LCZ696/Entresto®
Pediatric patients with heart failure

CLCZ696B2319 (PANORAMA)

AMNOG Analysis

Baseline and Safety

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1 Patient disposition

Table 1.1 Patient disposition (RAN)

	Treatment Groups		
Patient disposition (RAN)	**LCZ696 (N=182) n (%)**	**Enalapril (N=185) n (%)**	**Total (N=367) n (%)**
Randomized (RAN)	**182**	**185**	**367**
Completed the double-blind epoch	**166 (91.2)**	**161 (87.0)**	**327 (89.1)**
Discontinued the study during the double-blind epoch	**16 (8.8)**	**24 (13.0)**	**40 (10.9)**
Primary reason for discontinuation of study [1]			
Adverse event	1 (6.3)	2 (8.3)	3 (7.5)
Death	7 (43.8)	12 (50.0)	19 (47.5)
Lost to follow-up	0 (0.0)	2 (8.3)	2 (5.0)
Technical problems	3 (18.8)	3 (12.5)	6 (15.0)
Withdrawal by parent/guardian	5 (31.3)	5 (20.8)	10 (25.0)
Took at least one dose of study drug	**182 (100.0)**	**184 (99.5)**	**366 (99.7)**
Completed the study drug during the double-blind epoch	**145 (79.7)**	**138 (74.6)**	**283 (77.1)**
Permantently discontinued the study drug during the double-blind epoch	**37 (20.3)**	**46 (24.9)**	**83 (22.6)**
Primary reason for discontinuation of study drug [2]			
Adverse event	19 (51.4)	21 (45.7)	40 (48.2)
Death	3 (8.1)	4 (8.7)	7 (8.4)
Lost to follow-up	0 (0.0)	1 (2.2)	1 (1.2)
Physician decision	4 (10.8)	5 (10.9)	9 (10.8)
Technical problems	8 (21.6)	7 (15.2)	15 (18.1)
Withdrawal by parent/guardian	3 (8.1)	8 (17.4)	11 (13.3)

N: Number of patients
n (%): Number and percentage of patients
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[1] Percentage based on number of patients who discontinued study
[2] Percentage based on number of patients who discontinued study drug

Table 1.2 Analysis sets (RAN)

	Treatment Groups		
Analysis sets (RAN)	**LCZ696 (N=182) n (%)**	**Enalapril (N=185) n (%)**	**Total (N=367) n (%)**
Randomized (RAN)	**182**	**185**	**367**
Full analysis set (FAS)	**182 (100.0)**	**184 (99.5)**	**366 (99.7)**
Safety set (SAF)	**182 (100.0)**	**184 (99.5)**	**366 (99.7)**

N: Number of patients
n (%): Number and percentage of patients
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2 Demographics and disease characteristics

Table 2.1 Demographics (FAS)

	Treatment Groups		
Demographics (FAS)	**LCZ696 (N=182)**	**Enalapril (N=184)**	**Total (N=366)**
Age group at randomization, n (%)			
6 years to < 18 years	109 (59.9)	111 (60.3)	220 (60.1)
1 year to < 6 years	73 (40.1)	73 (39.7)	146 (39.9)
Age at randomization (years) Part2			
n	182	184	366
Mean ± SD	8.2 ± 5.41	8.4 ± 5.66	8.3 ± 5.53
Median	8.0	9.0	8.0
Range 1st to 3rd quartile	3.0 to 13	2.0 to 13	3.0 to 13
Range minimum to maximum	1.1 to 17	1 to 18	1 to 18
Gender, n (%)			
Male	88 (48.4)	91 (49.5)	179 (48.9)
Female	94 (51.6)	93 (50.5)	187 (51.1)
Race, n (%)			
Caucasian	86 (47.3)	90 (48.9)	176 (48.1)
Black	23 (12.6)	25 (13.6)	48 (13.1)
Asian	55 (30.2)	45 (24.5)	100 (27.3)
Unknown or other	18 (9.9)	24 (13.0)	42 (11.5)
Ethnicity, n (%)			
Hispanic or Latino	24 (13.2)	15 (8.2)	39 (10.7)
Not Hispanic or Latino	130 (71.4)	124 (67.4)	254 (69.4)
Not Reported	22 (12.1)	26 (14.1)	48 (13.1)
Unknown	6 (3.3)	19 (10.3)	25 (6.8)
Weight (kg) at randomization Part2			
n	182	184	366
Mean ± SD	32.9 ± 24.51	33.8 ± 26.15	33.3 ± 25.32
Median	23.5	27.8	25.2
Range 1st to 3rd quartile	12.8 to 49.5	12.4 to 46.25	12.8 to 48.8
Range minimum to maximum	7.6 to 112.8	6.89 to 163.2	6.89 to 163.2

	Treatment Groups		
Demographics (FAS)	**LCZ696 (N=182)**	**Enalapril (N=184)**	**Total (N=366)**
Height (cm) at pre-randomization Part2			
n	182	183	365
Mean ± SD	123.8 ± 33.23	124.9 ± 34.80	124.3 ± 33.98
Median	124.6	130.0	128.0
Range 1st to 3rd quartile	92.0 to 154.8	92.0 to 155	92.0 to 154.8
Range minimum to maximum	69 to 190	65 to 198	65 to 198
Body mass index (kg/m2) at randomization Part2			
n	182	183	365
Mean ± SD	18.3 ± 5.40	18.6 ± 6.01	18.5 ± 5.70
Median	16.4	17.1	16.8
Range 1st to 3rd quartile	14.8 to 20.4	14.8 to 19.9	14.8 to 20.3
Range minimum to maximum	10.6 to 40.7	10.6 to 44	10.6 to 44
Head circumference (cm) at randomization Part2			
n	54	52	106
Mean ± SD	46.9 ± 3.33	46.4 ± 2.95	46.7 ± 3.14
Median	47.0	46.0	46.5
Range 1st to 3rd quartile	45.5 to 49	45.0 to 48	45.0 to 48.6
Range minimum to maximum	34 to 53	35 to 53.3	34 to 53.3

N: Number of patients
n (%): Number and percentage of patients with event
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Table 2.2 Disease history and baseline disease characteristics (FAS)

	Treatment Groups		
Disease history and baseline disease characteristics (FAS)	**LCZ696 (N=182)**	**Enalapril (N=184)**	**Total (N=366)**
Prior heart failure medication (ACEI), n (%)			
Yes	163 (89.6)	167 (90.8)	330 (90.2)
Prior heart failure medication (ARB), n (%)			
Yes	6 (3.3)	9 (4.9)	15 (4.1)
Prior history of heart failure, n (%)			
Yes	182 (100.0)	184 (100.0)	366 (100.0)
Primary heart failure etiology, n (%)			
Acquired/chemotherapy	8 (4.4)	5 (2.7)	13 (3.6)
Cardiomyopathy related	112 (61.5)	119 (64.7)	231 (63.1)
Congenital cardiac malformation	20 (11.0)	27 (14.7)	47 (12.8)
Familial/genetic	28 (15.4)	30 (16.3)	58 (15.8)
Inborn error of metabolism	3 (1.6)	1 (0.5)	4 (1.1)
Idiopathic	62 (34.1)	61 (33.2)	123 (33.6)
Ischemic	8 (4.4)	7 (3.8)	15 (4.1)
Left-ventricular non-compaction	19 (10.4)	18 (9.8)	37 (10.1)
Mitochondrial disorder	2 (1.1)	0 (0.0)	2 (0.5)
Myocarditis	20 (11.0)	28 (15.2)	48 (13.1)
Neuromuscular disorder	8 (4.4)	5 (2.7)	13 (3.6)
Other	7 (3.8)	7 (3.8)	14 (3.8)
Time from diagnosis to randomization date[1], n (%)			
0 to < 3 months	25 (13.7)	25 (13.6)	50 (13.7)
3 to 12 months	37 (20.3)	43 (23.4)	80 (21.9)
> 1 year	119 (65.4)	116 (63.0)	235 (64.2)
Missing	1 (0.5)	0 (0.0)	1 (0.3)
Prior heart failure hospitalization, n (%)			
Yes	125 (68.7)	123 (66.8)	248 (67.8)
Number of heart failure hospitalizations in the last 12 months prior to screening, n (%)			
0	52 (28.6)	48 (26.1)	100 (27.3)
1	50 (27.5)	49 (26.6)	99 (27.0)
2	14 (7.7)	17 (9.2)	31 (8.5)
>2	9 (4.9)	9 (4.9)	18 (4.9)
Missing	57 (31.3)	61 (33.2)	118 (32.2)
On a heart transplant list, n (%)			
No	174 (95.6)	179 (97.3)	353 (96.4)

	Treatment Groups		
Disease history and baseline disease characteristics (FAS)	**LCZ696 (N=182)**	**Enalapril (N=184)**	**Total (N=366)**
Yes, UNOS status 1B, 2 or equivalent	8 (4.4)	5 (2.7)	13 (3.6)
Diastolic blood pressure (mmHg) at randomization Part2			
n	180	183	363
Mean ± SD	60.6 ± 10.60	60.5 ± 10.40	60.5 ± 10.48
Median	60.0	60.0	60.0
Range 1st to 3rd quartile	54.0 to 68	54.0 to 67	54.0 to 67
Range minimum to maximum	35 to 98	36 to 100	35 to 100
Systolic blood pressure (mmHg) at randomization Part2			
n	182	184	366
Mean ± SD	100.7 ± 13.37	100.6 ± 12.32	100.6 ± 12.83
Median	98.0	100.0	99.0
Range 1st to 3rd quartile	90.0 to 109	92.0 to 108	92.0 to 109
Range minimum to maximum	74 to 145	74 to 144	74 to 145
Heart rate (beats/min) at randomization Part2			
n	182	184	366
Mean ± SD	93.2 ± 20.84	94.9 ± 21.94	94.1 ± 21.39
Median	91.0	94.0	92.0
Range 1st to 3rd quartile	79.0 to 104	79.0 to 109	79.0 to 107
Range minimum to maximum	51 to 158	44 to 164	44 to 164
Left ventricular ejection fraction (%) Category Part2, n (%)			
35 to < 40	63 (34.6)	53 (28.8)	116 (31.7)
< 35	91 (50.0)	104 (56.5)	195 (53.3)
≥ 40	27 (14.8)	26 (14.1)	53 (14.5)
Missing	1 (0.5)	1 (0.5)	2 (0.5)
Left ventricular ejection fraction (%) Part2			
n	181	183	364
Mean ± SD	32.7 ± 7.46	31.5 ± 7.90	32.1 ± 7.70
Median	34.7	33.0	34.0
Range 1st to 3rd quartile	28.0 to 38	26.0 to 37	27.0 to 38
Range minimum to maximum	9.4 to 49	6.5 to 48.5	6.5 to 49
Left ventricular shortening fraction (%) Category Part2, n (%)			
< 20	94 (51.6)	93 (50.5)	187 (51.1)
≥ 20	22 (12.1)	25 (13.6)	47 (12.8)
Missing	66 (36.3)	66 (35.9)	132 (36.1)

	Treatment Groups		
Disease history and baseline disease characteristics (FAS)	**LCZ696 (N=182)**	**Enalapril (N=184)**	**Total (N=366)**
Left ventricular shortening fraction (%) Part2			
n	116	118	234
Mean ± SD	16.2 ± 3.96	16.2 ± 4.38	16.2 ± 4.17
Median	16.5	16.0	16.0
Range 1st to 3rd quartile	13.0 to 19	13.0 to 19	13.0 to 19
Range minimum to maximum	5.4 to 24.2	4.12 to 27.1	4.12 to 27.1
NYHA/ROSS class at Baseline, n (%)			
Class I	24 (13.2)	34 (18.5)	58 (15.8)
Class II	132 (72.5)	121 (65.8)	253 (69.1)
Class III	26 (14.3)	27 (14.7)	53 (14.5)
Class IV	0 (0.0)	2 (1.1)	2 (0.5)
NYHA class at randomization, n (%)			
CLASS I	13 (7.1)	11 (6.0)	24 (6.6)
CLASS II	78 (42.9)	81 (44.0)	159 (43.4)
CLASS III	18 (9.9)	18 (9.8)	36 (9.8)
CLASS IV	0 (0.0)	1 (0.5)	1 (0.3)
Missing	73 (40.1)	73 (39.7)	146 (39.9)
ROSS class at randomization, n (%)			
CLASS I	11 (6.0)	23 (12.5)	34 (9.3)
CLASS II	54 (29.7)	40 (21.7)	94 (25.7)
CLASS III	8 (4.4)	9 (4.9)	17 (4.6)
CLASS IV	0 (0.0)	1 (0.5)	1 (0.3)
Missing	109 (59.9)	111 (60.3)	220 (60.1)
NYHA/ROSS class group at randomization stratum, n (%)			
CLASS I/II	157 (86.3)	157 (85.3)	314 (85.8)
CLASS III/IV	25 (13.7)	27 (14.7)	52 (14.2)

N: Number of patients
n (%): Number and percentage of patients with event
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[1] Time from diagnosis to randomization date = date of randomization - date of diagnosis + 1

3 Duration of study participation, treatment exposure, compliance and dose adjustments

Table 3.1 Duration of study participation and treatment exposure during double-blind epoch (SAF)

