 / 74			
n (%)	21 (22.3)	22 (23.7)	0.93 [0.44; 1.98] 0.857	0.94 [0.56; 1.60] 0.831	-0.01 [-0.13; 0.11] 0.831

N: Number of patients
N': Number of patients in the analysis
N'': Number of patients with non-missing value (not imputed)
n (%): Number and percentage of patients with event
CI: Confidence interval
OR: Odds ratio
RR: Relative risk
RD: Risk difference
*: $p < 0.05$
.....

Imputation method: Missing values after the first category-1-event (investigator reported or positively adjudicated) were set to the worst value. Other missing values were replaced by non-response imputation (NRI).

Analysis method:
Interaction test and OR with Wald CI and p-value obtained from logistic regression model: logit(proportion) = treatment + gender + treatment * gender + baseline score + age group + NYHA/Ross class
RR and RD with Wald CI and p-value calculated directly

Clinically relevant response on the PedsQL scale is defined by an improvement by more than 15 points.
Not considering cutoff date:
Nominal week 52 assessments that were performed later than 58 weeks after baseline were included in the analysis.

Table 25.6 PedsQL parent reported clinically relevant response not considering cutoff by COVID-19 period (FAS), binary analysis

	Treatment Groups		Comparison		
PedsQL parent reported clinically relevant response not considering cutoff by COVID-19 period (FAS)	**LCZ696 (N=182)**	**Enalapril (N=184)**	**OR [95% CI] p-value**	**RR [95% CI] p-value**	**RD [95% CI] p-value**
Pre-pandemic, N	79	83			
Pre- and during-pandemic, N	62	59			
During-pandemic, N	41	42			
PedsQL parent reported 15 points response					
Week 52					
Interaction test	**p = 0.527**				
Pre-pandemic					
N' / N''	79 / 60	83 / 56			
n (%)	10 (12.7)	13 (15.7)	0.89 [0.34; 2.32] 0.819	0.81 [0.38; 1.74] 0.585	-0.03 [-0.14; 0.08] 0.583
Pre- and during-pandemic					
N' / N''	62 / 55	59 / 52			
n (%)	19 (30.6)	13 (22.0)	1.49 [0.60; 3.71] 0.389	1.39 [0.76; 2.56] 0.288	0.09 [-0.07; 0.24] 0.279
During-pandemic					
N' / N''	41 / 37	42 / 39			
n (%)	13 (31.7)	7 (16.7)	2.03 [0.67; 6.15] 0.210	1.90 [0.84; 4.28] 0.121	0.15 [-0.03; 0.33] 0.105

N: Number of patients
N': Number of patients in the analysis
N'': Number of patients with non-missing value (not imputed)
n (%): Number and percentage of patients with event
CI: Confidence interval
OR: Odds ratio
RR: Relative risk
RD: Risk difference
.....

Imputation method: Missing values after the first category-1-event (investigator reported or positively adjudicated) were set to the worst value. Other missing values were replaced by non-response imputation (NRI).

Analysis method:
Interaction test and OR with Wald CI and p-value obtained from logistic regression model: logit(proportion) = treatment + COVID-19 period + treatment * COVID-19 period + baseline score + age group + NYHA/Ross class
RR and RD with Wald CI and p-value calculated directly

Clinically relevant response on the PedsQL scale is defined by an improvement by more than 15 points.
Not considering cutoff date:
Nominal week 52 assessments that were performed later than 58 weeks after baseline were included in the analysis.

Table 25.7 PedsQL parent reported clinically relevant response not considering cutoff by race (FAS), binary analysis

	Treatment Groups		Comparison		
PedsQL parent reported clinically relevant response not considering cutoff by race (FAS)	**LCZ696 (N=182)**	**Enalapril (N=184)**	**OR [95% CI] p-value**	**RR [95% CI] p-value**	**RD [95% CI] p-value**
Caucasian, N	86	90			
Black, N	23	25			
Asian, N	55	45			
Unknown or other, N	18	24			
PedsQL parent reported 15 points response					
Week 52					
Interaction test	**p = 0.372**				
Caucasian					
N' / N"	86 / 72	90 / 73			
n (%)	18 (20.9)	11 (12.2)	1.88 [0.78; 4.53] 0.161	1.71 [0.86; 3.41] 0.126	0.09 [-0.02; 0.20] 0.119
Black					
N' / N"	23 / 18	25 / 17			
n (%)	5 (21.7)	7 (28.0)	0.56 [0.13; 2.38] 0.434	0.78 [0.29; 2.11] 0.619	-0.06 [-0.31; 0.18] 0.615
Asian					
N' / N"	55 / 45	45 / 39			
n (%)	15 (27.3)	12 (26.7)	1.00 [0.37; 2.70] 1.000	1.02 [0.53; 1.96] 0.946	0.01 [-0.17; 0.18] 0.946
Unknown or other					
N' / N"	18 / 17	24 / 18			
n (%)	4 (22.2)	3 (12.5)	3.14 [0.53; 18.73] 0.209	1.78 [0.45; 6.97] 0.409	0.10 [-0.14; 0.33] 0.414

	Treatment Groups		Comparison		
PedsQL parent reported clinically relevant response not considering cutoff by race (FAS)	**LCZ696 (N=182)**	**Enalapril (N=184)**	**OR [95% CI] p-value**	**RR [95% CI] p-value**	**RD [95% CI] p-value**

N: Number of patients
N': Number of patients in the analysis
N'': Number of patients with non-missing value (not imputed)
n (%): Number and percentage of patients with event
CI: Confidence interval
OR: Odds ratio
RR: Relative risk
RD: Risk difference
.....

Imputation method: Missing values after the first category-1-event (investigator reported or positively adjudicated) were set to the worst value. Other missing values were replaced by non-response imputation (NRI).

Analysis method:
Interaction test and OR with Wald CI and p-value obtained from logistic regression model: logit(proportion) = treatment + race + treatment * race + baseline score + age group + NYHA/Ross class
RR and RD with Wald CI and p-value calculated directly

Clinically relevant response on the PedsQL scale is defined by an improvement by more than 15 points.
Not considering cutoff date:
Nominal week 52 assessments that were performed later than 58 weeks after baseline were included in the analysis.

26 Global rank endpoint, considering cutoff date for the last visit

26.0 Global rank endpoint considering cutoff, frequency of strata

Stratum Age | NYHA/Ross Class	LCZ696 (N=182) n (%)	Enalapril (N=184) n (%)	Total (N=366)
6 to < 18 years | class I/II	93 (51.1)	94 (51.1)	187 (51.1)
6 to < 18 years | class III/IV	16 (8.8)	17 (9.2)	33 (9.0)
1 to < 6 years | class I/II	64 (35.2)	63 (34.2)	127 (34.7)
1 to < 6 years | class III/IV	9 (4.9)	10 (5.4)	19 (5.2)
Overall	182	184	366

N: Number of patients
.....

Percentages are based on the number of patients in the overall row.

26.1 Global rank endpoint considering cutoff, stratified Mann-Whitney analysis

Stratum Age | NYHA/Ross Class	% LCZ Wins	% ENA Wins	% LCZ equals ENA	Mann-Whitney Probability [95% CI]	Mann-Whitney Odds [95% CI]	P-value
6 to < 18 years | class I/II	54.7	44.7	0.6	0.550 [0.467; 0.630]	0.82 [0.59; 1.14]	0.244
6 to < 18 years | class III/IV	34.2	65.1	0.7	0.346 [0.185; 0.551]	1.89 [0.81; 4.41]	0.165
1 to < 6 years | class I/II	48.6	40.9	10.5	0.538 [0.438; 0.635]	0.86 [0.57; 1.28]	0.461
1 to < 6 years | class III/IV	46.7	45.6	7.8	0.506 [0.264; 0.744]	0.98 [0.34; 2.78]	0.967
Overall	50.3	45.2	4.4	0.525 [0.466; 0.584]	0.90 [0.71; 1.14]	0.408

N: Number of patients
CI: Confidence interval
PACE = positively adjudicated clinical events
LOCF = last observation carry forward
.....

Patients were classified into Category 1 or Category 2 based on PACE.

Imputation method:
Patients who discontinued from the study during the double-blind epoch without Category 1 event were classified into Category 1 with event date imputed by the last known alive date.
For patients in Category 3 to Category 5, the LOCF approach was used for missing data of NYHA/ROSS class, PGIS and PedsQL ranking items.

Analysis method: p-value from stratified Wilcoxon rank sum test. Mann-Whitney probability > 0.5 favours LCZ696, equivalently, Mann-Whitney odds < 1.

Considering cutoff date: Nominal week 52 assessments that were performed later than 58 weeks after baseline were excluded from the analysis.

27 Global rank endpoint, not considering cutoff date for the last visit

27.0 Global rank endpoint not considering cutoff, frequency of strata

Stratum Age | NYHA/Ross Class	LCZ696 (N=182) n (%)	Enalapril (N=184) n (%)	Total (N=366)
6 to < 18 years | class I/II	93 (51.1)	94 (51.1)	187 (51.1)
6 to < 18 years | class III/IV	16 (8.8)	17 (9.2)	33 (9.0)
1 to < 6 years | class I/II	64 (35.2)	63 (34.2)	127 (34.7)
1 to < 6 years | class III/IV	9 (4.9)	10 (5.4)	19 (5.2)
Overall	182	184	366

N: Number of patients
.....

Percentages are based on the number of patients in the overall row.

27.1 Global rank endpoint not considering cutoff, stratified Mann-Whitney analysis

Stratum Age | NYHA/Ross Class	% LCZ Wins	% ENA Wins	% LCZ equals ENA	Mann-Whitney Probability [95% CI]	Mann-Whitney Odds [95% CI]	P-value
6 to < 18 years | class I/II	54.1	45.2	0.7	0.545 [0.461; 0.625]	0.84 [0.60; 1.17]	0.296
6 to < 18 years | class III/IV	34.2	65.1	0.7	0.346 [0.185; 0.551]	1.89 [0.81; 4.41]	0.165
1 to < 6 years | class I/II	49.5	39.8	10.7	0.549 [0.448; 0.646]	0.82 [0.55; 1.23]	0.345
1 to < 6 years | class III/IV	46.7	45.6	7.8	0.506 [0.264; 0.744]	0.98 [0.34; 2.78]	0.967
Overall	50.4	45.1	4.5	0.527 [0.468; 0.585]	0.90 [0.71; 1.14]	0.388

N: Number of patients
CI: Confidence interval
PACE = positively adjudicated clinical events
LOCF = last observation carry forward
.....

Patients were classified into Category 1 or Category 2 based on PACE.

Imputation method:
Patients who discontinued from the study during the double-blind epoch without Category 1 event were classified into Category 1 with event date imputed by the last known alive date.
For patients in Category 3 to Category 5, the LOCF approach was used for missing data of NYHA/ROSS class, PGIS and PedsQL ranking items.

Analysis method: p-value from stratified Wilcoxon rank sum test. Mann-Whitney probability > 0.5 favours LCZ696, equivalently, Mann-Whitney odds < 1.

Not considering cutoff date: Nominal week 52 assessments that were performed later than 58 weeks after baseline were included in the analysis.

28 Selected adjudicated category 1 or 2 events

Table 28.1 Selected adjudicated category 1 or 2 events (FAS), time to event analysis

	Treatment Groups		Comparison	
Selected adjudicated category 1 or 2 events (FAS)	**LCZ696 (N=182)**	**Enalapril (N=184)**	**HR [95% CI] p-value**	**Logrank test p-value**
First selected adjudicated category 1 or 2 event				
N'	182	184		
Patients with event, n (%)	31 (17.0)	31 (16.8)		
Median time to event (in weeks) [95% CI]	N.E.	N.E.		
Patients with event at end of study, % KM estimate [95% CI]	17.1 [11.6; 22.6]	17.0 [11.6; 22.5]	1.01 [0.61; 1.66] 0.977	0.965

N: Number of patients
N': Number of patients in the analysis
CI: Confidence interval
HR: Hazard ratio
KM: Kaplan-Meier
N.E.: Not estimable
.....

