Supplementary Table I. Prespecified Renal Endpoint Definitions

Endpoint	Criteria
End-stage renal disease	One of the following: a) Initiation of dialysis (e.g., hemodialysis, peritoneal dialysis, or continuous veno-venous hemodialysis), continuing for ≥ 30 days without known recovery of renal function, Sites were queried to provide evidence of continuation of dialysis for over 90 days. b) Initiation of dialysis with death before 30 days (excludes dialysis events associated with acute kidney injury with death before 30 days) c) A drop in eGFR from baseline (randomization, i.e. Visit 199/201) to a value <15 mL/min/1.73m2 on two consecutive central laboratory measurements separated by ≥ 30 days. This event was identified programmatically by the sponsor d) Occurrence of kidney transplantation

Worsening Renal Function	Sustained reduction in estimated GFR (eGFR) by 50% from baseline (Randomization, Visit 199/201) as determined by 2 consecutive post-baseline central laboratory measurements separated by > 30 days. This event was identified programmatically by the sponsor.
Death from Renal Causes	Death occurring from complications of renal failure (e.g. hyperkalemia, uremia, acidosis) after a patient refuses or a physician withholds renal replacement therapy (i.e. initiation of chronic dialysis or renal transplantation) or in cases where dialysis is unavailable. Such events were adjudicated as renal death only when another cause of death was not adjudicated.

Supplementary Table 2. Characteristics of the Patients at Baseline, According to Categories of Estimated Glomerular Filtration Rate (eGFR).[*]

Characteristic	eGFR ≥60 ml/min/1.73m^2 (N=7,792)	eGFR ≥45 to <60 ml/min/1.73m^2 (N=3,584)	eGFR <45 ml/min/1.73m^2 (N=1,818)	P
Age, yrs	64 ± 11	70 ± 10	73 ± 9	<0.001
Female, no. (%)	2210 (28)	1307 (36)	794 (44)	<0.001
Race, no. (%)				<0.001
White	5269 (68)	2728 (76)	1454 (80)	
Black	385 (5)	104 (3)	41 (2)	
Asian	1432 (18)	479 (13)	204 (11)	
Other	706 (9)	273 (8)	119 (7)	
Geographic Region, no. (%)				<0.001
North America	499 (6)	407 (11)	255 (14)	
Latin America	1134 (15)	462 (13)	207 (11)	
Western Europe	1791 (23)	1024 (29)	625 (34)	
Central Europe	2865 (37)	1175 (33)	501 (28)	
Asia-Pacific or other	1503 (19)	516 (14)	230 (13)	
Systolic blood pressure, mmHg	125 ± 16	124 ± 16	125 ± 16	0.22
Heart rate, beats/min	72 ± 12	71 ± 12	71 ± 12	<0.001
Body-mass index[#]	28.7 ± 5.5	29.0 ± 5.3	29.5 ± 5.3	<0.001
Serum creatinine, mg/dL [$]	0.9 ± 0.2	1.2 ± 0.2	1.6 ± 0.3	<0.001
eGFR,[%] mL/min/1.73 m^2	78 ± 16	53 ± 4	38 ± 5	<0.001
Clinical features of heart failure				
Ischemic Cause, no. (%)	3935 (51)	1894 (53)	930 (51)	0.06

Left ventricular ejection fraction, %	38.2 ± 14.5	41.0 ± 15.5	43.5 ± 16.1	<0.001
Median NT-proBNP (25th-75th percentile), pg/mL	1198 [659, 2243]	1415 [760, 2703]	1640 [830, 3178]	<0.001
NYHA Classification, no. (%)				<0.001
I	339 (4)	129 (4)	58 (3)	
II	5764 (74)	2609 (73)	1251 (69)	
III	1629 (21)	825 (23)	496 (27)	
IV	52 (1)	16 (0)	11 (1)	
Medical History, no. (%)				
Hypertension	5942 (76)	2993 (84)	1588 (87)	<0.001
Diabetes	2736 (35)	1386 (39)	846 (47)	<0.001
Atrial fibrillation or flutter	2485 (32)	1414 (40)	744 (41)	<0.001
Stroke	613 (8)	361 (10)	259 (14)	<0.001
Hospitalization for heart failure	4494 (58)	2044 (57)	1042 (57)	0.81
Myocardial infarction	2702 (35)	1354 (38)	661 (36)	0.005
Treatment, no. (%)				
Diuretic at randomization	6479 (83)	3153 (88)	1690 (93)	<0.001
ACE inhibitor or ARB at screening	7476 (96)	3373 (94)	1669 (92)	<0.001
Mineralocorticoid-receptor antagonist at randomization	3664 (47)	1521 (42)	725 (40)	<0.001
Beta-blocker at randomization	6966 (89)	3096 (86)	1569 (86)	<0.001
Sacubitril/valsartan, n (%)	3889 (50)	1810 (51)	895 (49)	0.67