	Treatment Groups		
Duration of study participation and treatment exposure during double-blind epoch (FAS)	**LCZ696 (N=182)**	**Enalapril (N=184)**	**Total (N=366)**
Duration of study participation [days][1]			
n	182	184	366
Mean ± SD	365.2 ± 60.04	350.7 ± 79.42	357.9 ± 70.73
Median	367.0	365.0	366.0
Range 1st to 3rd quartile	365.0 to 382	362.0 to 379	363.0 to 379
Range minimum to maximum	47 to 497	17 to 516	17 to 516
Duration of treatment exposure [days][2]			
n	182	184	366
Mean ± SD	347.4 ± 103.18	327.3 ± 120.32	337.3 ± 112.42
Median	365.0	364.0	365.0
Range 1st to 3rd quartile	357.0 to 378	329.5 to 376.5	353.0 to 378
Range minimum to maximum	4 to 642	7 to 686	4 to 686

N: Number of patients
.....
[1] Duration of study participation = end of study date - date of randomization + 1
[2] Duration of treatment exposure = end of treatment date - date of first dose of study drug + 1

4 Subgroups

Table 4.1 Subgroups (FAS)

	Treatment Groups		
Subgroups (FAS)	**LCZ696 (N=182)**	**Enalapril (N=184)**	**Total (N=366)**
Age group at randomization, n (%)			
6 years to < 18 years	109 (59.9)	111 (60.3)	220 (60.1)
1 year to < 6 years	73 (40.1)	73 (39.7)	146 (39.9)
NYHA/Ross class CRF, n (%)			
Class I/II	157 (86.3)	157 (85.3)	314 (85.8)
Class III/IV	25 (13.7)	27 (14.7)	52 (14.2)
NYHA/Ross class IRT, n (%)			
Class I/II	157 (86.3)	157 (85.3)	314 (85.8)
Class III/IV	25 (13.7)	27 (14.7)	52 (14.2)
Geographical region, n (%)			
America	58 (31.9)	69 (37.5)	127 (34.7)
Europe	58 (31.9)	55 (29.9)	113 (30.9)
Asia/Pacific and other	66 (36.3)	60 (32.6)	126 (34.4)
Gender, n (%)			
Male	88 (48.4)	91 (49.5)	179 (48.9)
Female	94 (51.6)	93 (50.5)	187 (51.1)
COVID-19 period, n (%)			
Pre-pandemic	79 (43.4)	83 (45.1)	162 (44.3)
Pre- and during-pandemic	62 (34.1)	59 (32.1)	121 (33.1)
During-pandemic	41 (22.5)	42 (22.8)	83 (22.7)
Race, n (%)			
Caucasian	86 (47.3)	90 (48.9)	176 (48.1)
Black	23 (12.6)	25 (13.6)	48 (13.1)
Asian	55 (30.2)	45 (24.5)	100 (27.3)
Unknown or other	18 (9.9)	24 (13.0)	42 (11.5)
Prior ACEI/ARB use, n (%)			
ACEI only	161 (88.5)	162 (88.0)	323 (88.3)
ARB only	4 (2.2)	4 (2.2)	8 (2.2)
ACEI and ARB	2 (1.1)	5 (2.7)	7 (1.9)
None	15 (8.2)	13 (7.1)	28 (7.7)

N: Number of patients
n (%): Number and percentage of patients with event
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5 Dossier Subpopulation

Table 5.1 Definition of Dossier Subpopulation (Total Study Population)

	Treatment Groups		
Age at baseline n (%)	**LCZ696 (N=187)**	**Enalapril (N=188)**	**Total (N=375)**
< 1 year	5 (2.7)	4 (2.1)	9 (2.4)
1 year to < 18 years	182 (97.3)	184 (97.9)	366 (97.6)
Analysis population: FAS total population CLCZ696B2319			

29 Adverse events overview

Table 29.1 Adverse events overview (SAF), binary analysis

	Treatment Groups		Comparison		
Adverse events overview (SAF)	**LCZ696 (N=182)**	**Enalapril (N=184)**	**OR [95% CI] p-value**	**RR [95% CI] p-value**	**RD [95% CI] p-value**
Any adverse event, n (%)	163 (89.6)	162 (88.0)	1.17 [0.61; 2.23] 0.646	1.02 [0.95; 1.09] 0.645	0.02 [-0.05; 0.08] 0.645
Any serious adverse event, n (%)	68 (37.4)	61 (33.2)	1.20 [0.78; 1.85] 0.399	1.13 [0.85; 1.49] 0.400	0.04 [-0.06; 0.14] 0.399
Any severe adverse event, n (%)	31 (17.0)	40 (21.7)	0.74 [0.44; 1.25] 0.256	0.78 [0.51; 1.19] 0.257	-0.05 [-0.13; 0.03] 0.254
Any adverse event leading to study discontinuation, n (%)	8 (4.4)	14 (7.6)	0.56 [0.23; 1.36] 0.201	0.58 [0.25; 1.34] 0.203	-0.03 [-0.08; 0.02] 0.194
Any adverse event leading to study drug discontinuation, n (%)	20 (11.0)	21 (11.4)	0.96 [0.50; 1.84] 0.898	0.96 [0.54; 1.71] 0.898	-0.00 [-0.07; 0.06] 0.898

N: Number of patients
n (%): Number and percentage of patients with event
CI: Confidence interval
OR: Odds ratio
RR: Relative risk
RD: Risk difference
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Imputation method: None

Analysis method:
OR with Wald CI and p-value obtained from logistic regression model: logit(proportion) = treatment.
RR and RD with Wald CI and p-value calculated directly.

Table 29.2 Adverse events overview by age group (SAF), binary analysis

	Treatment Groups		Comparison		
Adverse events overview by age group (SAF)	**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			
Any adverse event					
Interaction test	**p = 0.565**				
6 years to < 18 years, n (%)	98 (89.9)	100 (90.1)	0.98 [0.41; 2.36] 0.964	1.00 [0.91; 1.09] 0.964	-0.00 [-0.08; 0.08] 0.964
1 year to < 6 years, n (%)	65 (89.0)	62 (84.9)	1.44 [0.54; 3.82] 0.462	1.05 [0.92; 1.19] 0.461	0.04 [-0.07; 0.15] 0.460
Any serious adverse event					
Interaction test	**p = 0.354**				
6 years to < 18 years, n (%)	42 (38.5)	42 (37.8)	1.03 [0.60; 1.77] 0.916	1.02 [0.73; 1.43] 0.916	0.01 [-0.12; 0.14] 0.916
1 year to < 6 years, n (%)	26 (35.6)	19 (26.0)	1.57 [0.77; 3.19] 0.211	1.37 [0.83; 2.24] 0.214	0.10 [-0.05; 0.24] 0.207
Any severe adverse event					
Interaction test	**p = 0.817**				
6 years to < 18 years, n (%)	21 (19.3)	28 (25.2)	0.71 [0.37; 1.34] 0.289	0.76 [0.46; 1.26] 0.291	-0.06 [-0.17; 0.05] 0.287
1 year to < 6 years, n (%)	10 (13.7)	12 (16.4)	0.81 [0.32; 2.00] 0.644	0.83 [0.38; 1.81] 0.644	-0.03 [-0.14; 0.09] 0.643
Any adverse event leading to study discontinuation					
Interaction test	**p = 0.839**				
6 years to < 18 years, n (%)	6 (5.5)	11 (9.9)	0.53 [0.19; 1.49] 0.227	0.56 [0.21; 1.45] 0.229	-0.04 [-0.11; 0.03] 0.218
1 year to < 6 years, n (%)	2 (2.7)	3 (4.1)	0.66 [0.11; 4.05] 0.651	0.67 [0.11; 3.87] 0.652	-0.01 [-0.07; 0.05] 0.649
Any adverse event leading to study drug discontinuation					
Interaction test	**p = 0.492**				
6 years to < 18 years, n (%)	16 (14.7)	15 (13.5)	1.10 [0.51; 2.35] 0.804	1.09 [0.57; 2.09] 0.804	0.01 [-0.08; 0.10] 0.804

	Treatment Groups		Comparison		
Adverse events overview by age group (SAF)	**LCZ696 (N=182)**	**Enalapril (N=184)**	**OR [95% CI] p-value**	**RR [95% CI] p-value**	**RD [95% CI] p-value**
1 year to < 6 years, n (%)	4 (5.5)	6 (8.2)	0.65 [0.17; 2.40] 0.515	0.67 [0.20; 2.26] 0.516	-0.03 [-0.11; 0.05] 0.512

N: Number of patients
n (%): Number and percentage of patients with event
CI: Confidence interval
OR: Odds ratio
RR: Relative risk
RD: Risk difference
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Imputation method: None

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.
RR and RD with Wald CI and p-value calculated directly.

Table 29.3 Adverse events overview by NYHA/Ross class (SAF), binary analysis

	Treatment Groups		Comparison		
Adverse events overview by NYHA/Ross class (SAF)	**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			
Any adverse event					
Interaction test	**p = 0.443**				
Class I/II, n (%)	141 (89.8)	137 (87.3)	1.29 [0.64; 2.59] 0.479	1.03 [0.95; 1.11] 0.479	0.03 [-0.04; 0.10] 0.478
Class III/IV, n (%)	22 (88.0)	25 (92.6)	0.59 [0.09; 3.84] 0.578	0.95 [0.79; 1.14] 0.579	-0.05 [-0.21; 0.12] 0.577
Any serious adverse event					
Interaction test	**p = 0.075**				
Class I/II, n (%)	50 (31.8)	49 (31.2)	1.03 [0.64; 1.66] 0.903	1.02 [0.74; 1.41] 0.903	0.01 [-0.10; 0.11] 0.903
Class III/IV, n (%)	18 (72.0)	12 (44.4)	3.21 [1.01; 10.22] 0.048 *	1.62 [0.99; 2.64] 0.052	0.28 [0.02; 0.53] 0.036 *
Any severe adverse event					
Interaction test	**p = 0.447**				
Class I/II, n (%)	23 (14.6)	32 (20.4)	0.67 [0.37; 1.21] 0.183	0.72 [0.44; 1.17] 0.185	-0.06 [-0.14; 0.03] 0.180
Class III/IV, n (%)	8 (32.0)	8 (29.6)	1.12 [0.34; 3.63] 0.853	1.08 [0.48; 2.44] 0.853	0.02 [-0.23; 0.27] 0.853
Any adverse event leading to study discontinuation					
Interaction test	**p = 0.481**				
Class I/II, n (%)	6 (3.8)	12 (7.6)	0.48 [0.18; 1.31] 0.153	0.50 [0.19; 1.30] 0.155	-0.04 [-0.09; 0.01] 0.144
Class III/IV, n (%)	2 (8.0)	2 (7.4)	1.09 [0.14; 8.36] 0.936	1.08 [0.16; 7.10] 0.936	0.01 [-0.14; 0.15] 0.936
Any adverse event leading to study drug discontinuation					
Interaction test	**p = 0.169**				
Class I/II, n (%)	13 (8.3)	17 (10.8)	0.74 [0.35; 1.59] 0.444	0.76 [0.38; 1.52] 0.444	-0.03 [-0.09; 0.04] 0.442

	Treatment Groups		Comparison		
Adverse events overview by NYHA/Ross class (SAF)	**LCZ696 (N=182)**	**Enalapril (N=184)**	**OR [95% CI] p-value**	**RR [95% CI] p-value**	**RD [95% CI] p-value**
Class III/IV, n (%)	7 (28.0)	4 (14.8)	2.24 [0.57; 8.84] 0.251	1.89 [0.63; 5.69] 0.257	0.13 [-0.09; 0.35] 0.243

N: Number of patients
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: None

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.
RR and RD with Wald CI and p-value calculated directly.