Analysis method:
HR obtained from Cox proportional hazards model: log(hazard ratio) = treatment + age group + NYHA/Ross class

Selected adjudicated category 1 or 2 events are all cause death (adjudicated), UNOS status 1A listing for heart transplant or equivalent (adjudicated), VAD / ECMO / mechanical ventilation / intra-aortic balloon pump requirement for life support (adjudicated), HF hospitalization with intensive care unit stay, HF hospitalization without intensive care unit stay.

Table 28.2 Selected adjudicated category 1 or 2 events by age group (FAS), time to event analysis

	Treatment Groups		Comparison	
Selected adjudicated category 1 or 2 events by age group (FAS)	**LCZ696 (N=182)**	**Enalapril (N=184)**	**HR [95% CI] p-value**	**Logrank test p-value**
6 years to < 18 years, N	109	111		
1 year to < 6 years, N	73	73		
First selected adjudicated category 1 or 2 event				
Interaction test	**p = 0.730**			
6 years to < 18 years				
N'	109	111		
Patients with event, n (%)	23 (21.1)	24 (21.6)		
Median time to event (in weeks) [95% CI]	N.E.	N.E.		
Patients with event at end of study, % KM estimate [95% CI]	21.2 [13.5; 28.9]	22.0 [14.2; 29.8]	0.96 [0.54; 1.70] 0.885	0.815
1 year to < 6 years				
N'	73	73		
Patients with event, n (%)	8 (11.0)	7 (9.6)		
Median time to event (in weeks) [95% CI]	N.E.	N.E.		
Patients with event at end of study, % KM estimate [95% CI]	11.0 [3.8; 18.2]	9.6 [2.8; 16.3]	1.18 [0.43; 3.25] 0.753	0.769

N: Number of patients
N': Number of patients in the analysis
CI: Confidence interval
HR: Hazard ratio
KM: Kaplan-Meier
N.E.: Not estimable
.....

Analysis method:
Interaction test and HR obtained from Cox proportional hazards model: log(hazard ratio) = treatment + age group + treatment * age group + NYHA/Ross class

Selected adjudicated category 1 or 2 events are all cause death (adjudicated), UNOS status 1A listing for heart transplant or equivalent (adjudicated), VAD / ECMO / mechanical ventilation / intra-aortic balloon pump requirement for life support (adjudicated), HF hospitalization with intensive care unit stay, HF hospitalization without intensive care unit stay.

Table 28.3 Selected adjudicated category 1 or 2 events by NYHA/Ross class (FAS), time to event analysis

	Treatment Groups		Comparison	
Selected adjudicated category 1 or 2 events by NYHA/Ross class (FAS)	**LCZ696 (N=182)**	**Enalapril (N=184)**	**HR [95% CI] p-value**	**Logrank test p-value**
Class I/II, N	157	157		
Class III/IV, N	25	27		
First selected adjudicated category 1 or 2 event				
Interaction test	**p = 0.250**			
Class I/II				
N'	157	157		
Patients with event, n (%)	21 (13.4)	24 (15.3)		
Median time to event (in weeks) [95% CI]	N.E.	N.E.		
Patients with event at end of study, % KM estimate [95% CI]	13.5 [8.1; 18.8]	15.5 [9.8; 21.2]	0.84 [0.47; 1.51] 0.562	0.580
Class III/IV				
N'	25	27		
Patients with event, n (%)	10 (40.0)	7 (25.9)		
Median time to event (in weeks) [95% CI]	N.E.	N.E.		
Patients with event at end of study, % KM estimate [95% CI]	40.0 [20.8; 59.2]	25.9 [9.4; 42.5]	1.63 [0.62; 4.29] 0.321	0.323

N: Number of patients
N': Number of patients in the analysis
CI: Confidence interval
HR: Hazard ratio
KM: Kaplan-Meier
N.E.: Not estimable
.....

Analysis method:
Interaction test and HR obtained from Cox proportional hazards model: log(hazard ratio) = treatment + NYHA/Ross class + treatment * NYHA/Ross class + age group

Selected adjudicated category 1 or 2 events are all cause death (adjudicated), UNOS status 1A listing for heart transplant or equivalent (adjudicated), VAD / ECMO / mechanical ventilation / intra-aortic balloon pump requirement for life support (adjudicated), HF hospitalization with intensive care unit stay, HF hospitalization without intensive care unit stay.

Table 28.4 Selected adjudicated category 1 or 2 events by region (FAS), time to event analysis

	Treatment Groups		Comparison	
Selected adjudicated category 1 or 2 events by region (FAS)	**LCZ696 (N=182)**	**Enalapril (N=184)**	**HR [95% CI] p-value**	**Logrank test p-value**
America, N	58	69		
Europe, N	58	55		
Asia/Pacific and other, N	66	60		
First selected adjudicated category 1 or 2 event				
Interaction test	**p = 0.892**			
America				
N'	58	69		
Patients with event, n (%)	8 (13.8)	11 (15.9)		
Median time to event (in weeks) [95% CI]	N.E.	N.E.		
Patients with event at end of study, % KM estimate [95% CI]	13.9 [4.9; 22.8]	16.3 [7.5; 25.1]	0.83 [0.33; 2.07] 0.690	0.752
Europe				
N'	58	55		
Patients with event, n (%)	10 (17.2)	9 (16.4)		
Median time to event (in weeks) [95% CI]	N.E.	N.E.		
Patients with event at end of study, % KM estimate [95% CI]	17.2 [7.5; 27.0]	16.4 [6.6; 26.1]	1.04 [0.42; 2.55] 0.939	0.886
Asia/Pacific and other				
N'	66	60		
Patients with event, n (%)	13 (19.7)	11 (18.3)		
Median time to event (in weeks) [95% CI]	N.E.	N.E.		
Patients with event at end of study, % KM estimate [95% CI]	19.9 [10.2; 29.6]	18.6 [8.7; 28.5]	1.11 [0.50; 2.48] 0.801	0.999

	Treatment Groups		Comparison	
Selected adjudicated category 1 or 2 events by region (FAS)	**LCZ696 (N=182)**	**Enalapril (N=184)**	**HR [95% CI] p-value**	**Logrank test p-value**

N: Number of patients
N': Number of patients in the analysis
CI: Confidence interval
HR: Hazard ratio
KM: Kaplan-Meier
N.E.: Not estimable
.....

Analysis method:
Interaction test and HR obtained from Cox proportional hazards model: log(hazard ratio) = treatment + region + treatment * region + age group + NYHA/Ross class

Selected adjudicated category 1 or 2 events are all cause death (adjudicated), UNOS status 1A listing for heart transplant or equivalent (adjudicated), VAD / ECMO / mechanical ventilation / intra-aortic balloon pump requirement for life support (adjudicated), HF hospitalization with intensive care unit stay, HF hospitalization without intensive care unit stay.

Table 28.5 Selected adjudicated category 1 or 2 events by gender (FAS), time to event analysis

	Treatment Groups		Comparison	
Selected adjudicated category 1 or 2 events by gender (FAS)	**LCZ696 (N=182)**	**Enalapril (N=184)**	**HR [95% CI] p-value**	**Logrank test p-value**
Male, N	88	91		
Female, N	94	93		
First selected adjudicated category 1 or 2 event				
Interaction test	**p = 0.495**			
Male				
N'	88	91		
Patients with event, n (%)	17 (19.3)	14 (15.4)		
Median time to event (in weeks) [95% CI]	N.E.	N.E.		
Patients with event at end of study, % KM estimate [95% CI]	19.6 [11.2; 27.9]	15.7 [8.1; 23.2]	1.20 [0.59; 2.44] 0.616	0.556
Female				
N'	94	93		
Patients with event, n (%)	14 (14.9)	17 (18.3)		
Median time to event (in weeks) [95% CI]	N.E.	N.E.		
Patients with event at end of study, % KM estimate [95% CI]	14.9 [7.7; 22.1]	18.4 [10.5; 26.3]	0.85 [0.42; 1.72] 0.643	0.517

N: Number of patients
N': Number of patients in the analysis
CI: Confidence interval
HR: Hazard ratio
KM: Kaplan-Meier
N.E.: Not estimable
.....

Analysis method:
Interaction test and HR obtained from Cox proportional hazards model: log(hazard ratio) = treatment + gender + treatment * gender + age group + NYHA/Ross class

Selected adjudicated category 1 or 2 events are all cause death (adjudicated), UNOS status 1A listing for heart transplant or equivalent (adjudicated), VAD / ECMO / mechanical ventilation / intra-aortic balloon pump requirement for life support (adjudicated), HF hospitalization with intensive care unit stay, HF hospitalization without intensive care unit stay.

Table 28.6 Selected adjudicated category 1 or 2 events by COVID-19 period (FAS), time to event analysis

	Treatment Groups		Comparison	
Selected adjudicated category 1 or 2 events by COVID-19 period (FAS)	**LCZ696 (N=182)**	**Enalapril (N=184)**	**HR [95% CI] p-value**	**Logrank test p-value**
Pre-pandemic, N	79	83		
Pre- and during-pandemic, N	62	59		
During-pandemic, N	41	42		
First selected adjudicated category 1 or 2 event				
Interaction test	**p = 0.329**			
Pre-pandemic				
N'	79	83		
Patients with event, n (%)	17 (21.5)	18 (21.7)		
Median time to event (in weeks) [95% CI]	N.E.	N.E.		
Patients with event at end of study, % KM estimate [95% CI]	21.6 [12.5; 30.7]	22.3 [13.2; 31.4]	0.94 [0.48; 1.82] 0.854	0.925
Pre- and during-pandemic				
N'	62	59		
Patients with event, n (%)	7 (11.3)	9 (15.3)		
Median time to event (in weeks) [95% CI]	N.E.	N.E.		
Patients with event at end of study, % KM estimate [95% CI]	11.3 [3.4; 19.2]	15.3 [6.1; 24.4]	0.69 [0.26; 1.84] 0.453	0.461
During-pandemic				
N'	41	42		
Patients with event, n (%)	7 (17.1)	4 (9.5)		
Median time to event (in weeks) [95% CI]	N.E.	N.E.		
Patients with event at end of study, % KM estimate [95% CI]	17.1 [5.6; 28.6]	9.5 [0.6; 18.4]	2.23 [0.65; 7.65] 0.202	0.331

	Treatment Groups		Comparison	
Selected adjudicated category 1 or 2 events by COVID-19 period (FAS)	**LCZ696 (N=182)**	**Enalapril (N=184)**	**HR [95% CI] p-value**	**Logrank test p-value**

N: Number of patients
N': Number of patients in the analysis
CI: Confidence interval
HR: Hazard ratio
KM: Kaplan-Meier
N.E.: Not estimable
.....

Analysis method:
Interaction test and HR obtained from Cox proportional hazards model: log(hazard ratio) = treatment + COVID-19 period + treatment * COVID-19 period + age group + NYHA/Ross class

Selected adjudicated category 1 or 2 events are all cause death (adjudicated), UNOS status 1A listing for heart transplant or equivalent (adjudicated), VAD / ECMO / mechanical ventilation / intra-aortic balloon pump requirement for life support (adjudicated), HF hospitalization with intensive care unit stay, HF hospitalization without intensive care unit stay.

Table 28.7 Selected adjudicated category 1 or 2 events by race (FAS), time to event analysis

	Treatment Groups		Comparison	
Selected adjudicated category 1 or 2 events by race (FAS)	**LCZ696 (N=182)**	**Enalapril (N=184)**	**HR [95% CI] p-value**	**Logrank test p-value**
Caucasian, N	86	90		
Black, N	23	25		
Asian, N	55	45		
Unknown or other, N	18	24		
First selected adjudicated category 1 or 2 event				
Interaction test	**p = 0.862**			
Caucasian				
N'	86	90		
Patients with event, n (%)	9 (10.5)	11 (12.2)		
Median time to event (in weeks) [95% CI]	N.E.	N.E.		
Patients with event at end of study, % KM estimate [95% CI]	10.5 [4.0; 17.0]	12.3 [5.5; 19.0]	0.82 [0.34; 1.98] 0.656	0.729
Black				
N'	23	25		
Patients with event, n (%)	9 (39.1)	10 (40.0)		
Median time to event (in weeks) [95% CI]	N.E.	N.E.		
Patients with event at end of study, % KM estimate [95% CI]	39.1 [19.2; 59.1]	41.1 [21.4; 60.7]	1.08 [0.44; 2.65] 0.873	0.993
Asian				
N'	55	45		
Patients with event, n (%)	11 (20.0)	7 (15.6)		
Median time to event (in weeks) [95% CI]	N.E.	N.E.		
Patients with event at end of study, % KM estimate [95% CI]	20.3 [9.6; 31.0]	15.9 [5.1; 26.7]	1.42 [0.55; 3.66] 0.474	0.718
Unknown or other				
N'	18	24		
Patients with event, n (%)	2 (11.1)	3 (12.5)		
Median time to event (in weeks) [95% CI]	N.E.	N.E.		
Patients with event at end of study, % KM estimate [95% CI]	11.1 [0.0; 25.6]	12.5 [0.0; 25.7]	0.84 [0.14; 5.06] 0.848	0.830

	Treatment Groups		Comparison	
Selected adjudicated category 1 or 2 events by race (FAS)	**LCZ696 (N=182)**	**Enalapril (N=184)**	**HR [95% CI] p-value**	**Logrank test p-value**

N: Number of patients
N': Number of patients in the analysis
CI: Confidence interval
HR: Hazard ratio
KM: Kaplan-Meier
N.E.: Not estimable
.....