[*] Plus-minus values are mean +/- SD.

[#] The body-mass index is the weight in kilograms divided by the square of the height in meters.

[$] This characteristic was measured at the randomization visit instead of the screening visit.

[%] The GFR at baseline was estimated according to the four-variable Modification of Diet in Renal Disease formula.

NYHA, New York Heart Association; BMI, Body Mass Index; ACE, Angiotensin Converting Enzyme; ARB, Angiotensin Receptor Blocker

Supplementary Table 3. Baseline Characteristics according to parent trial

Characteristic	PARADIGM-HF (N=8,399)	PARAGON-HF (N=4,796)
Age, yrs	64 ± 11	73 ± 8
Female, no. (%)	1832 (22)	2479 (52)
Race, no. (%)		
White	5544 (64)	3907 (81)
Black	428 (5)	102 (2)
Asian	1509 (18)	607 (13)
Other	918 (11)	180 (4)
Geographic Region, no. (%)		
North America	602 (7)	559 (12)
Latin America	1433 (17)	370 (8)
Western Europe	2051 (24)	1390 (29)
Central Europe	2826 (34)	1115 (36)
Asia-Pacific or other	1487 (18)	762 (16)
Systolic blood pressure, mmHg	121 ± 15	131 ± 15
Heart rate, beats/min	72 ± 12	70 ± 12
Body-mass index[#]	28.2 ± 5.5	30.2 ± 5.0
Serum creatinine, mg/dL [$]	1.1 ± 0.3	1.1 ± 0.3
eGFR,[%] mL/min/1.73 m^2	68 ± 20	63 ± 19
Clinical features of heart failure		
Ischemic Cause, no. (%)	5036 (60)	1723 (36)
Left ventricular ejection fraction, %	29.5 ± 6.2	57.5 ± 7.9
Median NT-proBNP (25th-75th percentile), pg/mL	1612 [886, 3224]	911 [464, 1613]
NYHA Classification, no. (%)		
I	389 (5)	137 (3)
II	5919 (71)	3706 (77)
III	2018 (24)	932 (19)
IV	60 (1)	19 (0)
Medical History, no. (%)		
Hypertension	5940 (71)	4584 (96)
Diabetes	2907 (35)	2062 (43)
Atrial fibrillation or flutter	3091 (37)	1552 (32)
Stroke	725 (9)	508 (11)
Hospitalization for heart failure	5274 (63)	2306 (48)
Myocardial infarction	3634 (43)	1083 (23)
Treatment, no. (%)		

Diuretic at randomization	6738 (80)	4585 (96)
ACE inhibitor or ARB at screening	8379 (100)	4139 (86)
Mineralocorticoid-receptor antagonist at randomization	4671 (56)	1239 (26)
Beta-blocker at randomization	7811 (93)	3821 (80)
Sacubitril/valsartan, n (%)	4187 (50)	2407 (50)

[*] Plus-minus values are mean +/- SD.

[#] The body-mass index is the weight in kilograms divided by the square of the height in meters.

[$] This characteristic was measured at the randomization visit instead of the screening visit.

[%] The GFR at baseline was estimated according to the four-variable Modification of Diet in Renal Disease formula.

NYHA, New York Heart Association; BMI, Body Mass Index; ACE, Angiotensin Converting Enzyme; ARB, Angiotensin Receptor Blocker

Supplementary Figure 1. Incidence rates of the renal composite outcome according to baseline ejection fraction

Supplementary Figure 2. Subgroup analyses of the treatment effect on difference in rate of eGFR decline (mL/min/1.72 m^2 with 95% confidence intervals)