Table 29.4 Adverse events overview by region (SAF), binary analysis

	Treatment Groups		Comparison		
Adverse events overview by region (SAF)	**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			
Any adverse event					
Interaction test	**p = 0.600**				
America, n (%)	51 (87.9)	62 (89.9)	0.82 [0.27; 2.50] 0.730	0.98 [0.86; 1.11] 0.732	-0.02 [-0.13; 0.09] 0.732
Europe, n (%)	54 (93.1)	48 (87.3)	1.97 [0.54; 7.14] 0.303	1.07 [0.94; 1.21] 0.302	0.06 [-0.05; 0.17] 0.297
Asia/Pacific and other, n (%)	58 (87.9)	52 (86.7)	1.12 [0.39; 3.18] 0.838	1.01 [0.89; 1.16] 0.839	0.01 [-0.10; 0.13] 0.839
Any serious adverse event					
Interaction test	**p = 0.819**				
America, n (%)	24 (41.4)	26 (37.7)	1.17 [0.57; 2.38] 0.671	1.10 [0.71; 1.69] 0.670	0.04 [-0.13; 0.21] 0.671
Europe, n (%)	22 (37.9)	20 (36.4)	1.07 [0.50; 2.30] 0.863	1.04 [0.65; 1.69] 0.863	0.02 [-0.16; 0.19] 0.863
Asia/Pacific and other, n (%)	22 (33.3)	15 (25.0)	1.50 [0.69; 3.26] 0.307	1.33 [0.77; 2.32] 0.310	0.08 [-0.07; 0.24] 0.301
Any severe adverse event					
Interaction test	**p = 0.147**				
America, n (%)	7 (12.1)	19 (27.5)	0.36 [0.14; 0.93] 0.036 *	0.44 [0.20; 0.97] 0.042 *	-0.15 [-0.29; -0.02] 0.024 *
Europe, n (%)	11 (19.0)	8 (14.5)	1.37 [0.51; 3.72] 0.531	1.30 [0.57; 3.00] 0.532	0.04 [-0.09; 0.18] 0.528
Asia/Pacific and other, n (%)	13 (19.7)	13 (21.7)	0.89 [0.37; 2.10] 0.785	0.91 [0.46; 1.80] 0.785	-0.02 [-0.16; 0.12] 0.785
Any adverse event leading to study discontinuation					
Interaction test	**p = 0.822**				
America, n (%)	2 (3.4)	6 (8.7)	0.38 [0.07; 1.93] 0.241	0.40 [0.08; 1.89] 0.246	-0.05 [-0.13; 0.03] 0.206

	Treatment Groups		Comparison		
Adverse events overview by region (SAF)	**LCZ696 (N=182)**	**Enalapril (N=184)**	**OR [95% CI] p-value**	**RR [95% CI] p-value**	**RD [95% CI] p-value**
Europe, n (%)	1 (1.7)	1 (1.8)	0.95 [0.06; 15.53] 0.970	0.95 [0.06; 14.79] 0.970	-0.00 [-0.05; 0.05] 0.970
Asia/Pacific and other, n (%)	5 (7.6)	7 (11.7)	0.62 [0.19; 2.07] 0.438	0.65 [0.22; 1.94] 0.439	-0.04 [-0.14; 0.06] 0.438
Any adverse event leading to study drug discontinuation					
Interaction test	**p = 0.627**				
America, n (%)	5 (8.6)	9 (13.0)	0.63 [0.20; 1.99] 0.431	0.66 [0.23; 1.86] 0.433	-0.04 [-0.15; 0.06] 0.420
Europe, n (%)	6 (10.3)	4 (7.3)	1.47 [0.39; 5.52] 0.567	1.42 [0.42; 4.77] 0.568	0.03 [-0.07; 0.13] 0.563
Asia/Pacific and other, n (%)	9 (13.6)	8 (13.3)	1.03 [0.37; 2.86] 0.960	1.02 [0.42; 2.48] 0.960	0.00 [-0.12; 0.12] 0.960

N: Number of patients
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: None

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

Table 29.5 Adverse events overview by gender (SAF), binary analysis

	Treatment Groups		Comparison		
Adverse events overview by gender (SAF)	**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			
Any adverse event					
Interaction test	**p = 0.032 ***				
Male, n (%)	77 (87.5)	85 (93.4)	0.49 [0.17; 1.40] 0.185	0.94 [0.85; 1.03] 0.182	-0.06 [-0.14; 0.03] 0.178
Female, n (%)	86 (91.5)	77 (82.8)	2.23 [0.91; 5.51] 0.081	1.11 [0.99; 1.24] 0.079	0.09 [-0.01; 0.18] 0.074
Any serious adverse event					
Interaction test	**p = 0.919**				
Male, n (%)	29 (33.0)	26 (28.6)	1.23 [0.65; 2.32] 0.526	1.15 [0.74; 1.79] 0.526	0.04 [-0.09; 0.18] 0.525
Female, n (%)	39 (41.5)	35 (37.6)	1.18 [0.65; 2.11] 0.590	1.10 [0.77; 1.57] 0.590	0.04 [-0.10; 0.18] 0.590
Any severe adverse event					
Interaction test	**p = 0.666**				
Male, n (%)	15 (17.0)	18 (19.8)	0.83 [0.39; 1.78] 0.637	0.86 [0.46; 1.60] 0.638	-0.03 [-0.14; 0.09] 0.637
Female, n (%)	16 (17.0)	22 (23.7)	0.66 [0.32; 1.36] 0.261	0.72 [0.40; 1.28] 0.263	-0.07 [-0.18; 0.05] 0.258
Any adverse event leading to study discontinuation					
Interaction test	**p = 0.534**				
Male, n (%)	5 (5.7)	7 (7.7)	0.72 [0.22; 2.37] 0.592	0.74 [0.24; 2.24] 0.593	-0.02 [-0.09; 0.05] 0.590
Female, n (%)	3 (3.2)	7 (7.5)	0.41 [0.10; 1.62] 0.201	0.42 [0.11; 1.59] 0.203	-0.04 [-0.11; 0.02] 0.187
Any adverse event leading to study drug discontinuation					
Interaction test	**p = 0.789**				
Male, n (%)	12 (13.6)	12 (13.2)	1.04 [0.44; 2.46] 0.930	1.03 [0.49; 2.18] 0.930	0.00 [-0.10; 0.10] 0.930

	Treatment Groups		Comparison		
Adverse events overview by gender (SAF)	**LCZ696 (N=182)**	**Enalapril (N=184)**	**OR [95% CI] p-value**	**RR [95% CI] p-value**	**RD [95% CI] p-value**
Female, n (%)	8 (8.5)	9 (9.7)	0.87 [0.32; 2.36] 0.782	0.88 [0.35; 2.18] 0.782	-0.01 [-0.09; 0.07] 0.781

N: Number of patients
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: None

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

Table 29.6 Adverse events overview by COVID-19 period (SAF), binary analysis

	Treatment Groups		Comparison		
Adverse events overview by COVID-19 period (SAF)	**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			
Any adverse event					
Interaction test	**p = 0.634**				
Pre-pandemic, n (%)	71 (89.9)	76 (91.6)	0.82 [0.28; 2.37] 0.711	0.98 [0.89; 1.08] 0.711	-0.02 [-0.11; 0.07] 0.711
Pre- and during-pandemic, n (%)	55 (88.7)	51 (86.4)	1.23 [0.42; 3.64] 0.705	1.03 [0.90; 1.17] 0.706	0.02 [-0.09; 0.14] 0.705
During-pandemic, n (%)	37 (90.2)	35 (83.3)	1.85 [0.50; 6.87] 0.358	1.08 [0.91; 1.28] 0.354	0.07 [-0.08; 0.21] 0.349
Any serious adverse event					
Interaction test	**p = 0.252**				
Pre-pandemic, n (%)	31 (39.2)	34 (41.0)	0.93 [0.50; 1.75] 0.823	0.96 [0.66; 1.40] 0.823	-0.02 [-0.17; 0.13] 0.823
Pre- and during-pandemic, n (%)	23 (37.1)	20 (33.9)	1.15 [0.55; 2.42] 0.713	1.09 [0.68; 1.77] 0.714	0.03 [-0.14; 0.20] 0.713
During-pandemic, n (%)	14 (34.1)	7 (16.7)	2.59 [0.92; 7.31] 0.072	2.05 [0.92; 4.55] 0.078	0.17 [-0.01; 0.36] 0.062
Any severe adverse event					
Interaction test	**p = 0.279**				
Pre-pandemic, n (%)	16 (20.3)	24 (28.9)	0.62 [0.30; 1.29] 0.203	0.70 [0.40; 1.22] 0.207	-0.09 [-0.22; 0.05] 0.198
Pre- and during-pandemic, n (%)	8 (12.9)	12 (20.3)	0.58 [0.22; 1.54] 0.275	0.63 [0.28; 1.44] 0.277	-0.07 [-0.21; 0.06] 0.271
During-pandemic, n (%)	7 (17.1)	4 (9.5)	1.96 [0.53; 7.27] 0.317	1.79 [0.57; 5.67] 0.320	0.08 [-0.07; 0.22] 0.309

	Treatment Groups		Comparison		
Adverse events overview by COVID-19 period (SAF)	**LCZ696 (N=182)**	**Enalapril (N=184)**	**OR [95% CI] p-value**	**RR [95% CI] p-value**	**RD [95% CI] p-value**
Any adverse event leading to study discontinuation					
Interaction test	**N.E.**				
Pre-pandemic, n (%)	7 (8.9)	13 (15.7)	0.52 [0.20; 1.39] 0.194	0.57 [0.24; 1.34] 0.197	-0.07 [-0.17; 0.03] 0.183
Pre- and during-pandemic, n (%)	0 (0.0)	1 (1.7)	N.E.	0.32 [0.01; 7.64] 0.480	-0.02 [-0.05; 0.02] 0.313
During-pandemic, n (%)	1 (2.4)	0 (0.0)	N.E.	3.07 [0.13; 73.29] 0.488	0.02 [-0.02; 0.07] 0.311
Any adverse event leading to study drug discontinuation					
Interaction test	**p = 0.813**				
Pre-pandemic, n (%)	13 (16.5)	14 (16.9)	0.97 [0.42; 2.22] 0.944	0.98 [0.49; 1.94] 0.944	-0.00 [-0.12; 0.11] 0.944
Pre- and during-pandemic, n (%)	2 (3.2)	3 (5.1)	0.62 [0.10; 3.86] 0.611	0.63 [0.11; 3.66] 0.611	-0.02 [-0.09; 0.05] 0.609
During-pandemic, n (%)	5 (12.2)	4 (9.5)	1.32 [0.33; 5.31] 0.696	1.28 [0.37; 4.44] 0.697	0.03 [-0.11; 0.16] 0.696

N: Number of patients
n (%): Number and percentage of patients with event
N.E.: Not estimable
CI: Confidence interval
OR: Odds ratio
RR: Relative risk
RD: Risk difference
.....

Imputation method: None

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.
RR and RD with Wald CI and p-value calculated directly.

Table 29.7 Adverse events overview by race (SAF), binary analysis

	Treatment Groups		Comparison		
Adverse events overview by race (SAF)	**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			
Any adverse event					
Interaction test	**p = 0.704**				
Caucasian, n (%)	79 (91.9)	81 (90.0)	1.25 [0.45; 3.53] 0.668	1.02 [0.93; 1.12] 0.667	0.02 [-0.07; 0.10] 0.667
Black, n (%)	20 (87.0)	23 (92.0)	0.58 [0.09; 3.83] 0.571	0.95 [0.78; 1.15] 0.573	-0.05 [-0.22; 0.12] 0.570
Asian, n (%)	47 (85.5)	38 (84.4)	1.08 [0.36; 3.25] 0.888	1.01 [0.86; 1.19] 0.888	0.01 [-0.13; 0.15] 0.888
Unknown or other, n (%)	17 (94.4)	20 (83.3)	3.40 [0.35; 33.39] 0.294	1.13 [0.92; 1.40] 0.245	0.11 [-0.07; 0.29] 0.234
Any serious adverse event					
Interaction test	**p = 0.177**				
Caucasian, n (%)	28 (32.6)	30 (33.3)	0.97 [0.51; 1.81] 0.913	0.98 [0.64; 1.49] 0.913	-0.01 [-0.15; 0.13] 0.913
Black, n (%)	11 (47.8)	15 (60.0)	0.61 [0.19; 1.92] 0.399	0.80 [0.47; 1.36] 0.405	-0.12 [-0.40; 0.16] 0.395
Asian, n (%)	20 (36.4)	10 (22.2)	2.00 [0.82; 4.88] 0.128	1.64 [0.86; 3.13] 0.137	0.14 [-0.03; 0.32] 0.115
Unknown or other, n (%)	9 (50.0)	6 (25.0)	3.00 [0.81; 11.08] 0.099	2.00 [0.87; 4.60] 0.103	0.25 [-0.04; 0.54] 0.090
Any severe adverse event					
Interaction test	**p = 0.591**				
Caucasian, n (%)	12 (14.0)	16 (17.8)	0.75 [0.33; 1.69] 0.489	0.78 [0.39; 1.56] 0.490	-0.04 [-0.15; 0.07] 0.487
Black, n (%)	6 (26.1)	12 (48.0)	0.38 [0.11; 1.29] 0.122	0.54 [0.24; 1.21] 0.135	-0.22 [-0.48; 0.05] 0.106

	Treatment Groups		Comparison		
Adverse events overview by race (SAF)	**LCZ696 (N=182)**	**Enalapril (N=184)**	**OR [95% CI] p-value**	**RR [95% CI] p-value**	**RD [95% CI] p-value**
Asian, n (%)	11 (20.0)	8 (17.8)	1.16 [0.42; 3.18] 0.778	1.13 [0.49; 2.56] 0.779	0.02 [-0.13; 0.18] 0.777
Unknown or other, n (%)	2 (11.1)	4 (16.7)	0.63 [0.10; 3.86] 0.613	0.67 [0.14; 3.25] 0.616	-0.06 [-0.26; 0.15] 0.601
Any adverse event leading to study drug discontinuation					
Interaction test	**p = 0.370**				
Caucasian, n (%)	7 (8.1)	4 (4.4)	1.91 [0.54; 6.76] 0.318	1.83 [0.56; 6.03] 0.320	0.04 [-0.03; 0.11] 0.313
Black, n (%)	4 (17.4)	9 (36.0)	0.37 [0.10; 1.45] 0.154	0.48 [0.17; 1.36] 0.167	-0.19 [-0.43; 0.06] 0.135
Asian, n (%)	8 (14.5)	6 (13.3)	1.11 [0.35; 3.46] 0.862	1.09 [0.41; 2.91] 0.862	0.01 [-0.12; 0.15] 0.862
Unknown or other, n (%)	1 (5.6)	2 (8.3)	0.65 [0.05; 7.75] 0.731	0.67 [0.07; 6.79] 0.732	-0.03 [-0.18; 0.13] 0.722

N: Number of patients
n (%): Number and percentage of patients with event
CI: Confidence interval
OR: Odds ratio
RR: Relative risk
RD: Risk difference
.....