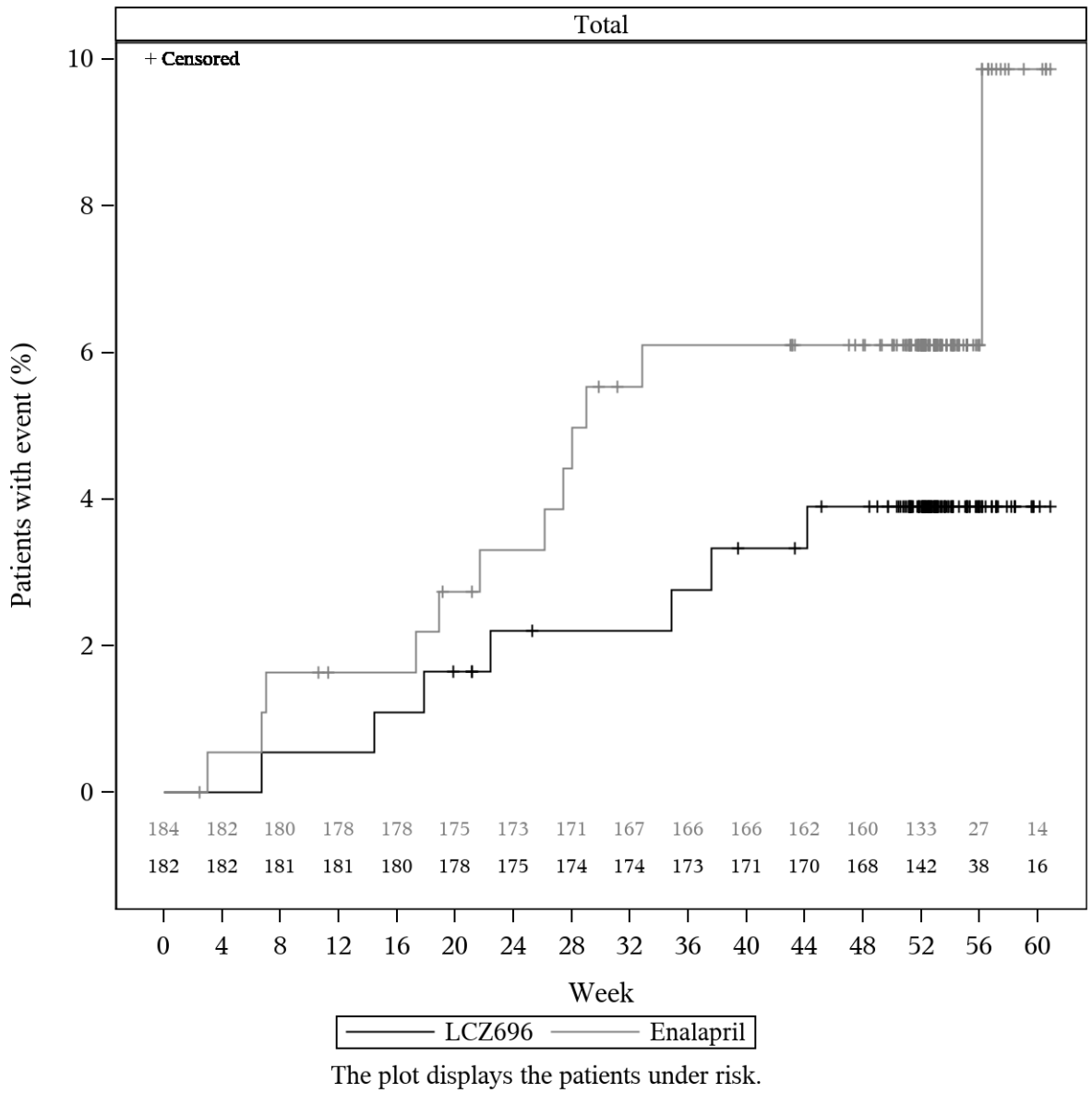
Analysis method:
Interaction test and HR obtained from Cox proportional hazards model: log(hazard ratio) = treatment + race + treatment * race + age group + NYHA/Ross class

Selected adjudicated category 1 or 2 events are all cause death (adjudicated), UNOS status 1A listing for heart transplant or equivalent (adjudicated), VAD / ECMO / mechanical ventilation / intra-aortic balloon pump requirement for life support (adjudicated), HF hospitalization with intensive care unit stay, HF hospitalization without intensive care unit stay.

Figures

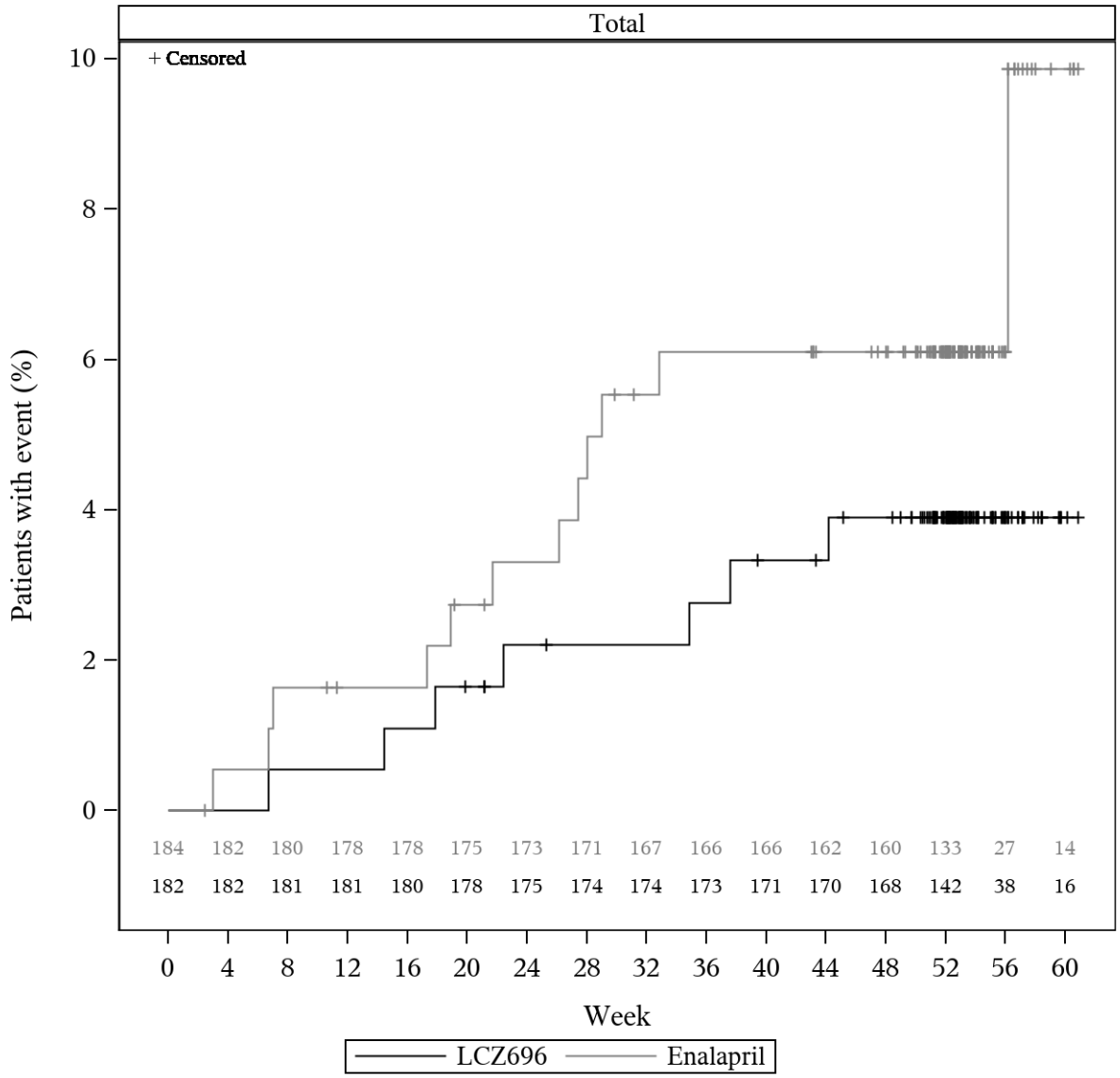
6 All cause death

Figure 6.1.1 All cause death (adjudicated) (FAS), Kaplan-Meier plot



The plot displays the patients under risk.

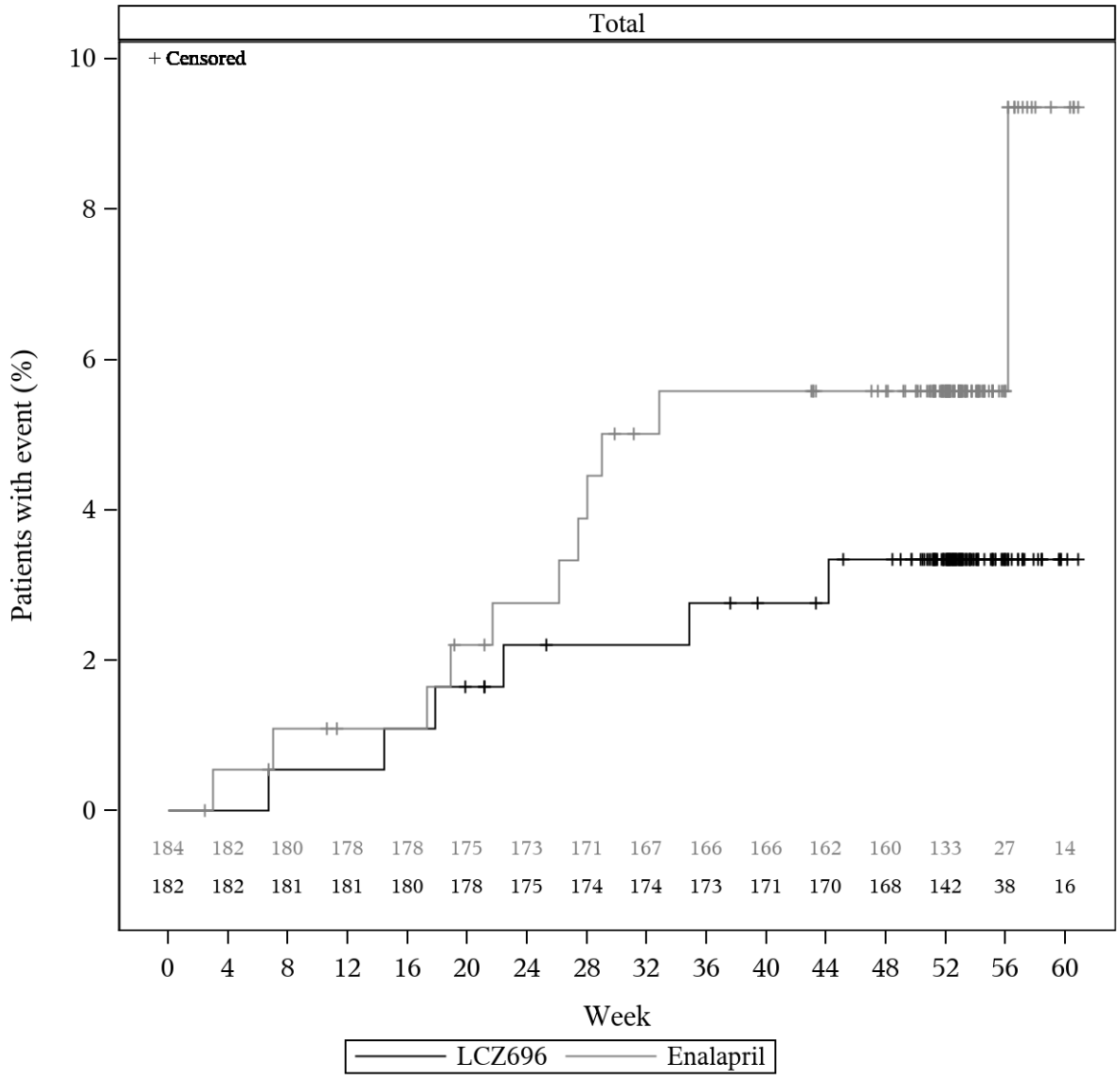
Figure 6.1.2 All cause death (investigator reported) (FAS), Kaplan-Meier plot



The plot displays the patients under risk.

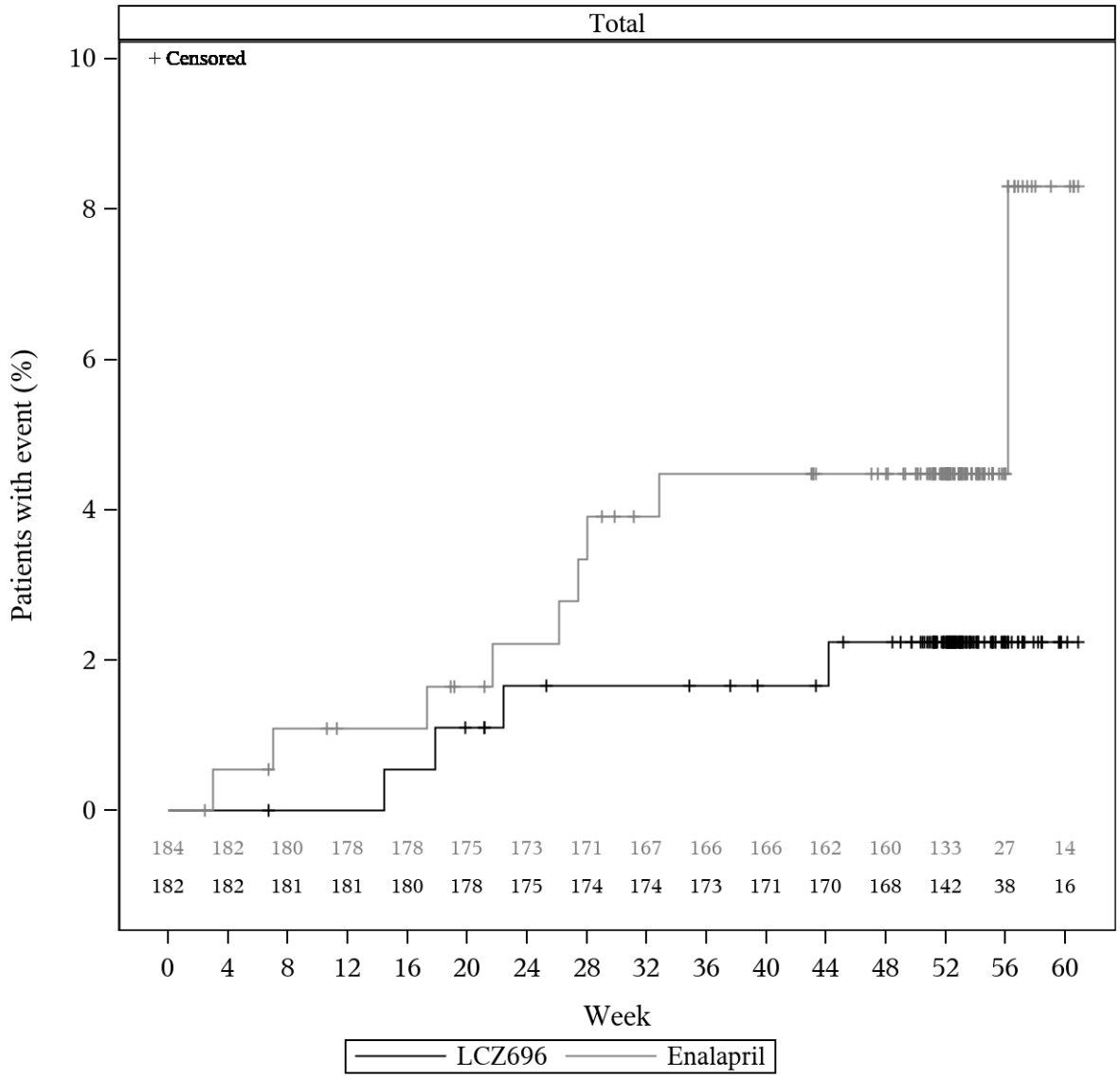
7 CV death

Figure 7.1.1 CV death (adjudicated) (FAS), Kaplan-Meier plot



The plot displays the patients under risk.

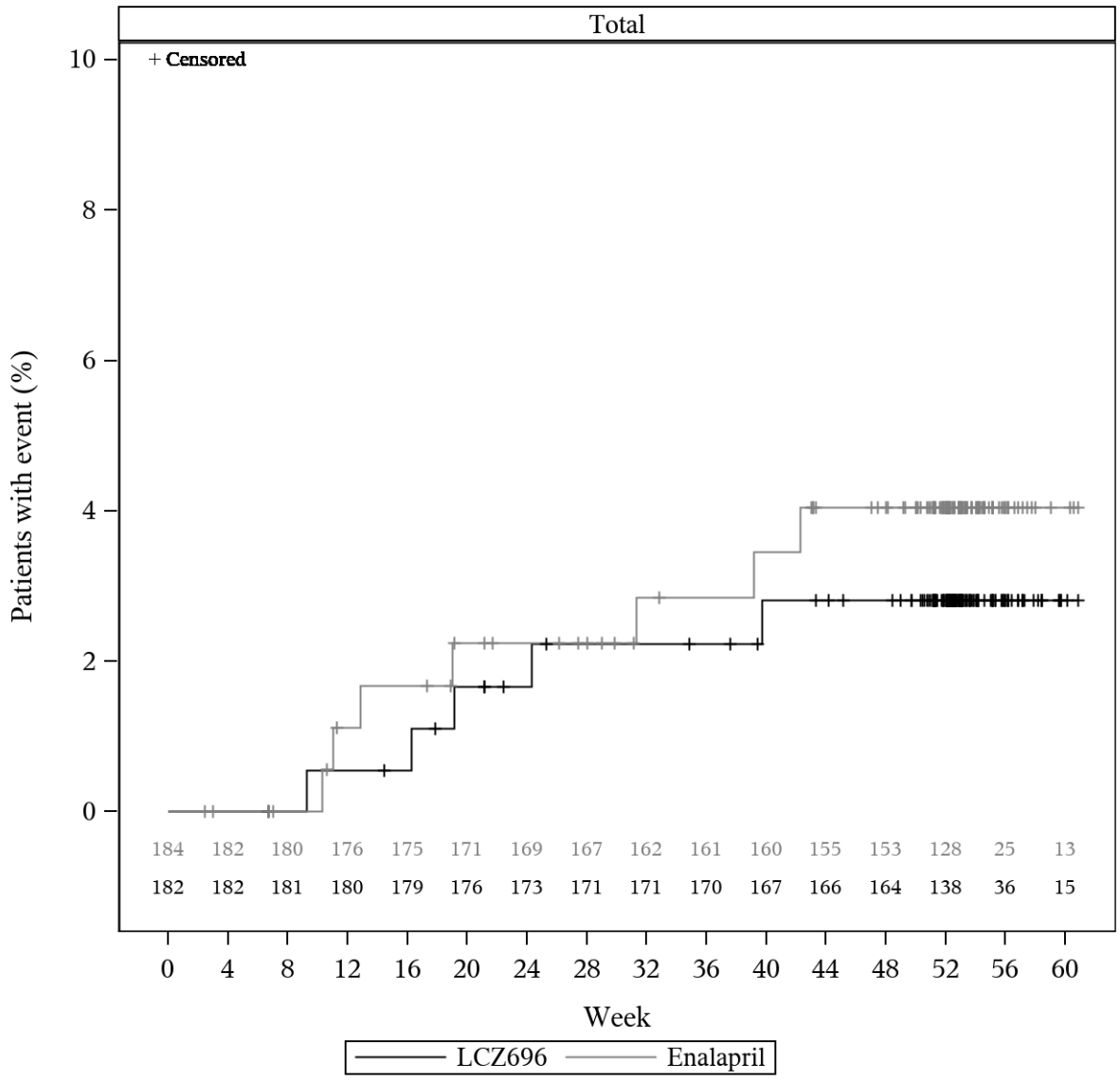
Figure 7.1.2 CV death (investigator reported) (FAS), Kaplan-Meier plot



The plot displays the patients under risk.

8 UNOS status 1A listing for heart transplant or equivalent (adjudicated)

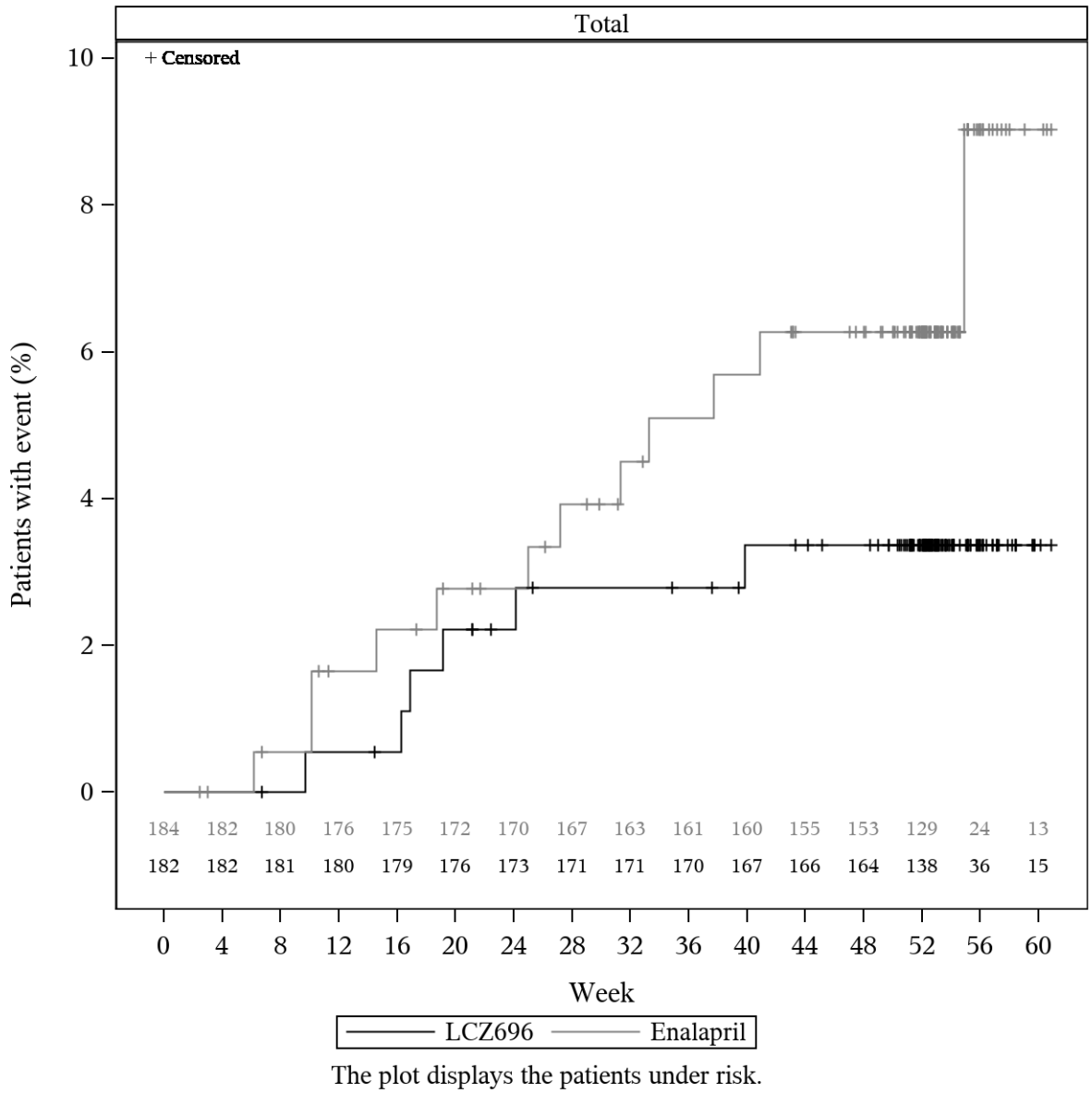
Figure 8.1 UNOS status 1A listing for heart transplant or equivalent (adjudicated) (FAS), Kaplan-Meier plot



The plot displays the patients under risk.