Imputation method: None

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

30 Adverse events by SOC and PT

Table 30.1 Adverse events by SOC and PT (SAF), binary analysis

	Treatment Groups		Comparison		
Adverse events by SOC and PT (SAF)	**LCZ696 (N=182)**	**Enalapril (N=184)**	**OR [95% CI] p-value**	**RR [95% CI] p-value**	**RD [95% CI] p-value**
Infections and infestations, n (%)	115 (63.2)	108 (58.7)	1.21 [0.79; 1.84] 0.379	1.08 [0.91; 1.27] 0.379	0.04 [-0.05; 0.14] 0.378
Upper respiratory tract infection, n (%)	39 (21.4)	35 (19.0)	1.16 [0.70; 1.93] 0.567	1.13 [0.75; 1.69] 0.567	0.02 [-0.06; 0.11] 0.566
Nasopharyngitis, n (%)	29 (15.9)	16 (8.7)	1.99 [1.04; 3.81] 0.038 *	1.83 [1.03; 3.26] 0.039 *	0.07 [0.01; 0.14] 0.034 *
Influenza, n (%)	13 (7.1)	14 (7.6)	0.93 [0.43; 2.05] 0.865	0.94 [0.45; 1.94] 0.865	-0.00 [-0.06; 0.05] 0.865
Bronchitis, n (%)	12 (6.6)	9 (4.9)	1.37 [0.56; 3.34] 0.485	1.35 [0.58; 3.12] 0.486	0.02 [-0.03; 0.06] 0.484
Gastroenteritis, n (%)	10 (5.5)	12 (6.5)	0.83 [0.35; 1.98] 0.680	0.84 [0.37; 1.90] 0.680	-0.01 [-0.06; 0.04] 0.679
Rhinitis, n (%)	8 (4.4)	10 (5.4)	0.80 [0.31; 2.08] 0.646	0.81 [0.33; 2.00] 0.646	-0.01 [-0.05; 0.03] 0.645
General disorders and administration site conditions, n (%)	76 (41.8)	61 (33.2)	1.45 [0.94; 2.21] 0.089	1.26 [0.96; 1.65] 0.091	0.09 [-0.01; 0.18] 0.088
Pyrexia, n (%)	39 (21.4)	33 (17.9)	1.25 [0.74; 2.09] 0.401	1.19 [0.79; 1.81] 0.402	0.03 [-0.05; 0.12] 0.400
Fatigue, n (%)	19 (10.4)	14 (7.6)	1.42 [0.69; 2.92] 0.346	1.37 [0.71; 2.65] 0.347	0.03 [-0.03; 0.09] 0.344
Gastrointestinal disorders, n (%)	72 (39.6)	78 (42.4)	0.89 [0.59; 1.35] 0.582	0.93 [0.73; 1.19] 0.582	-0.03 [-0.13; 0.07] 0.582
Vomiting, n (%)	33 (18.1)	39 (21.2)	0.82 [0.49; 1.38] 0.461	0.86 [0.56; 1.30] 0.462	-0.03 [-0.11; 0.05] 0.461
Diarrhoea, n (%)	24 (13.2)	22 (12.0)	1.12 [0.60; 2.08] 0.723	1.10 [0.64; 1.89] 0.723	0.01 [-0.06; 0.08] 0.723
Abdominal pain, n (%)	15 (8.2)	11 (6.0)	1.41 [0.63; 3.16] 0.401	1.38 [0.65; 2.92] 0.402	0.02 [-0.03; 0.08] 0.399

	Treatment Groups		Comparison		
Adverse events by SOC and PT (SAF)	**LCZ696 (N=182)**	**Enalapril (N=184)**	**OR [95% CI] p-value**	**RR [95% CI] p-value**	**RD [95% CI] p-value**
Nausea, n (%)	10 (5.5)	9 (4.9)	1.13 [0.45; 2.85] 0.795	1.12 [0.47; 2.70] 0.795	0.01 [-0.04; 0.05] 0.795
Abdominal pain upper, n (%)	6 (3.3)	10 (5.4)	0.59 [0.21; 1.67] 0.322	0.61 [0.23; 1.63] 0.323	-0.02 [-0.06; 0.02] 0.316
Respiratory, thoracic and mediastinal disorders, n (%)	62 (34.1)	63 (34.2)	0.99 [0.64; 1.53] 0.972	0.99 [0.75; 1.32] 0.972	-0.00 [-0.10; 0.10] 0.972
Cough, n (%)	36 (19.8)	37 (20.1)	0.98 [0.59; 1.64] 0.937	0.98 [0.65; 1.48] 0.937	-0.00 [-0.09; 0.08] 0.937
Epistaxis, n (%)	10 (5.5)	6 (3.3)	1.72 [0.61; 4.85] 0.301	1.68 [0.63; 4.54] 0.302	0.02 [-0.02; 0.06] 0.296
Cardiac disorders, n (%)	48 (26.4)	46 (25.0)	1.07 [0.67; 1.72] 0.764	1.05 [0.74; 1.50] 0.764	0.01 [-0.08; 0.10] 0.764
Cardiac failure, n (%)	26 (14.3)	26 (14.1)	1.01 [0.56; 1.82] 0.966	1.01 [0.61; 1.67] 0.966	0.00 [-0.07; 0.07] 0.966
Nervous system disorders, n (%)	48 (26.4)	43 (23.4)	1.17 [0.73; 1.89] 0.506	1.13 [0.79; 1.61] 0.507	0.03 [-0.06; 0.12] 0.506
Dizziness, n (%)	23 (12.6)	15 (8.2)	1.63 [0.82; 3.23] 0.163	1.55 [0.84; 2.87] 0.164	0.04 [-0.02; 0.11] 0.159
Headache, n (%)	22 (12.1)	20 (10.9)	1.13 [0.59; 2.15] 0.715	1.11 [0.63; 1.97] 0.715	0.01 [-0.05; 0.08] 0.715
Investigations, n (%)	39 (21.4)	43 (23.4)	0.89 [0.55; 1.46] 0.656	0.92 [0.63; 1.34] 0.656	-0.02 [-0.10; 0.07] 0.656
Glomerular filtration rate decreased, n (%)	9 (4.9)	11 (6.0)	0.82 [0.33; 2.02] 0.664	0.83 [0.35; 1.95] 0.664	-0.01 [-0.06; 0.04] 0.663
Skin and subcutaneous tissue disorders, n (%)	33 (18.1)	23 (12.5)	1.55 [0.87; 2.76] 0.137	1.45 [0.89; 2.37] 0.138	0.06 [-0.02; 0.13] 0.134
Vascular disorders, n (%)	27 (14.8)	25 (13.6)	1.11 [0.62; 1.99] 0.732	1.09 [0.66; 1.81] 0.732	0.01 [-0.06; 0.08] 0.732
Hypotension, n (%)	23 (12.6)	22 (12.0)	1.07 [0.57; 1.99] 0.843	1.06 [0.61; 1.83] 0.843	0.01 [-0.06; 0.07] 0.843
Metabolism and nutrition disorders, n (%)	26 (14.3)	28 (15.2)	0.93 [0.52; 1.66] 0.802	0.94 [0.57; 1.54] 0.802	-0.01 [-0.08; 0.06] 0.802

	Treatment Groups		Comparison		
Adverse events by SOC and PT (SAF)	**LCZ696 (N=182)**	**Enalapril (N=184)**	**OR [95% CI] p-value**	**RR [95% CI] p-value**	**RD [95% CI] p-value**
Musculoskeletal and connective tissue disorders, n (%)	19 (10.4)	11 (6.0)	1.83 [0.85; 3.97] 0.124	1.75 [0.86; 3.57] 0.126	0.04 [-0.01; 0.10] 0.119
Renal and urinary disorders, n (%)	19 (10.4)	9 (4.9)	2.27 [1.00; 5.15] 0.051	2.13 [0.99; 4.59] 0.052	0.06 [0.00; 0.11] 0.045 *
Injury, poisoning and procedural complications, n (%)	14 (7.7)	25 (13.6)	0.53 [0.27; 1.06] 0.071	0.57 [0.30; 1.05] 0.073	-0.06 [-0.12; 0.00] 0.066
Psychiatric disorders, n (%)	12 (6.6)	14 (7.6)	0.86 [0.39; 1.91] 0.706	0.87 [0.41; 1.82] 0.706	-0.01 [-0.06; 0.04] 0.705
Blood and lymphatic system disorders, n (%)	11 (6.0)	8 (4.3)	1.42 [0.56; 3.60] 0.467	1.39 [0.57; 3.38] 0.467	0.02 [-0.03; 0.06] 0.465
Reproductive system and breast disorders, n (%)	3 (1.6)	10 (5.4)	0.29 [0.08; 1.08] 0.065	0.30 [0.08; 1.08] 0.066	-0.04 [-0.08; -0.00] 0.049 *

N: Number of patients
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: None

Analysis method:
OR with Wald CI and p-value obtained from logistic regression model: logit(proportion) = treatment.
RR and RD with Wald CI and p-value calculated directly.

Table 30.2 Adverse events by SOC and PT, by age group (SAF), binary analysis

	Treatment Groups		Comparison		
Adverse events by SOC and PT, by age group (SAF)	**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			
Nasopharyngitis					
Interaction test	**p = 0.498**				
6 years to < 18 years, n (%)	14 (12.8)	6 (5.4)	2.58 [0.95; 6.98] 0.062	2.38 [0.95; 5.96] 0.065	0.07 [-0.00; 0.15] 0.054
1 year to < 6 years, n (%)	15 (20.5)	10 (13.7)	1.63 [0.68; 3.91] 0.275	1.50 [0.72; 3.12] 0.277	0.07 [-0.05; 0.19] 0.270

N: Number of patients
n (%): Number and percentage of patients with event
CI: Confidence interval
OR: Odds ratio
RR: Relative risk
RD: Risk difference
.....

Imputation method: None

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.
RR and RD with Wald CI and p-value calculated directly.

Table 30.3 Adverse events by SOC and PT, by NYHA/Ross class (SAF), binary analysis

	Treatment Groups		Comparison		
Adverse events by SOC and PT, by NYHA/Ross class (SAF)	**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			
Nasopharyngitis					
Interaction test	**p = 0.543**				
Class I/II, n (%)	27 (17.2)	14 (8.9)	2.12 [1.07; 4.22] 0.032 *	1.93 [1.05; 3.54] 0.034 *	0.08 [0.01; 0.16] 0.028 *
Class III/IV, n (%)	2 (8.0)	2 (7.4)	1.09 [0.14; 8.36] 0.936	1.08 [0.16; 7.10] 0.936	0.01 [-0.14; 0.15] 0.936

N: Number of patients
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: None

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.
RR and RD with Wald CI and p-value calculated directly.

Table 30.4 Adverse events by SOC and PT, by region (SAF), binary analysis

	Treatment Groups		Comparison		
Adverse events by SOC and PT, by region (SAF)	**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			
Nasopharyngitis					
Interaction test	**p = 0.954**				
America, n (%)	7 (12.1)	5 (7.2)	1.76 [0.53; 5.86] 0.359	1.67 [0.56; 4.97] 0.360	0.05 [-0.06; 0.15] 0.362
Europe, n (%)	9 (15.5)	5 (9.1)	1.84 [0.57; 5.87] 0.305	1.71 [0.61; 4.78] 0.309	0.06 [-0.06; 0.18] 0.295
Asia/Pacific and other, n (%)	13 (19.7)	6 (10.0)	2.21 [0.78; 6.24] 0.135	1.97 [0.80; 4.85] 0.141	0.10 [-0.03; 0.22] 0.120

N: Number of patients
n (%): Number and percentage of patients with event
CI: Confidence interval
OR: Odds ratio
RR: Relative risk
RD: Risk difference
.....

Imputation method: None

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

Table 30.5 Adverse events by SOC and PT, by gender (SAF), binary analysis

	Treatment Groups		Comparison		
Adverse events by SOC and PT, by gender (SAF)	**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			
Nasopharyngitis					
Interaction test	**p = 0.705**				
Male, n (%)	11 (12.5)	7 (7.7)	1.71 [0.63; 4.65] 0.289	1.63 [0.66; 4.00] 0.291	0.05 [-0.04; 0.14] 0.285
Female, n (%)	18 (19.1)	9 (9.7)	2.21 [0.94; 5.21] 0.070	1.98 [0.94; 4.18] 0.073	0.09 [-0.00; 0.19] 0.063

N: Number of patients
n (%): Number and percentage of patients with event
CI: Confidence interval
OR: Odds ratio
RR: Relative risk
RD: Risk difference
.....

Imputation method: None

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

Table 30.6 Adverse events by SOC and PT, by COVID-19 period (SAF), binary analysis

	Treatment Groups		Comparison		
Adverse events by SOC and PT, by COVID-19 period (SAF)	**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			
Nasopharyngitis					
Interaction test	**p = 0.573**				
Pre-pandemic, n (%)	15 (19.0)	7 (8.4)	2.54 [0.98; 6.62] 0.056	2.25 [0.97; 5.23] 0.059	0.11 [0.00; 0.21] 0.049 *
Pre- and during-pandemic, n (%)	9 (14.5)	7 (11.9)	1.26 [0.44; 3.64] 0.667	1.22 [0.49; 3.07] 0.668	0.03 [-0.09; 0.15] 0.666
During-pandemic, n (%)	5 (12.2)	2 (4.8)	2.78 [0.51; 15.21] 0.239	2.56 [0.53; 12.46] 0.244	0.07 [-0.04; 0.19] 0.221

N: Number of patients
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: None

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.
RR and RD with Wald CI and p-value calculated directly.