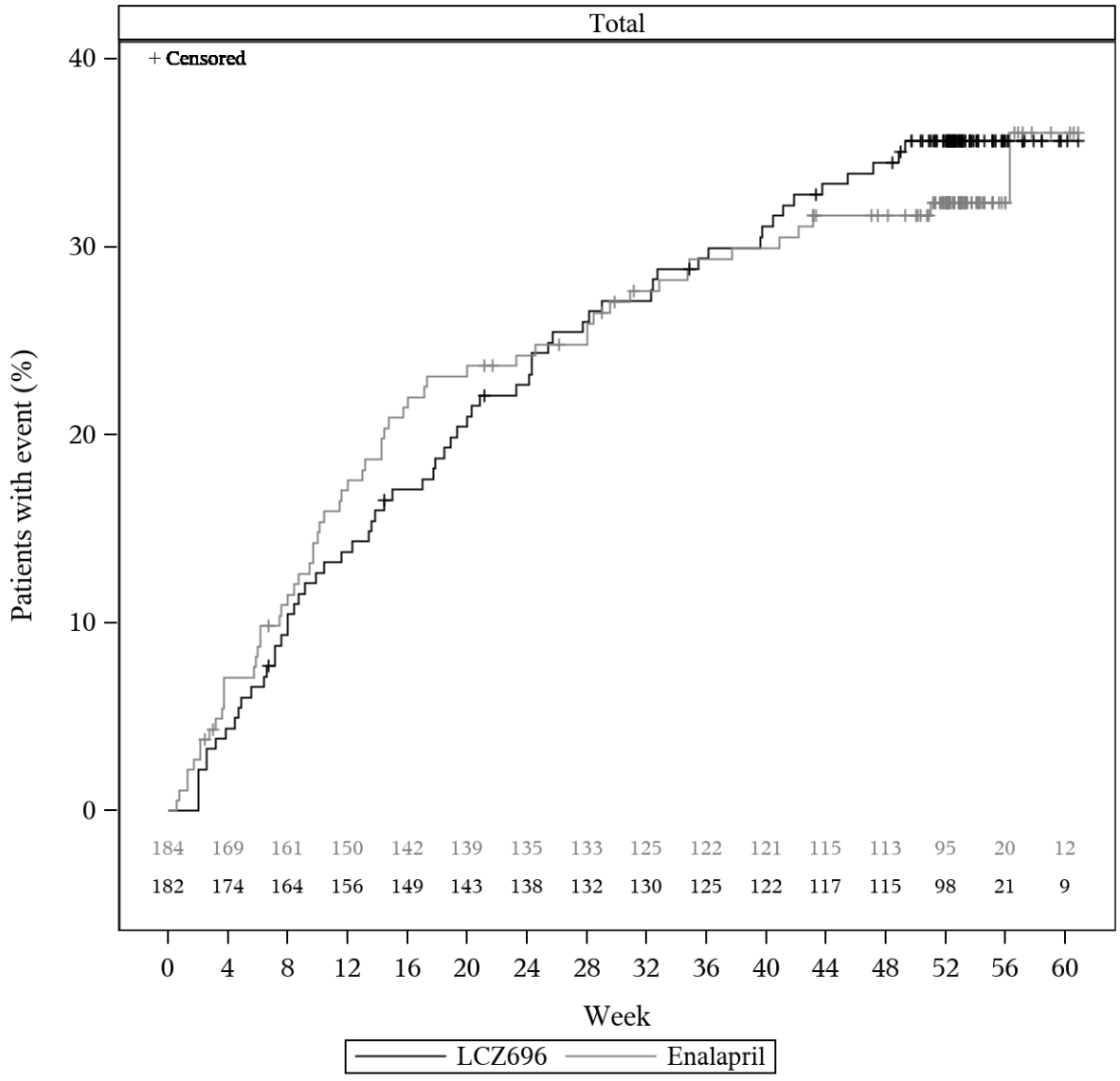
9 VAD / ECMO / mechanical ventilation / intra-aortic balloon pump requirement for life support (adjudicated)

Figure 9.1 VAD / ECMO / mechanical ventilation / intra-aortic balloon pump requirement for life support (adjudicated) (FAS), Kaplan-Meier plot



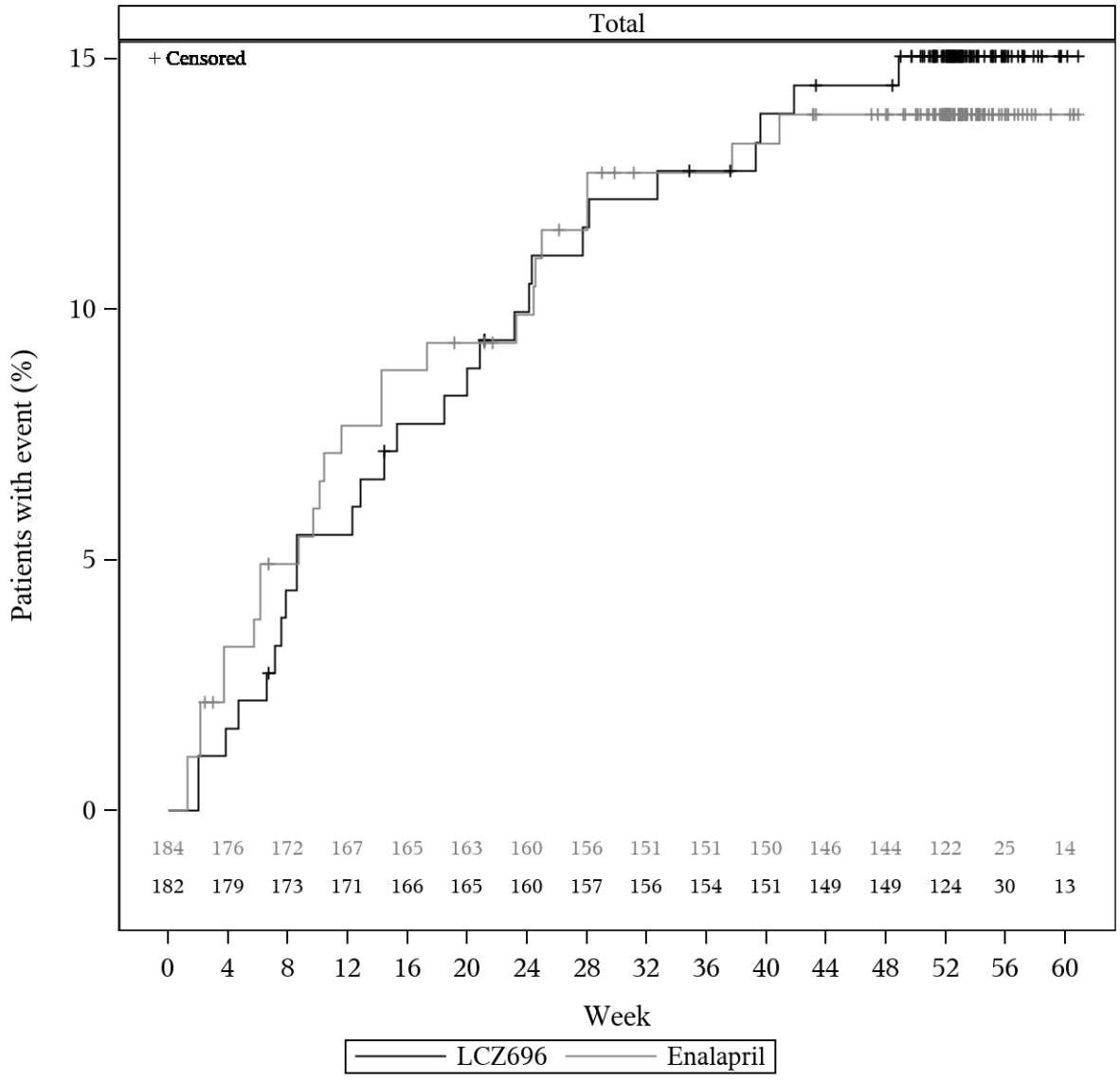
11 All cause hospitalization, time to first event

Figure 11.1 All cause hospitalization (FAS), Kaplan-Meier plot



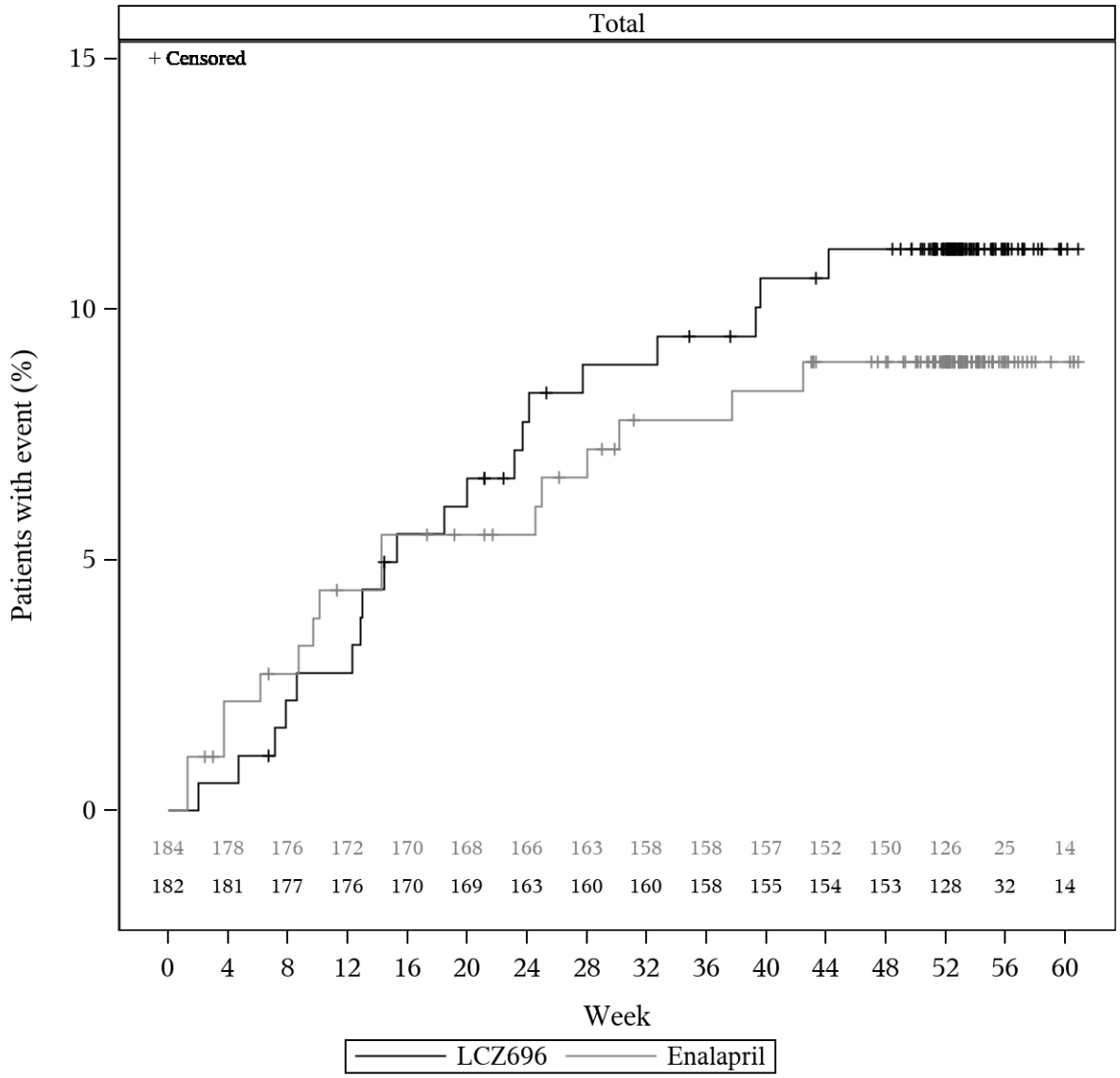
13 HF hospitalization and worsening of heart failure events, time to first event

Figure 13.1.1 HF hospitalization (FAS), Kaplan-Meier plot



The plot displays the patients under risk.

Figure 13.1.2 HF hospitalization with intensive care unit stay (FAS), Kaplan-Meier plot



The plot displays the patients under risk.

Figure 13.1.3 HF hospitalization without intensive care unit stay (FAS), Kaplan-Meier plot

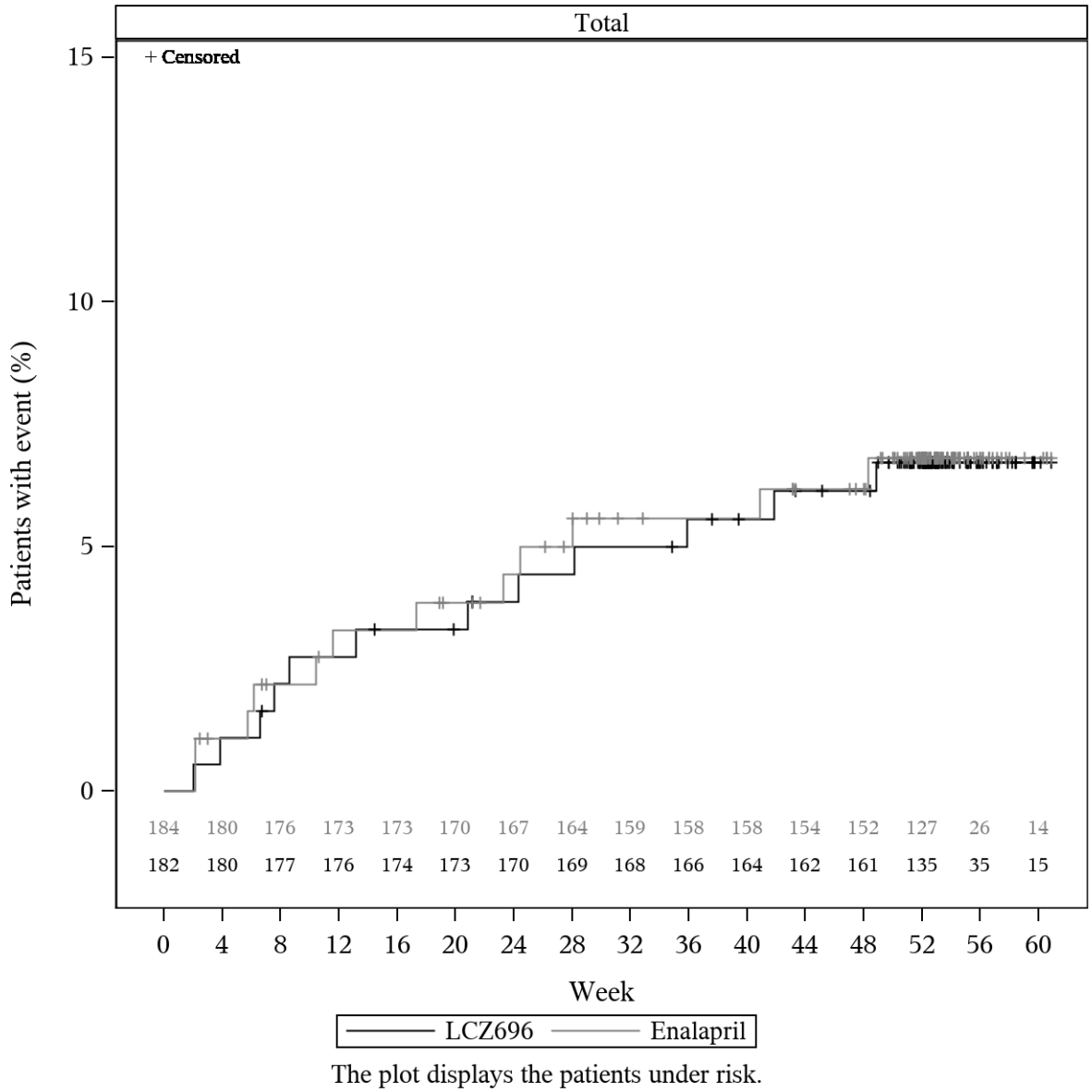
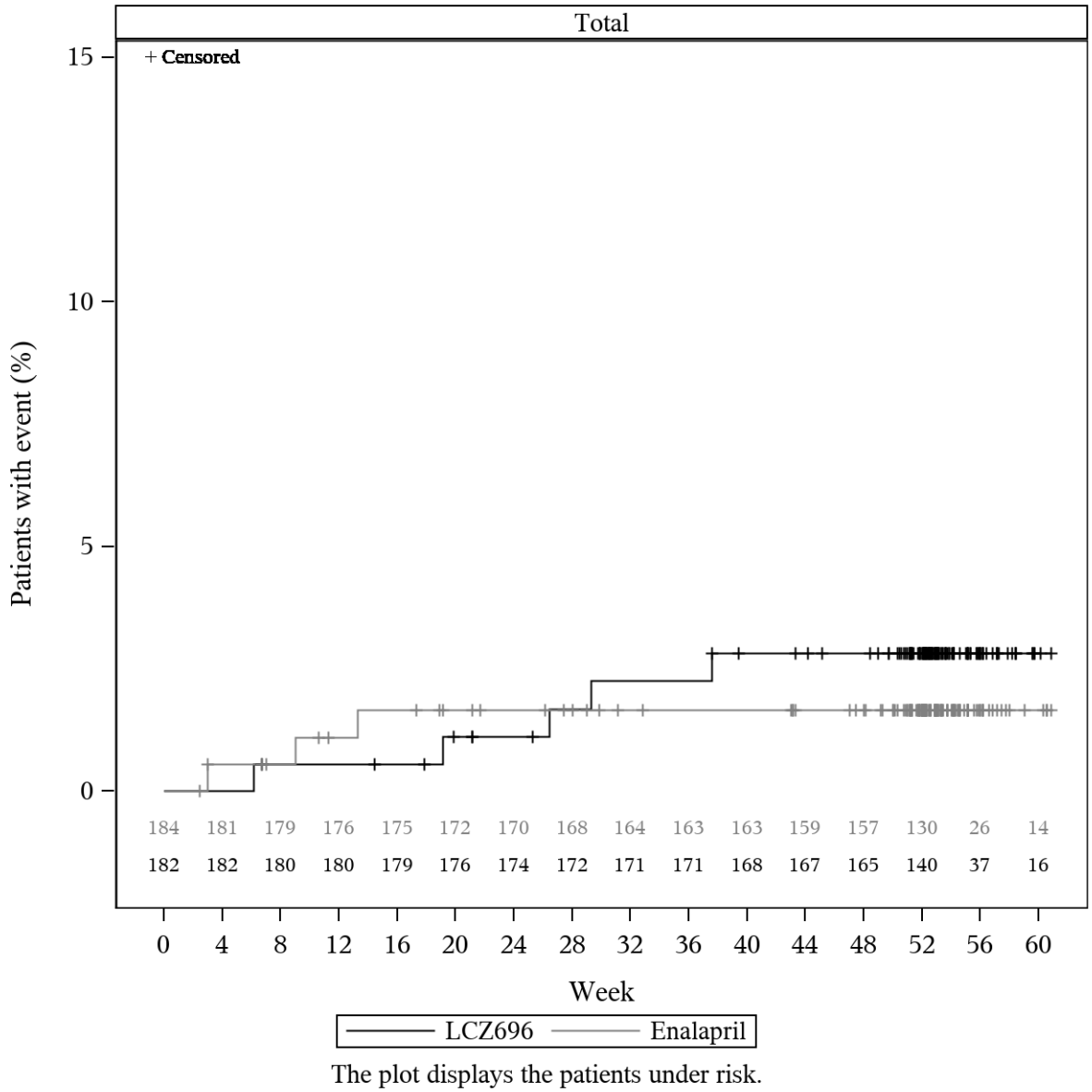


Figure 13.1.4 Worsening of heart failure without hospitalization (FAS), Kaplan-Meier plot



The plot displays the patients under risk.

18 PedsQL patient reported total score in the age group 5 to < 18 years, considering cutoff date for the last visit

Figure 18.1 PedsQL patient reported total score in the age group 5 to < 18 years considering cutoff (FAS), boxplot