Table 30.7 Adverse events by SOC and PT, by race (SAF), binary analysis

	Treatment Groups		Comparison		
Adverse events by SOC and PT, by race (SAF)	**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			
Nasopharyngitis					
Interaction test	**p = 0.555**				
Caucasian, n (%)	12 (14.0)	5 (5.6)	2.76 [0.93; 8.19] 0.068	2.51 [0.92; 6.83] 0.071	0.08 [-0.00; 0.17] 0.059
Black, n (%)	1 (4.3)	1 (4.0)	1.09 [0.06; 18.51] 0.952	1.09 [0.07; 16.39] 0.952	0.00 [-0.11; 0.12] 0.952
Asian, n (%)	13 (23.6)	5 (11.1)	2.48 [0.81; 7.58] 0.112	2.13 [0.82; 5.52] 0.121	0.13 [-0.02; 0.27] 0.091
Unknown or other, n (%)	3 (16.7)	5 (20.8)	0.76 [0.16; 3.70] 0.734	0.80 [0.22; 2.92] 0.735	-0.04 [-0.28; 0.20] 0.730

N: Number of patients
n (%): Number and percentage of patients with event
CI: Confidence interval
OR: Odds ratio
RR: Relative risk
RD: Risk difference
.....

Imputation method: None

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

31 Serious adverse events by SOC and PT

Table 31.1 Serious adverse events by SOC and PT (SAF), binary analysis

	Treatment Groups		Comparison		
Serious adverse events by SOC and PT (SAF)	**LCZ696 (N=182)**	**Enalapril (N=184)**	**OR [95% CI] p-value**	**RR [95% CI] p-value**	**RD [95% CI] p-value**
Cardiac disorders, n (%)	36 (19.8)	33 (17.9)	1.13 [0.67; 1.91] 0.652	1.10 [0.72; 1.69] 0.652	0.02 [-0.06; 0.10] 0.652
Cardiac failure, n (%)	23 (12.6)	22 (12.0)	1.07 [0.57; 1.99] 0.843	1.06 [0.61; 1.83] 0.843	0.01 [-0.06; 0.07] 0.843
Infections and infestations, n (%)	20 (11.0)	19 (10.3)	1.07 [0.55; 2.08] 0.837	1.06 [0.59; 1.93] 0.837	0.01 [-0.06; 0.07] 0.837
Gastrointestinal disorders, n (%)	10 (5.5)	5 (2.7)	2.08 [0.70; 6.21] 0.189	2.02 [0.70; 5.80] 0.190	0.03 [-0.01; 0.07] 0.180
Respiratory, thoracic and mediastinal disorders, n (%)	10 (5.5)	5 (2.7)	2.08 [0.70; 6.21] 0.189	2.02 [0.70; 5.80] 0.190	0.03 [-0.01; 0.07] 0.180
Nervous system disorders, n (%)	4 (2.2)	12 (6.5)	0.32 [0.10; 1.02] 0.054	0.34 [0.11; 1.03] 0.055	-0.04 [-0.08; -0.00] 0.041 *

N: Number of patients
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: None

Analysis method:
OR with Wald CI and p-value obtained from logistic regression model: logit(proportion) = treatment.
RR and RD with Wald CI and p-value calculated directly.

Table 31.2 Serious adverse events by SOC and PT, by age group (SAF), binary analysis

There is no data meeting the display criteria for this table.

Table 31.3 Serious adverse events by SOC and PT, by NYHA/Ross class (SAF), binary analysis

There is no data meeting the display criteria for this table.

Table 31.4 Serious adverse events by SOC and PT, by region (SAF), binary analysis

There is no data meeting the display criteria for this table.

Table 31.5 Serious adverse events by SOC and PT, by gender (SAF), binary analysis

There is no data meeting the display criteria for this table.

Table 31.6 Serious adverse events by SOC and PT, by COVID-19 period (SAF), binary analysis

There is no data meeting the display criteria for this table.

Table 31.7 Serious adverse events by SOC and PT, by race (SAF), binary analysis

There is no data meeting the display criteria for this table.

32 Severe adverse events by SOC and PT

Table 32.1 Severe adverse events by SOC and PT (SAF), binary analysis

	Treatment Groups		Comparison		
Severe adverse events by SOC and PT (SAF)	**LCZ696 (N=182)**	**Enalapril (N=184)**	**OR [95% CI] p-value**	**RR [95% CI] p-value**	**RD [95% CI] p-value**
Cardiac disorders, n (%)	20 (11.0)	27 (14.7)	0.72 [0.39; 1.33] 0.294	0.75 [0.44; 1.29] 0.295	-0.04 [-0.11; 0.03] 0.291
Cardiac failure, n (%)	11 (6.0)	18 (9.8)	0.59 [0.27; 1.29] 0.189	0.62 [0.30; 1.27] 0.191	-0.04 [-0.09; 0.02] 0.184

N: Number of patients
n (%): Number and percentage of patients with event
CI: Confidence interval
OR: Odds ratio
RR: Relative risk
RD: Risk difference
.....

Imputation method: None

Analysis method:
OR with Wald CI and p-value obtained from logistic regression model: logit(proportion) = treatment.
RR and RD with Wald CI and p-value calculated directly.

Table 32.2 Severe adverse events by SOC and PT, by age group (SAF), binary analysis

There is no data meeting the display criteria for this table.

Table 32.3 Severe adverse events by SOC and PT, by NYHA/Ross class (SAF), binary analysis

There is no data meeting the display criteria for this table.

Table 32.4 Severe adverse events by SOC and PT, by region (SAF), binary analysis

There is no data meeting the display criteria for this table.

Table 32.5 Severe adverse events by SOC and PT, by gender (SAF), binary analysis

There is no data meeting the display criteria for this table.

Table 32.6 Severe adverse events by SOC and PT, by COVID-19 period (SAF), binary analysis

There is no data meeting the display criteria for this table.

Table 32.7 Severe adverse events by SOC and PT, by race (SAF), binary analysis

There is no data meeting the display criteria for this table.

33 Adverse events leading to study discontinuation, by SOC and PT

Table 33.1 Adverse events leading to study discontinuation, by SOC and PT (SAF), frequency table

	Treatment groups	
Adverse events leading to study discontinuation, by SOC and PT (SAF)	**LCZ696 (N=182)**	**Enalapril (N=184)**
Cardiac disorders, n (%)	5 (2.7)	8 (4.3)
Cardiac arrest, n (%)	1 (0.5)	4 (2.2)
Cardiac failure, n (%)	1 (0.5)	2 (1.1)
Cardiac failure acute, n (%)	1 (0.5)	2 (1.1)
Cardiac failure congestive, n (%)	1 (0.5)	1 (0.5)
Cardio-respiratory arrest, n (%)	1 (0.5)	0 (0.0)
Arrhythmia, n (%)	0 (0.0)	1 (0.5)
Respiratory, thoracic and mediastinal disorders, n (%)	2 (1.1)	2 (1.1)
Acute respiratory failure, n (%)	1 (0.5)	0 (0.0)
Dyspnoea, n (%)	1 (0.5)	0 (0.0)
Respiratory distress, n (%)	0 (0.0)	1 (0.5)
Respiratory failure, n (%)	0 (0.0)	1 (0.5)
General disorders and administration site conditions, n (%)	1 (0.5)	2 (1.1)
Sudden death, n (%)	1 (0.5)	0 (0.0)
Death, n (%)	0 (0.0)	1 (0.5)
Pyrexia, n (%)	0 (0.0)	1 (0.5)
Renal and urinary disorders, n (%)	1 (0.5)	1 (0.5)
Dysuria, n (%)	1 (0.5)	0 (0.0)
Acute kidney injury, n (%)	1 (0.5)	0 (0.0)
Renal failure, n (%)	0 (0.0)	1 (0.5)
Infections and infestations, n (%)	0 (0.0)	1 (0.5)
Viral upper respiratory tract infection, n (%)	0 (0.0)	1 (0.5)
Encephalopathy, n (%)	0 (0.0)	0 (0.0)
Nervous system disorders, n (%)	0 (0.0)	2 (1.1)
Brain injury, n (%)	0 (0.0)	1 (0.5)
Hypoxic-ischaemic encephalopathy, n (%)	0 (0.0)	1 (0.5)
Skin and subcutaneous tissue disorders, n (%)	0 (0.0)	1 (0.5)
Dermatitis allergic, n (%)	0 (0.0)	1 (0.5)
Vascular disorders, n (%)	0 (0.0)	2 (1.1)
Circulatory collapse, n (%)	0 (0.0)	1 (0.5)

	Treatment groups	
Adverse events leading to study discontinuation, by SOC and PT (SAF)	**LCZ696 (N=182)**	**Enalapril (N=184)**
Hypotension, n (%)	0 (0.0)	1 (0.5)

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

34 Adverse events leading to study drug discontinuation, by SOC and PT

Table 34.1 Adverse events leading to study drug discontinuation, by SOC and PT (SAF), frequency table

	Treatment groups	
Adverse events leading to study drug discontinuation, by SOC and PT (SAF)	**LCZ696 (N=182)**	**Enalapril (N=184)**
Cardiac disorders, n (%)	13 (7.1)	12 (6.5)
Cardiac failure, n (%)	7 (3.8)	11 (6.0)
Cardiac failure congestive, n (%)	2 (1.1)	0 (0.0)
Bradycardia, n (%)	1 (0.5)	0 (0.0)
Cardiac arrest, n (%)	1 (0.5)	0 (0.0)
Cardiac failure acute, n (%)	1 (0.5)	1 (0.5)
Ventricular dysfunction, n (%)	1 (0.5)	0 (0.0)
Cardiac ventricular thrombosis, n (%)	0 (0.0)	1 (0.5)
Hepatobiliary disorders, n (%)	2 (1.1)	0 (0.0)
Hepatic function abnormal, n (%)	1 (0.5)	0 (0.0)
Hepatomegaly, n (%)	1 (0.5)	0 (0.0)
General disorders and administration site conditions, n (%)	1 (0.5)	2 (1.1)
Sudden death, n (%)	1 (0.5)	0 (0.0)
Chest pain, n (%)	0 (0.0)	1 (0.5)
Death, n (%)	0 (0.0)	1 (0.5)
Investigations, n (%)	1 (0.5)	0 (0.0)
Hepatic enzyme increased, n (%)	1 (0.5)	0 (0.0)
Nervous system disorders, n (%)	1 (0.5)	2 (1.1)
Cerebral infarction, n (%)	1 (0.5)	0 (0.0)
Brain injury, n (%)	0 (0.0)	1 (0.5)
Hypoxic-ischaemic encephalopathy, n (%)	0 (0.0)	1 (0.5)
Renal and urinary disorders, n (%)	1 (0.5)	1 (0.5)
Renal failure, n (%)	1 (0.5)	0 (0.0)
Renal impairment, n (%)	0 (0.0)	1 (0.5)
Respiratory, thoracic and mediastinal disorders, n (%)	1 (0.5)	2 (1.1)
Hypoxia, n (%)	1 (0.5)	0 (0.0)
Cough, n (%)	0 (0.0)	1 (0.5)
Respiratory distress, n (%)	0 (0.0)	1 (0.5)
Vascular disorders, n (%)	1 (0.5)	1 (0.5)
Hypotension, n (%)	1 (0.5)	0 (0.0)
Circulatory collapse, n (%)	0 (0.0)	1 (0.5)
Gastrointestinal disorders, n (%)	0 (0.0)	2 (1.1)

	Treatment groups	
Adverse events leading to study drug discontinuation, by SOC and PT (SAF)	**LCZ696 (N=182)**	**Enalapril (N=184)**
Abdominal pain upper, n (%)	0 (0.0)	1 (0.5)
Vomiting, n (%)	0 (0.0)	1 (0.5)
Metabolism and nutrition disorders, n (%)	0 (0.0)	1 (0.5)
Hyperkalaemia, n (%)	0 (0.0)	1 (0.5)
Musculoskeletal and connective tissue disorders, n (%)	0 (0.0)	1 (0.5)
Rhabdomyolysis, n (%)	0 (0.0)	1 (0.5)
Skin and subcutaneous tissue disorders, n (%)	0 (0.0)	2 (1.1)
Angioedema, n (%)	0 (0.0)	1 (0.5)
Dermatitis allergic, n (%)	0 (0.0)	1 (0.5)

N: Number of patients
n (%): Number and percentage of patients with event
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35 Adverse events of special interest