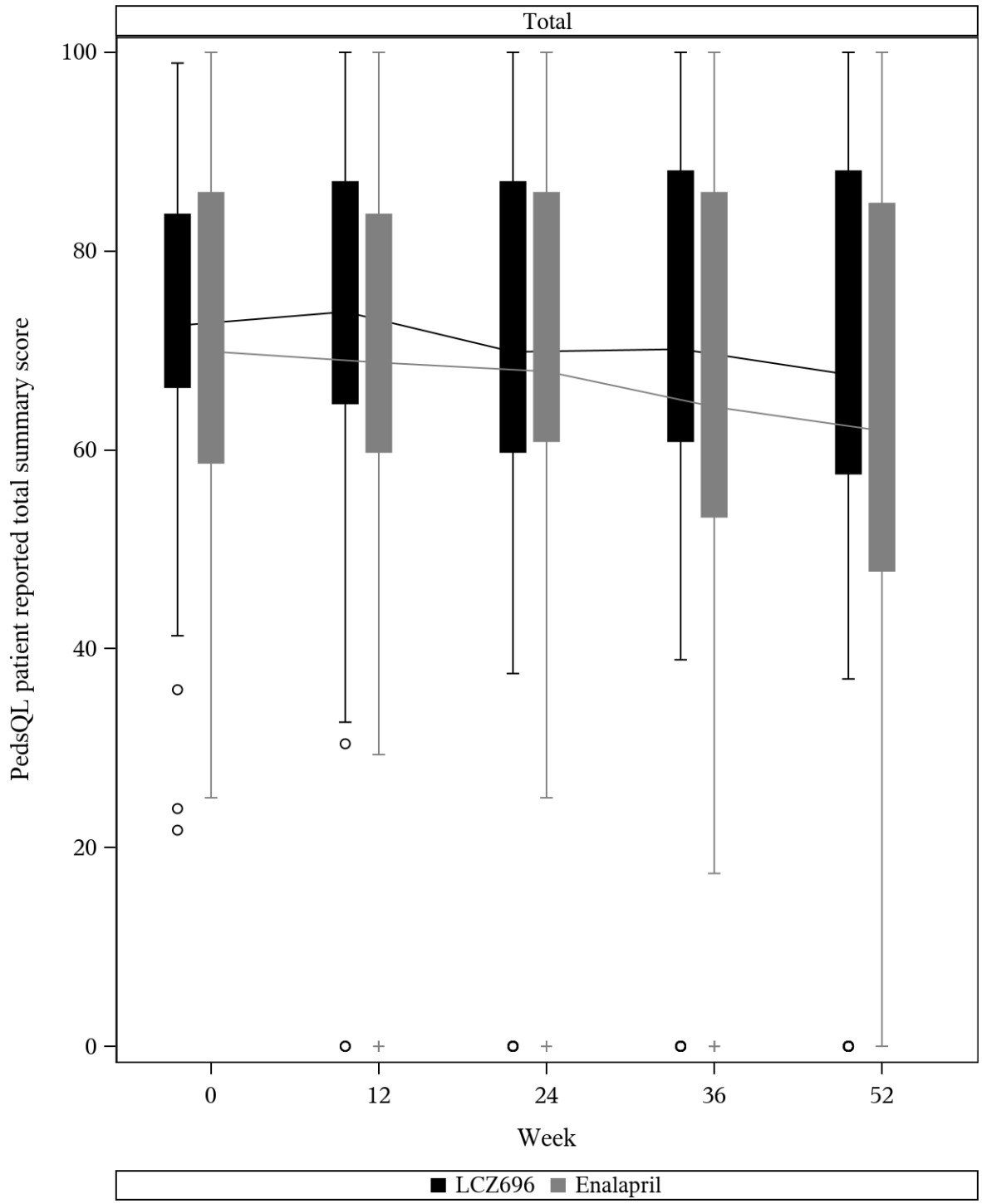
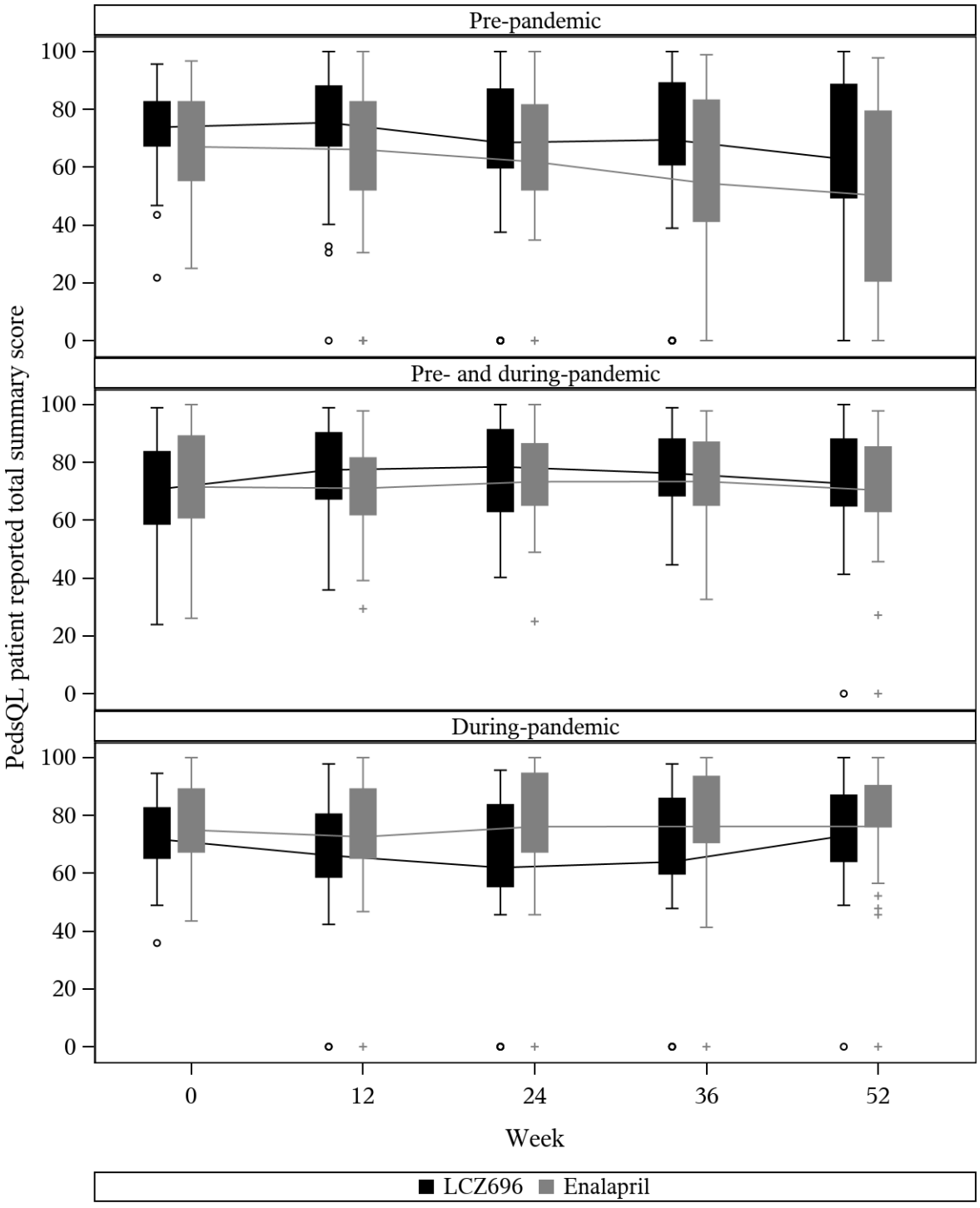


Figure 18.5 PedsQL patient reported total score in the age group 5 to < 18 years considering cutoff by COVID-19 period (FAS), boxplot



19 PedsQL patient reported total score in the age group 5 to < 18 years, not considering cutoff date for the last visit

Figure 19.1 PedsQL patient reported total score in the age group 5 to < 18 years not considering cutoff (FAS), boxplot

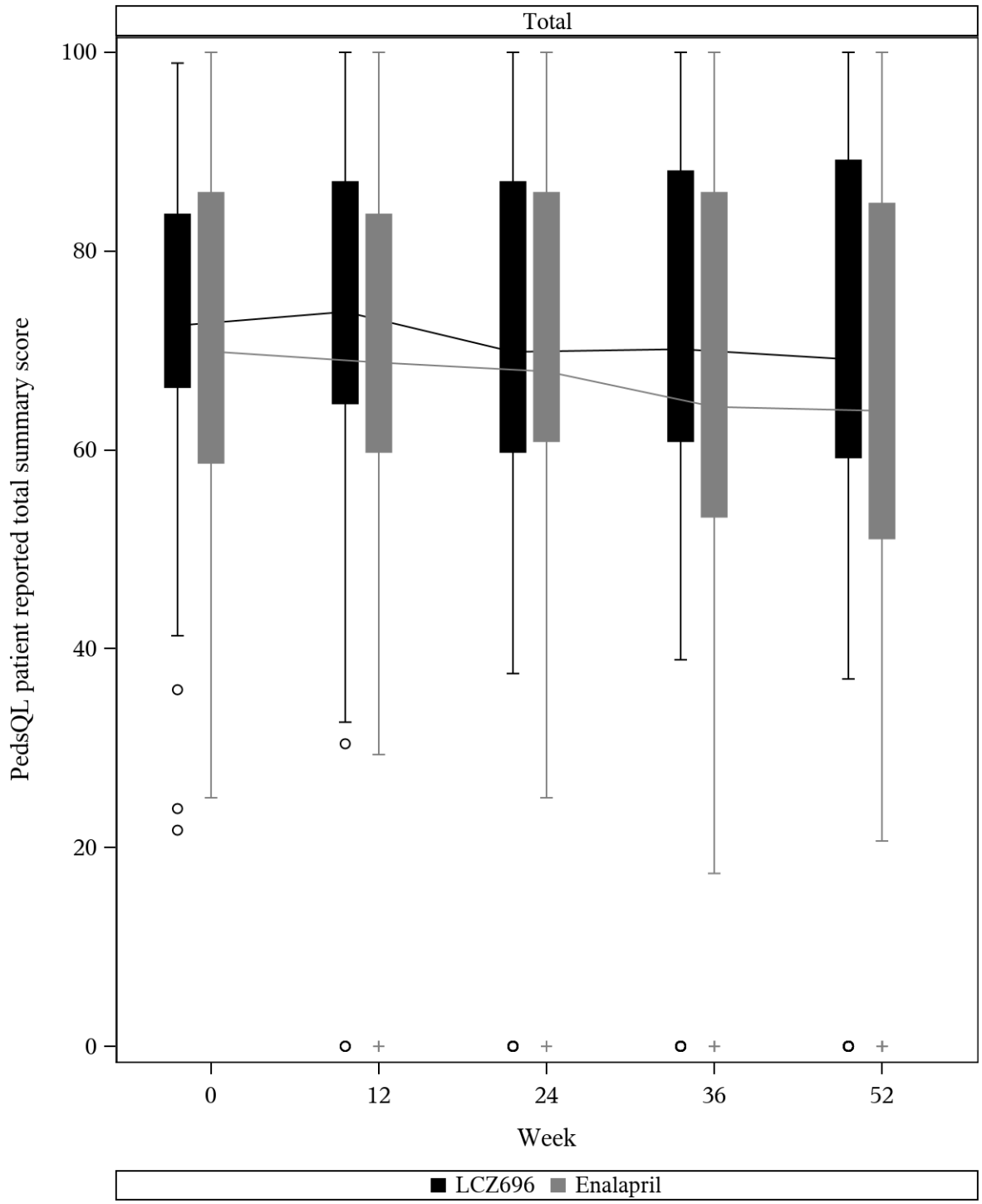
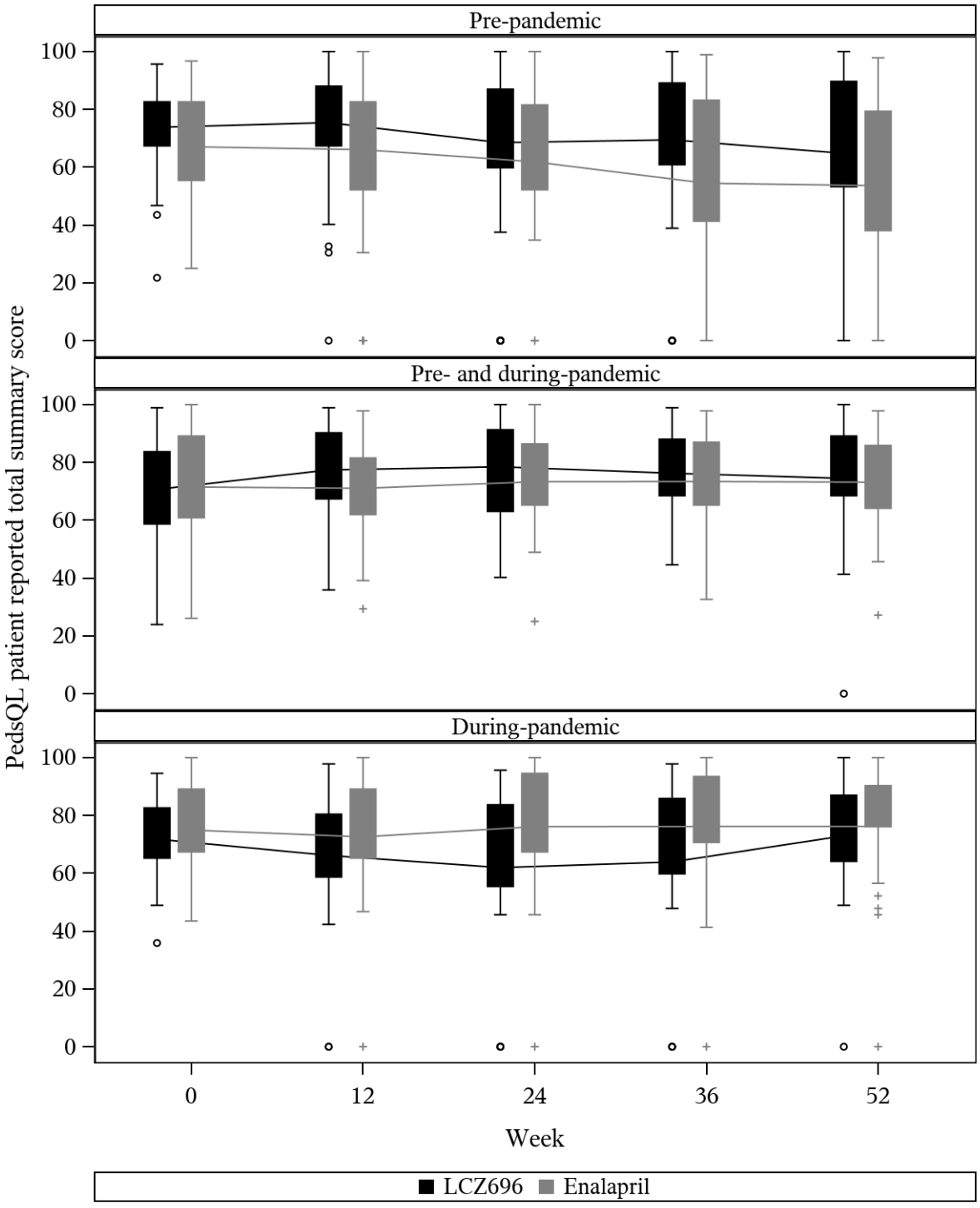
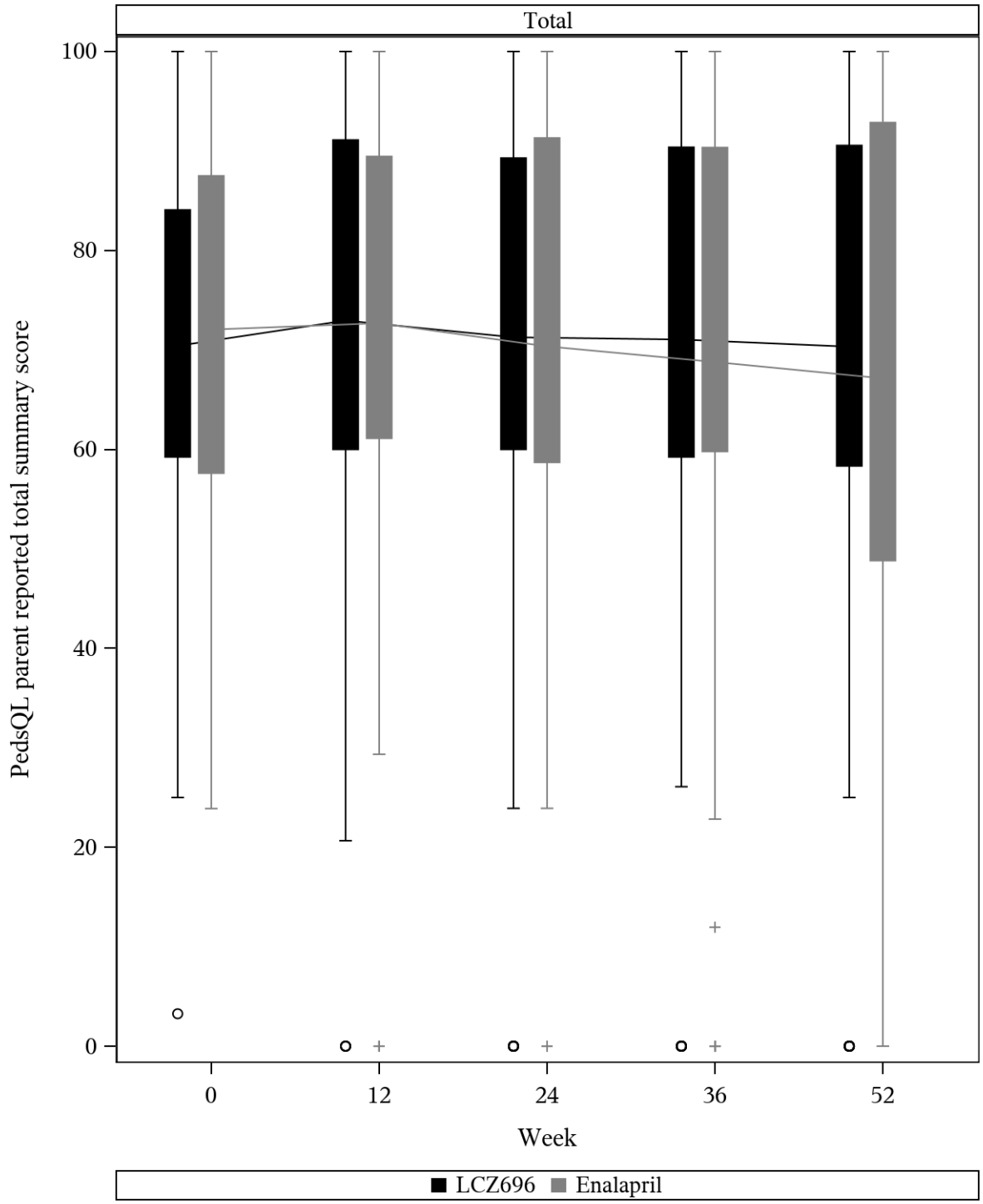