Table 35.1 Adverse events of special interest (SAF), binary analysis

	Treatment Groups		Comparison		
Adverse events of special interest (SAF)	**LCZ696 (N=182)**	**Enalapril (N=184)**	**OR [95% CI] p-value**	**RR [95% CI] p-value**	**RD [95% CI] p-value**
Anaphylaxis, n (%)	1 (0.5)	1 (0.5)	1.01 [0.06; 16.29] 0.994	1.01 [0.06; 16.04] 0.994	0.00 [-0.02; 0.02] 0.994
Serious anaphylaxis, n (%)	0 (0.0)	1 (0.5)	N.E.	0.34 [0.01; 8.22] 0.504	-0.01 [-0.02; 0.01] 0.316
Severe anaphylaxis, n (%)	0 (0.0)	1 (0.5)	N.E.	0.34 [0.01; 8.22] 0.504	-0.01 [-0.02; 0.01] 0.316
Angioedema, n (%)	0 (0.0)	1 (0.5)	N.E.	0.34 [0.01; 8.22] 0.504	-0.01 [-0.02; 0.01] 0.316
Serious angioedema, n (%)	0 (0.0)	1 (0.5)	N.E.	0.34 [0.01; 8.22] 0.504	-0.01 [-0.02; 0.01] 0.316
Severe angioedema, n (%)	0 (0.0)	1 (0.5)	N.E.	0.34 [0.01; 8.22] 0.504	-0.01 [-0.02; 0.01] 0.316
Change in bone growth and density, n (%)	2 (1.1)	2 (1.1)	1.01 [0.14; 7.26] 0.991	1.01 [0.14; 7.10] 0.991	0.00 [-0.02; 0.02] 0.991
Serious change in bone growth and density, n (%)	1 (0.5)	0 (0.0)	N.E.	3.03 [0.12; 73.96] 0.496	0.01 [-0.01; 0.02] 0.316
Severe change in bone growth and density, n (%)	1 (0.5)	0 (0.0)	N.E.	3.03 [0.12; 73.96] 0.496	0.01 [-0.01; 0.02] 0.316
Embryo-fetal toxicity or lethality, n (%)	1 (0.5)	1 (0.5)	1.01 [0.06; 16.29] 0.994	1.01 [0.06; 16.04] 0.994	0.00 [-0.02; 0.02] 0.994
Serious embryo-fetal toxicity or lethality, n (%)	1 (0.5)	1 (0.5)	1.01 [0.06; 16.29] 0.994	1.01 [0.06; 16.04] 0.994	0.00 [-0.02; 0.02] 0.994
Hepatotoxicity, n (%)	15 (8.2)	10 (5.4)	1.56 [0.68; 3.58] 0.290	1.52 [0.70; 3.29] 0.291	0.03 [-0.02; 0.08] 0.287
Serious hepatotoxicity, n (%)	1 (0.5)	0 (0.0)	N.E.	3.03 [0.12; 73.96] 0.496	0.01 [-0.01; 0.02] 0.316
Severe hepatotoxicity, n (%)	0 (0.0)	1 (0.5)	N.E.	0.34 [0.01; 8.22] 0.504	-0.01 [-0.02; 0.01] 0.316

	Treatment Groups		Comparison		
Adverse events of special interest (SAF)	**LCZ696 (N=182)**	**Enalapril (N=184)**	**OR [95% CI] p-value**	**RR [95% CI] p-value**	**RD [95% CI] p-value**
Hyperkalaemia, n (%)	9 (4.9)	9 (4.9)	1.01 [0.39; 2.61] 0.981	1.01 [0.41; 2.49] 0.981	0.00 [-0.04; 0.04] 0.981
Serious hyperkalaemia, n (%)	0 (0.0)	2 (1.1)	N.E.	0.20 [0.01; 4.18] 0.301	-0.01 [-0.03; 0.00] 0.155
Severe hyperkalaemia, n (%)	0 (0.0)	2 (1.1)	N.E.	0.20 [0.01; 4.18] 0.301	-0.01 [-0.03; 0.00] 0.155
Hypersensitivity (Narrow SMQ), n (%)	22 (12.1)	21 (11.4)	1.07 [0.56; 2.02] 0.841	1.06 [0.60; 1.86] 0.841	0.01 [-0.06; 0.07] 0.841
Serious hypersensitivity (Narrow SMQ), n (%)	0 (0.0)	2 (1.1)	N.E.	0.20 [0.01; 4.18] 0.301	-0.01 [-0.03; 0.00] 0.155
Severe hypersensitivity (Narrow SMQ), n (%)	0 (0.0)	2 (1.1)	N.E.	0.20 [0.01; 4.18] 0.301	-0.01 [-0.03; 0.00] 0.155
Hypotension, n (%)	43 (23.6)	40 (21.7)	1.11 [0.68; 1.82] 0.666	1.09 [0.74; 1.59] 0.667	0.02 [-0.07; 0.10] 0.666
Serious hypotension, n (%)	5 (2.7)	2 (1.1)	2.57 [0.49; 13.42] 0.263	2.53 [0.50; 12.86] 0.264	0.02 [-0.01; 0.04] 0.246
Severe hypotension, n (%)	2 (1.1)	2 (1.1)	1.01 [0.14; 7.26] 0.991	1.01 [0.14; 7.10] 0.991	0.00 [-0.02; 0.02] 0.991
Malignancy, n (%)	1 (0.5)	0 (0.0)	N.E.	3.03 [0.12; 73.96] 0.496	0.01 [-0.01; 0.02] 0.316
Renal impairment (Narrow SMQ), n (%)	12 (6.6)	8 (4.3)	1.55 [0.62; 3.89] 0.348	1.52 [0.63; 3.62] 0.349	0.02 [-0.02; 0.07] 0.345
Serious renal impairment (Narrow SMQ), n (%)	3 (1.6)	3 (1.6)	1.01 [0.20; 5.08] 0.989	1.01 [0.21; 4.94] 0.989	0.00 [-0.03; 0.03] 0.989

	Treatment Groups		Comparison		
Adverse events of special interest (SAF)	**LCZ696 (N=182)**	**Enalapril (N=184)**	**OR [95% CI] p-value**	**RR [95% CI] p-value**	**RD [95% CI] p-value**
Severe renal impairment (Narrow SMQ), n (%)	3 (1.6)	3 (1.6)	1.01 [0.20; 5.08] 0.989	1.01 [0.21; 4.94] 0.989	0.00 [-0.03; 0.03] 0.989

N: Number of patients
n (%): Number and percentage of patients with event
N.E.: Not estimable
CI: Confidence interval
OR: Odds ratio
RR: Relative risk
RD: Risk difference
.....

Imputation method: None

Analysis method:
OR with Wald CI and p-value obtained from logistic regression model: logit(proportion) = treatment.
RR and RD with Wald CI and p-value calculated directly.

The table shows all pre-specified AESIs which occured in at least one patient.

Table 35.2 Adverse events of special interest by age group (SAF), binary analysis

	Treatment Groups		Comparison		
Adverse events of special interest by age group (SAF)	**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			
Hepatotoxicity					
Interaction test	**p = 0.253**				
6 years to < 18 years, n (%)	12 (11.0)	6 (5.4)	2.16 [0.78; 5.99] 0.137	2.04 [0.79; 5.23] 0.140	0.06 [-0.02; 0.13] 0.129
1 year to < 6 years, n (%)	3 (4.1)	4 (5.5)	0.74 [0.16; 3.43] 0.699	0.75 [0.17; 3.23] 0.700	-0.01 [-0.08; 0.06] 0.698
Hypersensitivity (Narrow SMQ)					
Interaction test	**p = 0.866**				
6 years to < 18 years, n (%)	13 (11.9)	12 (10.8)	1.12 [0.49; 2.57] 0.794	1.10 [0.53; 2.31] 0.794	0.01 [-0.07; 0.10] 0.794
1 year to < 6 years, n (%)	9 (12.3)	9 (12.3)	1.00 [0.37; 2.68] 1.000	1.00 [0.42; 2.38] 1.000	0.00 [-0.11; 0.11] 1.000
Hypotension					
Interaction test	**p = 0.928**				
6 years to < 18 years, n (%)	36 (33.0)	34 (30.6)	1.12 [0.63; 1.97] 0.703	1.08 [0.73; 1.59] 0.703	0.02 [-0.10; 0.15] 0.703
1 year to < 6 years, n (%)	7 (9.6)	6 (8.2)	1.18 [0.38; 3.71] 0.772	1.17 [0.41; 3.30] 0.772	0.01 [-0.08; 0.11] 0.771
Renal impairment (Narrow SMQ)					
Interaction test	**p = 0.450**				
6 years to < 18 years, n (%)	7 (6.4)	6 (5.4)	1.20 [0.39; 3.70] 0.749	1.19 [0.41; 3.42] 0.750	0.01 [-0.05; 0.07] 0.749

	Treatment Groups		Comparison		
Adverse events of special interest by age group (SAF)	**LCZ696 (N=182)**	**Enalapril (N=184)**	**OR [95% CI] p-value**	**RR [95% CI] p-value**	**RD [95% CI] p-value**
1 year to < 6 years, n (%)	5 (6.8)	2 (2.7)	2.61 [0.49; 13.91] 0.261	2.50 [0.50; 12.47] 0.264	0.04 [-0.03; 0.11] 0.243

N: Number of patients
n (%): Number and percentage of patients with event
CI: Confidence interval
OR: Odds ratio
RR: Relative risk
RD: Risk difference
.....

Imputation method: None

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.
RR and RD with Wald CI and p-value calculated directly.

Table 35.3 Adverse events of special interest by NYHA/Ross class (SAF), binary analysis

	Treatment Groups		Comparison		
Adverse events of special interest by NYHA/Ross class (SAF)	**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			
Hepatotoxicity					
Interaction test	**p = 0.153**				
Class I/II, n (%)	10 (6.4)	9 (5.7)	1.12 [0.44; 2.83] 0.813	1.11 [0.46; 2.66] 0.813	0.01 [-0.05; 0.06] 0.813
Class III/IV, n (%)	5 (20.0)	1 (3.7)	6.50 [0.70; 60.13] 0.099	5.40 [0.68; 43.09] 0.112	0.16 [-0.01; 0.34] 0.064
Hyperkalaemia					
Interaction test	**N.E.**				
Class I/II, n (%)	8 (5.1)	9 (5.7)	0.88 [0.33; 2.35] 0.803	0.89 [0.35; 2.24] 0.803	-0.01 [-0.06; 0.04] 0.803
Class III/IV, n (%)	1 (4.0)	0 (0.0)	N.E.	3.23 [0.14; 75.83] 0.466	0.04 [-0.04; 0.12] 0.307
Hypersensitivity (Narrow SMQ)					
Interaction test	**p = 0.205**				
Class I/II, n (%)	20 (12.7)	16 (10.2)	1.29 [0.64; 2.59] 0.479	1.25 [0.67; 2.32] 0.480	0.03 [-0.04; 0.10] 0.478
Class III/IV, n (%)	2 (8.0)	5 (18.5)	0.38 [0.07; 2.18] 0.279	0.43 [0.09; 2.03] 0.288	-0.11 [-0.29; 0.08] 0.255
Hypotension					
Interaction test	**p = 0.470**				
Class I/II, n (%)	38 (24.2)	33 (21.0)	1.20 [0.71; 2.04] 0.500	1.15 [0.76; 1.74] 0.501	0.03 [-0.06; 0.12] 0.500
Class III/IV, n (%)	5 (20.0)	7 (25.9)	0.71 [0.19; 2.63] 0.613	0.77 [0.28; 2.12] 0.615	-0.06 [-0.29; 0.17] 0.610
Renal impairment (Narrow SMQ)					
Interaction test	**p = 0.697**				
Class I/II, n (%)	10 (6.4)	6 (3.8)	1.71 [0.61; 4.83] 0.310	1.67 [0.62; 4.47] 0.311	0.03 [-0.02; 0.07] 0.304

	Treatment Groups		Comparison		
Adverse events of special interest by NYHA/Ross class (SAF)	**LCZ696 (N=182)**	**Enalapril (N=184)**	**OR [95% CI] p-value**	**RR [95% CI] p-value**	**RD [95% CI] p-value**
Class III/IV, n (%)	2 (8.0)	2 (7.4)	1.09 [0.14; 8.36] 0.936	1.08 [0.16; 7.10] 0.936	0.01 [-0.14; 0.15] 0.936

N: Number of patients
n (%): Number and percentage of patients with event
N.E.: Not estimable
CI: Confidence interval
OR: Odds ratio
RR: Relative risk
RD: Risk difference
.....

Imputation method: None

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.
RR and RD with Wald CI and p-value calculated directly.

Exceptionally applied model (due to nonconvergence):
Hyperkalaemia / : logit(proportion) = treatment [by NYHA/Ross class].

Table 35.4 Adverse events of special interest by region (SAF), binary analysis

	Treatment Groups		Comparison		
Adverse events of special interest by region (SAF)	**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			
Hypersensitivity (Narrow SMQ)					
Interaction test	**p = 0.413**				
America, n (%)	12 (20.7)	9 (13.0)	1.74 [0.68; 4.48] 0.251	1.59 [0.72; 3.50] 0.253	0.08 [-0.05; 0.21] 0.253
Europe, n (%)	3 (5.2)	3 (5.5)	0.95 [0.18; 4.90] 0.947	0.95 [0.20; 4.50] 0.947	-0.00 [-0.09; 0.08] 0.947
Asia/Pacific and other, n (%)	7 (10.6)	9 (15.0)	0.67 [0.23; 1.93] 0.461	0.71 [0.28; 1.78] 0.462	-0.04 [-0.16; 0.07] 0.462
Hypotension					
Interaction test	**p = 0.667**				
America, n (%)	17 (29.3)	20 (29.0)	1.02 [0.47; 2.19] 0.968	1.01 [0.59; 1.74] 0.968	0.00 [-0.16; 0.16] 0.968
Europe, n (%)	10 (17.2)	10 (18.2)	0.94 [0.36; 2.46] 0.896	0.95 [0.43; 2.10] 0.896	-0.01 [-0.15; 0.13] 0.896
Asia/Pacific and other, n (%)	16 (24.2)	10 (16.7)	1.60 [0.66; 3.87] 0.296	1.45 [0.72; 2.95] 0.300	0.08 [-0.06; 0.22] 0.289

N: Number of patients
n (%): Number and percentage of patients with event
CI: Confidence interval
OR: Odds ratio
RR: Relative risk
RD: Risk difference
.....