Figure 19.5 PedsQL patient reported total score in the age group 5 to < 18 years not considering cutoff by COVID-19 period (FAS), boxplot



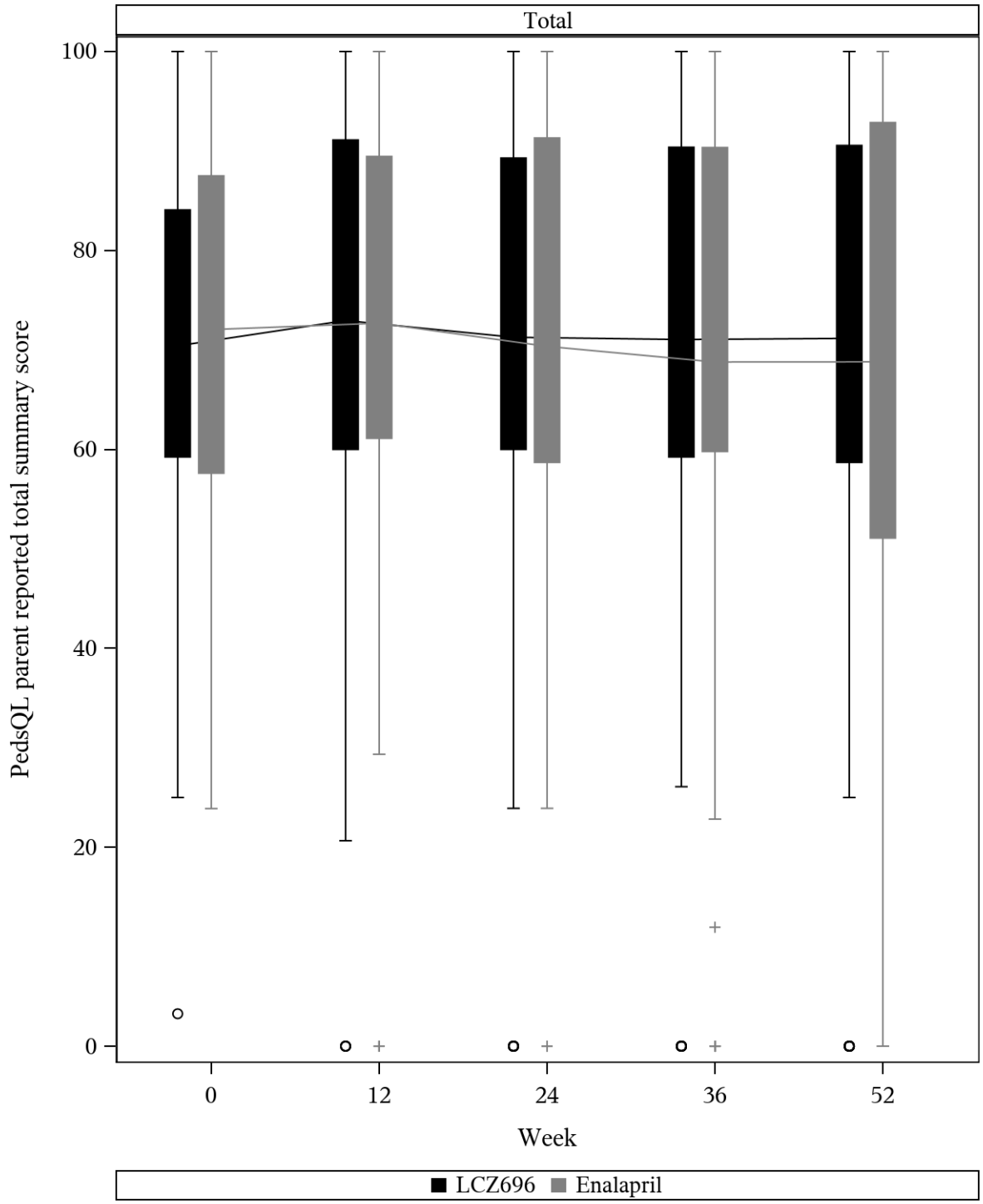
20 PedsQL parent reported total score, considering cutoff date for the last visit

Figure 20.1 PedsQL parent reported total score considering cutoff (FAS), boxplot



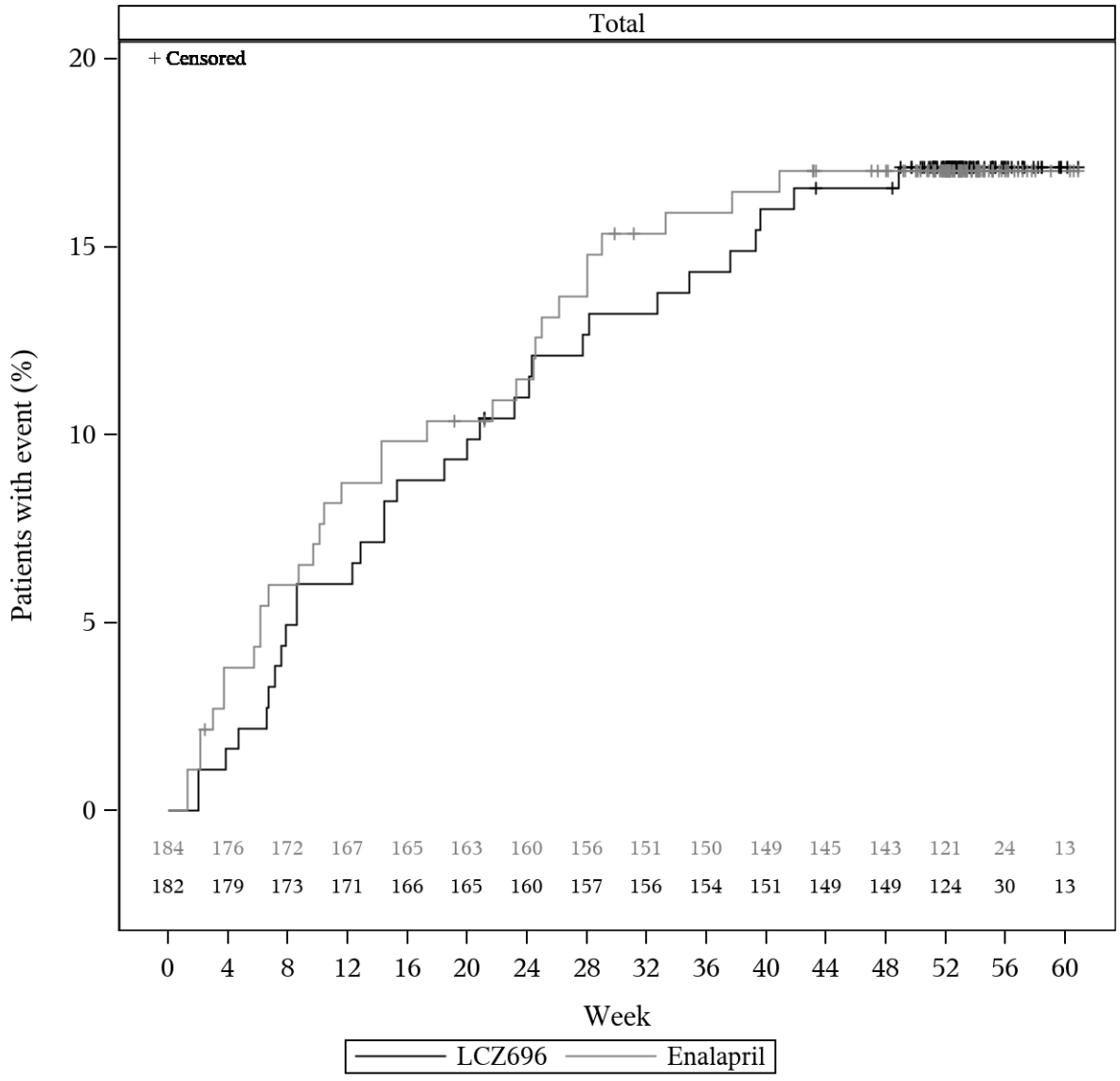
21 PedsQL parent reported total score, not considering cutoff date for the last visit

Figure 21.1 PedsQL parent reported total score not considering cutoff (FAS), boxplot



28 Selected adjudicated category 1 or 2 events

Figure 28.1 Selected adjudicated category 1 or 2 events (FAS), Kaplan-Meier plot



The plot displays the patients under risk.