Imputation method: None

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

Table 35.5 Adverse events of special interest by gender (SAF), binary analysis

	Treatment Groups		Comparison		
Adverse events of special interest by gender (SAF)	**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			
Hepatotoxicity					
Interaction test	**p = 0.221**				
Male, n (%)	8 (9.1)	3 (3.3)	2.93 [0.75; 11.44] 0.121	2.76 [0.76; 10.06] 0.124	0.06 [-0.01; 0.13] 0.107
Female, n (%)	7 (7.4)	7 (7.5)	0.99 [0.33; 2.94] 0.983	0.99 [0.36; 2.71] 0.983	-0.00 [-0.08; 0.07] 0.983
Hyperkalaemia					
Interaction test	**p = 0.359**				
Male, n (%)	3 (3.4)	5 (5.5)	0.61 [0.14; 2.62] 0.504	0.62 [0.15; 2.52] 0.504	-0.02 [-0.08; 0.04] 0.497
Female, n (%)	6 (6.4)	4 (4.3)	1.52 [0.41; 5.56] 0.529	1.48 [0.43; 5.09] 0.530	0.02 [-0.04; 0.09] 0.526
Hypersensitivity (Narrow SMQ)					
Interaction test	**p = 0.566**				
Male, n (%)	11 (12.5)	9 (9.9)	1.30 [0.51; 3.31] 0.580	1.26 [0.55; 2.90] 0.581	0.03 [-0.07; 0.12] 0.580
Female, n (%)	11 (11.7)	12 (12.9)	0.89 [0.37; 2.14] 0.803	0.91 [0.42; 1.95] 0.803	-0.01 [-0.11; 0.08] 0.803
Hypotension					
Interaction test	**p = 0.621**				
Male, n (%)	22 (25.0)	19 (20.9)	1.26 [0.63; 2.54] 0.512	1.20 [0.70; 2.05] 0.513	0.04 [-0.08; 0.16] 0.512
Female, n (%)	21 (22.3)	21 (22.6)	0.99 [0.50; 1.96] 0.969	0.99 [0.58; 1.69] 0.969	-0.00 [-0.12; 0.12] 0.969
Renal impairment (Narrow SMQ)					
Interaction test	**p = 0.131**				
Male, n (%)	7 (8.0)	2 (2.2)	3.85 [0.78; 19.05] 0.099	3.62 [0.77; 16.95] 0.102	0.06 [-0.01; 0.12] 0.078

	Treatment Groups		Comparison		
Adverse events of special interest by gender (SAF)	**LCZ696 (N=182)**	**Enalapril (N=184)**	**OR [95% CI] p-value**	**RR [95% CI] p-value**	**RD [95% CI] p-value**
Female, n (%)	5 (5.3)	6 (6.5)	0.81 [0.24; 2.77] 0.742	0.82 [0.26; 2.61] 0.743	-0.01 [-0.08; 0.06] 0.742

N: Number of patients
n (%): Number and percentage of patients with event
CI: Confidence interval
OR: Odds ratio
RR: Relative risk
RD: Risk difference
.....

Imputation method: None

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

Table 35.6 Adverse events of special interest by COVID-19 period (SAF), binary analysis

	Treatment Groups		Comparison		
Adverse events of special interest by COVID-19 period (SAF)	**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			
Hepatotoxicity					
Interaction test	**p = 0.794**				
Pre-pandemic, n (%)	8 (10.1)	6 (7.2)	1.45 [0.48; 4.37] 0.514	1.40 [0.51; 3.86] 0.514	0.03 [-0.06; 0.12] 0.513
Pre- and during-pandemic, n (%)	4 (6.5)	3 (5.1)	1.29 [0.28; 6.01] 0.748	1.27 [0.30; 5.43] 0.748	0.01 [-0.07; 0.10] 0.747
During-pandemic, n (%)	3 (7.3)	1 (2.4)	3.24 [0.32; 32.47] 0.318	3.07 [0.33; 28.35] 0.322	0.05 [-0.04; 0.14] 0.293
Hyperkalaemia					
Interaction test	**p = 0.334**				
Pre-pandemic, n (%)	4 (5.1)	7 (8.4)	0.58 [0.16; 2.06] 0.399	0.60 [0.18; 1.97] 0.400	-0.03 [-0.11; 0.04] 0.390
Pre- and during-pandemic, n (%)	4 (6.5)	1 (1.7)	4.00 [0.43; 36.88] 0.221	3.81 [0.44; 33.08] 0.226	0.05 [-0.02; 0.12] 0.180
During-pandemic, n (%)	1 (2.4)	1 (2.4)	1.02 [0.06; 16.95] 0.986	1.02 [0.07; 15.84] 0.986	0.00 [-0.07; 0.07] 0.986
Hypersensitivity (Narrow SMQ)					
Interaction test	**p = 0.836**				
Pre-pandemic, n (%)	14 (17.7)	12 (14.5)	1.27 [0.55; 2.96] 0.572	1.23 [0.60; 2.49] 0.572	0.03 [-0.08; 0.15] 0.572
Pre- and during-pandemic, n (%)	4 (6.5)	4 (6.8)	0.95 [0.23; 3.98] 0.942	0.95 [0.25; 3.63] 0.942	-0.00 [-0.09; 0.09] 0.942
During-pandemic, n (%)	4 (9.8)	5 (11.9)	0.80 [0.20; 3.22] 0.753	0.82 [0.24; 2.84] 0.754	-0.02 [-0.16; 0.11] 0.753

	Treatment Groups		Comparison		
Adverse events of special interest by COVID-19 period (SAF)	**LCZ696 (N=182)**	**Enalapril (N=184)**	**OR [95% CI] p-value**	**RR [95% CI] p-value**	**RD [95% CI] p-value**
Hypotension					
Interaction test	**p = 0.868**				
Pre-pandemic, n (%)	28 (35.4)	26 (31.3)	1.20 [0.63; 2.31] 0.579	1.13 [0.73; 1.75] 0.579	0.04 [-0.10; 0.19] 0.578
Pre- and during-pandemic, n (%)	9 (14.5)	7 (11.9)	1.26 [0.44; 3.64] 0.667	1.22 [0.49; 3.07] 0.668	0.03 [-0.09; 0.15] 0.666
During-pandemic, n (%)	6 (14.6)	7 (16.7)	0.86 [0.26; 2.81] 0.799	0.88 [0.32; 2.39] 0.799	-0.02 [-0.18; 0.14] 0.799
Renal impairment (Narrow SMQ)					
Interaction test	**N.E.**				
Pre-pandemic, n (%)	10 (12.7)	6 (7.2)	1.86 [0.64; 5.38] 0.253	1.75 [0.67; 4.59] 0.255	0.05 [-0.04; 0.15] 0.248
Pre- and during-pandemic, n (%)	0 (0.0)	1 (1.7)	N.E.	0.32 [0.01; 7.64] 0.480	-0.02 [-0.05; 0.02] 0.313
During-pandemic, n (%)	2 (4.9)	1 (2.4)	2.10 [0.18; 24.13] 0.551	2.05 [0.19; 21.73] 0.552	0.02 [-0.06; 0.11] 0.543

N: Number of patients
n (%): Number and percentage of patients with event
N.E.: Not estimable
CI: Confidence interval
OR: Odds ratio
RR: Relative risk
RD: Risk difference
.....

Imputation method: None

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.
RR and RD with Wald CI and p-value calculated directly.

Exceptionally applied model (due to nonconvergence):
Renal impairment (Narrow SMQ) / : logit(proportion) = treatment [by COVID-19 period].

Table 35.7 Adverse events of special interest by race (SAF), binary analysis

	Treatment Groups		Comparison		
Adverse events of special interest by race (SAF)	**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			
Hepatotoxicity					
Interaction test	**p = 0.747**				
Caucasian, n (%)	7 (8.1)	4 (4.4)	1.91 [0.54; 6.76] 0.318	1.83 [0.56; 6.03] 0.320	0.04 [-0.03; 0.11] 0.313
Black, n (%)	3 (13.0)	3 (12.0)	1.10 [0.20; 6.09] 0.913	1.09 [0.24; 4.86] 0.913	0.01 [-0.18; 0.20] 0.913
Asian, n (%)	4 (7.3)	1 (2.2)	3.45 [0.37; 32.03] 0.276	3.27 [0.38; 28.25] 0.281	0.05 [-0.03; 0.13] 0.222
Unknown or other, n (%)	1 (5.6)	2 (8.3)	0.65 [0.05; 7.75] 0.731	0.67 [0.07; 6.79] 0.732	-0.03 [-0.18; 0.13] 0.722
Hypersensitivity (Narrow SMQ)					
Interaction test	**p = 0.434**				
Caucasian, n (%)	9 (10.5)	9 (10.0)	1.05 [0.40; 2.79] 0.919	1.05 [0.44; 2.51] 0.919	0.00 [-0.08; 0.09] 0.919
Black, n (%)	5 (21.7)	2 (8.0)	3.19 [0.55; 18.42] 0.194	2.72 [0.58; 12.66] 0.203	0.14 [-0.06; 0.34] 0.177
Asian, n (%)	6 (10.9)	8 (17.8)	0.57 [0.18; 1.77] 0.329	0.61 [0.23; 1.64] 0.330	-0.07 [-0.21; 0.07] 0.332
Unknown or other, n (%)	2 (11.1)	2 (8.3)	1.37 [0.17; 10.82] 0.762	1.33 [0.21; 8.58] 0.762	0.03 [-0.15; 0.21] 0.765
Hypotension					
Interaction test	**p = 0.200**				
Caucasian, n (%)	19 (22.1)	22 (24.4)	0.88 [0.44; 1.77] 0.712	0.90 [0.53; 1.55] 0.713	-0.02 [-0.15; 0.10] 0.712
Black, n (%)	8 (34.8)	11 (44.0)	0.68 [0.21; 2.18] 0.515	0.79 [0.39; 1.61] 0.518	-0.09 [-0.37; 0.18] 0.512

	Treatment Groups		Comparison		
Adverse events of special interest by race (SAF)	**LCZ696 (N=182)**	**Enalapril (N=184)**	**OR [95% CI] p-value**	**RR [95% CI] p-value**	**RD [95% CI] p-value**
Asian, n (%)	12 (21.8)	3 (6.7)	3.91 [1.03; 14.84] 0.045 *	3.27 [0.98; 10.89] 0.053	0.15 [0.02; 0.28] 0.024 *
Unknown or other, n (%)	4 (22.2)	4 (16.7)	1.43 [0.30; 6.70] 0.651	1.33 [0.38; 4.63] 0.650	0.06 [-0.19; 0.30] 0.654

N: Number of patients
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: None

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

36 Adverse events by SMQ

Table 36.1 Adverse events by SMQ (SAF), binary analysis

	Treatment Groups		Comparison		
Adverse events by SMQ (SAF)	**LCZ696 (N=182)**	**Enalapril (N=184)**	**OR [95% CI] p-value**	**RR [95% CI] p-value**	**RD [95% CI] p-value**
Accidents and injuries (SMQ), n (%)	11 (6.0)	14 (7.6)	0.78 [0.34; 1.77] 0.554	0.79 [0.37; 1.70] 0.554	-0.02 [-0.07; 0.04] 0.553
Acute central respiratory depression (SMQ), n (%)	3 (1.6)	3 (1.6)	1.01 [0.20; 5.08] 0.989	1.01 [0.21; 4.94] 0.989	0.00 [-0.03; 0.03] 0.989
Acute renal failure (SMQ), n (%)	12 (6.6)	8 (4.3)	1.55 [0.62; 3.89] 0.348	1.52 [0.63; 3.62] 0.349	0.02 [-0.02; 0.07] 0.345
Anaphylactic reaction (SMQ), n (%)	1 (0.5)	1 (0.5)	1.01 [0.06; 16.29] 0.994	1.01 [0.06; 16.04] 0.994	0.00 [-0.02; 0.02] 0.994
Angioedema (SMQ), n (%)	5 (2.7)	6 (3.3)	0.84 [0.25; 2.80] 0.774	0.84 [0.26; 2.71] 0.774	-0.01 [-0.04; 0.03] 0.773
Asthma/bronchospasm (SMQ), n (%)	3 (1.6)	2 (1.1)	1.52 [0.25; 9.23] 0.646	1.52 [0.26; 8.97] 0.646	0.01 [-0.02; 0.03] 0.644
Biliary disorders (SMQ), n (%)	2 (1.1)	2 (1.1)	1.01 [0.14; 7.26] 0.991	1.01 [0.14; 7.10] 0.991	0.00 [-0.02; 0.02] 0.991
COVID-19 (SMQ), n (%)	8 (4.4)	2 (1.1)	4.18 [0.88; 19.98] 0.073	4.04 [0.87; 18.79] 0.075	0.03 [-0.00; 0.07] 0.052
Cardiac arrhythmias (SMQ), n (%)	11 (6.0)	16 (8.7)	0.68 [0.30; 1.50] 0.334	0.70 [0.33; 1.46] 0.335	-0.03 [-0.08; 0.03] 0.331
Cardiac failure (SMQ), n (%)	33 (18.1)	29 (15.8)	1.18 [0.68; 2.05] 0.546	1.15 [0.73; 1.81] 0.546	0.02 [-0.05; 0.10] 0.545
Cardiomyopathy (SMQ), n (%)	0 (0.0)	3 (1.6)	N.E.	0.14 [0.01; 2.78] 0.200	-0.02 [-0.03; 0.00] 0.081
Central nervous system vascular disorders (SMQ), n (%)	1 (0.5)	3 (1.6)	0.33 [0.03; 3.23] 0.343	0.34 [0.04; 3.21] 0.344	-0.01 [-0.03; 0.01] 0.318
Chronic kidney disease (SMQ), n (%)	3 (1.6)	2 (1.1)	1.52 [0.25; 9.23] 0.646	1.52 [0.26; 8.97] 0.646	0.01 [-0.02; 0.03] 0.644
Conjunctival disorders (SMQ), n (%)	1 (0.5)	3 (1.6)	0.33 [0.03; 3.23] 0.343	0.34 [0.04; 3.21] 0.344	-0.01 [-0.03; 0.01] 0.318

	Treatment Groups		Comparison		
Adverse events by SMQ (SAF)	**LCZ696 (N=182)**	**Enalapril (N=184)**	**OR [95% CI] p-value**	**RR [95% CI] p-value**	**RD [95% CI] p-value**
Convulsions (SMQ), n (%)	2 (1.1)	7 (3.8)	0.28 [0.06; 1.37] 0.117	0.29 [0.06; 1.37] 0.118	-0.03 [-0.06; 0.00] 0.092
Corneal disorders (SMQ), n (%)	1 (0.5)	0 (0.0)	N.E.	3.03 [0.12; 73.96] 0.496	0.01 [-0.01; 0.02] 0.316
Dehydration (SMQ), n (%)	3 (1.6)	4 (2.2)	0.75 [0.17; 3.42] 0.714	0.76 [0.17; 3.34] 0.715	-0.01 [-0.03; 0.02] 0.713
Depression and suicide/self-injury (SMQ), n (%)	3 (1.6)	1 (0.5)	3.07 [0.32; 29.75] 0.334	3.03 [0.32; 28.89] 0.335	0.01 [-0.01; 0.03] 0.310
Dyslipidaemia (SMQ), n (%)	1 (0.5)	0 (0.0)	N.E.	3.03 [0.12; 73.96] 0.496	0.01 [-0.01; 0.02] 0.316
Embolic and thrombotic events (SMQ), n (%)	3 (1.6)	7 (3.8)	0.42 [0.11; 1.67] 0.219	0.43 [0.11; 1.65] 0.220	-0.02 [-0.05; 0.01] 0.204
Extrapyramidal syndrome (SMQ), n (%)	1 (0.5)	0 (0.0)	N.E.	3.03 [0.12; 73.96] 0.496	0.01 [-0.01; 0.02] 0.316
Gastrointestinal nonspecific inflammation and dysfunctional conditions (SMQ), n (%)	66 (36.3)	73 (39.7)	0.87 [0.57; 1.32] 0.502	0.91 [0.70; 1.19] 0.502	-0.03 [-0.13; 0.07] 0.501
Gastrointestinal perforation, ulceration, haemorrhage or obstruction (SMQ), n (%)	3 (1.6)	1 (0.5)	3.07 [0.32; 29.75] 0.334	3.03 [0.32; 28.89] 0.335	0.01 [-0.01; 0.03] 0.310
Generalised convulsive seizures following immunisation (SMQ), n (%)	2 (1.1)	6 (3.3)	0.33 [0.07; 1.66] 0.178	0.34 [0.07; 1.65] 0.179	-0.02 [-0.05; 0.01] 0.155
Haematopoietic cytopenias (SMQ), n (%)	0 (0.0)	2 (1.1)	N.E.	0.20 [0.01; 4.18] 0.301	-0.01 [-0.03; 0.00] 0.155
Haemodynamic oedema, effusions and fluid overload (SMQ), n (%)	12 (6.6)	6 (3.3)	2.09 [0.77; 5.71] 0.148	2.02 [0.78; 5.27] 0.150	0.03 [-0.01; 0.08] 0.140
Haemorrhages (SMQ), n (%)	18 (9.9)	16 (8.7)	1.15 [0.57; 2.34] 0.694	1.14 [0.60; 2.16] 0.694	0.01 [-0.05; 0.07] 0.694
Hearing and vestibular disorders (SMQ), n (%)	1 (0.5)	1 (0.5)	1.01 [0.06; 16.29] 0.994	1.01 [0.06; 16.04] 0.994	0.00 [-0.02; 0.02] 0.994
Hepatic disorders (SMQ), n (%)	14 (7.7)	9 (4.9)	1.62 [0.68; 3.84] 0.273	1.57 [0.70; 3.54] 0.274	0.03 [-0.02; 0.08] 0.269

	Treatment Groups		Comparison		
Adverse events by SMQ (SAF)	**LCZ696 (N=182)**	**Enalapril (N=184)**	**OR [95% CI] p-value**	**RR [95% CI] p-value**	**RD [95% CI] p-value**
Hyperglycaemia/new onset diabetes mellitus (SMQ), n (%)	0 (0.0)	3 (1.6)	N.E.	0.14 [0.01; 2.78] 0.200	-0.02 [-0.03; 0.00] 0.081
Hypersensitivity (SMQ), n (%)	22 (12.1)	21 (11.4)	1.07 [0.56; 2.02] 0.841	1.06 [0.60; 1.86] 0.841	0.01 [-0.06; 0.07] 0.841
Hypertension (SMQ), n (%)	2 (1.1)	3 (1.6)	0.67 [0.11; 4.06] 0.663	0.67 [0.11; 3.99] 0.664	-0.01 [-0.03; 0.02] 0.661
Hypoglycaemia (SMQ), n (%)	1 (0.5)	2 (1.1)	0.50 [0.05; 5.59] 0.576	0.51 [0.05; 5.53] 0.576	-0.01 [-0.02; 0.01] 0.568
Hypokalaemia (SMQ), n (%)	5 (2.7)	3 (1.6)	1.70 [0.40; 7.24] 0.470	1.68 [0.41; 6.95] 0.470	0.01 [-0.02; 0.04] 0.465
Immune-mediated/autoimmune disorders (SMQ), n (%)	1 (0.5)	0 (0.0)	N.E.	3.03 [0.12; 73.96] 0.496	0.01 [-0.01; 0.02] 0.316
Infective pneumonia (SMQ), n (%)	11 (6.0)	13 (7.1)	0.85 [0.37; 1.94] 0.693	0.86 [0.39; 1.86] 0.693	-0.01 [-0.06; 0.04] 0.693
Interstitial lung disease (SMQ), n (%)	1 (0.5)	2 (1.1)	0.50 [0.05; 5.59] 0.576	0.51 [0.05; 5.53] 0.576	-0.01 [-0.02; 0.01] 0.568
Ischaemic heart disease (SMQ), n (%)	3 (1.6)	1 (0.5)	3.07 [0.32; 29.75] 0.334	3.03 [0.32; 28.89] 0.335	0.01 [-0.01; 0.03] 0.310
Lack of efficacy/effect (SMQ), n (%)	0 (0.0)	1 (0.5)	N.E.	0.34 [0.01; 8.22] 0.504	-0.01 [-0.02; 0.01] 0.316
Lacrimal disorders (SMQ), n (%)	0 (0.0)	1 (0.5)	N.E.	0.34 [0.01; 8.22] 0.504	-0.01 [-0.02; 0.01] 0.316
Malignancies (SMQ), n (%)	1 (0.5)	0 (0.0)	N.E.	3.03 [0.12; 73.96] 0.496	0.01 [-0.01; 0.02] 0.316
Medication errors (SMQ), n (%)	1 (0.5)	2 (1.1)	0.50 [0.05; 5.59] 0.576	0.51 [0.05; 5.53] 0.576	-0.01 [-0.02; 0.01] 0.568
Noninfectious diarrhoea (SMQ), n (%)	24 (13.2)	22 (12.0)	1.12 [0.60; 2.08] 0.723	1.10 [0.64; 1.89] 0.723	0.01 [-0.06; 0.08] 0.723
Noninfectious encephalopathy/delirium (SMQ), n (%)	1 (0.5)	1 (0.5)	1.01 [0.06; 16.29] 0.994	1.01 [0.06; 16.04] 0.994	0.00 [-0.02; 0.02] 0.994
Opportunistic infections (SMQ), n (%)	1 (0.5)	0 (0.0)	N.E.	3.03 [0.12; 73.96] 0.496	0.01 [-0.01; 0.02] 0.316

	Treatment Groups		Comparison		
Adverse events by SMQ (SAF)	**LCZ696 (N=182)**	**Enalapril (N=184)**	**OR [95% CI] p-value**	**RR [95% CI] p-value**	**RD [95% CI] p-value**
Oropharyngeal disorders (SMQ), n (%)	23 (12.6)	27 (14.7)	0.84 [0.46; 1.53] 0.571	0.86 [0.51; 1.44] 0.571	-0.02 [-0.09; 0.05] 0.570
Periorbital and eyelid disorders (SMQ), n (%)	3 (1.6)	1 (0.5)	3.07 [0.32; 29.75] 0.334	3.03 [0.32; 28.89] 0.335	0.01 [-0.01; 0.03] 0.310
Pregnancy and neonatal topics (SMQ), n (%)	3 (1.6)	2 (1.1)	1.52 [0.25; 9.23] 0.646	1.52 [0.26; 8.97] 0.646	0.01 [-0.02; 0.03] 0.644
Proteinuria (SMQ), n (%)	2 (1.1)	0 (0.0)	N.E.	5.05 [0.24; 104.56] 0.295	0.01 [-0.00; 0.03] 0.155
Pulmonary hypertension (SMQ), n (%)	0 (0.0)	3 (1.6)	N.E.	0.14 [0.01; 2.78] 0.200	-0.02 [-0.03; 0.00] 0.081
Renovascular disorders (SMQ), n (%)	1 (0.5)	0 (0.0)	N.E.	3.03 [0.12; 73.96] 0.496	0.01 [-0.01; 0.02] 0.316
Respiratory failure (SMQ), n (%)	4 (2.2)	5 (2.7)	0.80 [0.21; 3.05] 0.749	0.81 [0.22; 2.96] 0.749	-0.01 [-0.04; 0.03] 0.748
Rhabdomyolysis/myopathy (SMQ), n (%)	0 (0.0)	1 (0.5)	N.E.	0.34 [0.01; 8.22] 0.504	-0.01 [-0.02; 0.01] 0.316
Sepsis (SMQ), n (%)	1 (0.5)	3 (1.6)	0.33 [0.03; 3.23] 0.343	0.34 [0.04; 3.21] 0.344	-0.01 [-0.03; 0.01] 0.318
Severe cutaneous adverse reactions (SMQ), n (%)	1 (0.5)	0 (0.0)	N.E.	3.03 [0.12; 73.96] 0.496	0.01 [-0.01; 0.02] 0.316
Shock (SMQ), n (%)	9 (4.9)	11 (6.0)	0.82 [0.33; 2.02] 0.664	0.83 [0.35; 1.95] 0.664	-0.01 [-0.06; 0.04] 0.663
Tendinopathies and ligament disorders (SMQ), n (%)	1 (0.5)	1 (0.5)	1.01 [0.06; 16.29] 0.994	1.01 [0.06; 16.04] 0.994	0.00 [-0.02; 0.02] 0.994
Thyroid dysfunction (SMQ), n (%)	0 (0.0)	1 (0.5)	N.E.	0.34 [0.01; 8.22] 0.504	-0.01 [-0.02; 0.01] 0.316

	Treatment Groups		Comparison		
Adverse events by SMQ (SAF)	**LCZ696 (N=182)**	**Enalapril (N=184)**	**OR [95% CI] p-value**	**RR [95% CI] p-value**	**RD [95% CI] p-value**
Torsade de pointes/QT prolongation (SMQ), n (%)	5 (2.7)	4 (2.2)	1.27 [0.34; 4.81] 0.724	1.26 [0.34; 4.63] 0.724	0.01 [-0.03; 0.04] 0.723

N: Number of patients
n (%): Number and percentage of patients with event
N.E.: Not estimable
CI: Confidence interval
OR: Odds ratio
RR: Relative risk
RD: Risk difference
.....

Imputation method: None

Analysis method:
OR with Wald CI and p-value obtained from logistic regression model: logit(proportion) = treatment.
RR and RD with Wald CI and p-value calculated directly.

Table 36.2 Adverse events by SMQ, by age group (SAF), binary analysis

There is no data meeting the display criteria for this table.

Table 36.3 Adverse events by SMQ, by NYHA/Ross class (SAF), binary analysis

There is no data meeting the display criteria for this table.

Table36.4 Adverse events by SMQ, by region (SAF), binary analysis

There is no data meeting the display criteria for this table.

Table 36.5 Adverse events by SMQ, by gender (SAF), binary analysis

There is no data meeting the display criteria for this table.

Table 36.6 Adverse events by SMQ, by COVID-19 period (SAF), binary analysis

There is no data meeting the display criteria for this table.

Table 36.7 Adverse events by SMQ, by race (SAF), binary analysis

There is no data meeting the display criteria for this table.