Esaxerenone (CS-3150) in Patients with Type 2 Diabetes and Microalbuminuria (ESAX-DN): Phase 3 Randomized Controlled Clinical Trial

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Supplemental Methods

For patients with an estimated glomerular filtration rate (eGFR) ≥45 mL/min per 1.73 m^2 during the run-in period, the esaxerenone dosage was maintained at 1.25 mg/d if the most recent serum potassium level was ≥5.1 mEq/L, and increased to 2.5 mg/d if the most recent serum potassium level was <5.1 mEq/L. In patients with eGFR 30 to <45 mL/min per 1.73 m^2 during the run-in period, the esaxerenone dosage was maintained at 1.25 mg/d if the most recent serum potassium level was ≥4.8 mEq/L, and increased to 2.5 mg/d if the most recent serum potassium was <4.8 mEq/L.

During treatment with esaxerenone 2.5 mg/d, if the most recent serum potassium was ≥5.5 to <6.0 mEq/L, serum potassium was re-measured within 3 days. If the second measurement was <5.5 mEq/L, the esaxerenone dosage was maintained at 2.5 mg/d; if the second measurement was 5.5 to <6.0 mEq/L, treatment was interrupted followed by a clinic visit and dose reduction to 1.25 mg/d; and if the second serum potassium level was ≥6.0 mEq/L, esaxerenone was discontinued. If the most recent serum potassium level was ≥6.0 mEq/L, serum potassium was re-measured within 3 days. If the second value was <5.5 mEq/L, treatment was interrupted followed by a clinic visit and dose reduction to 1.25 mg/d, and if the second value was ≥5.5 mEq/L, esaxerenone was discontinued.

During treatment with esaxerenone 1.25 mg/d, if the most recent serum potassium measurement was ≥5.5–6.0 mEq/L, serum potassium was re-measured within 3 days. If the second measurement was <5.5 mEq/L, the esaxerenone dosage was maintained at 1.25 mg/d; if the second value was over 5.5 mEq/L, esaxerenone was discontinued.

Procedure for urine sample collection

Patients collected their early morning urine (3 mL) in a storage container and submitted it to the medical institution. Specimens were refrigerated and analyzed at a central laboratory (LSI Medience Co., Ltd.). Urinary albumin concentration and urinary creatinine concentration were

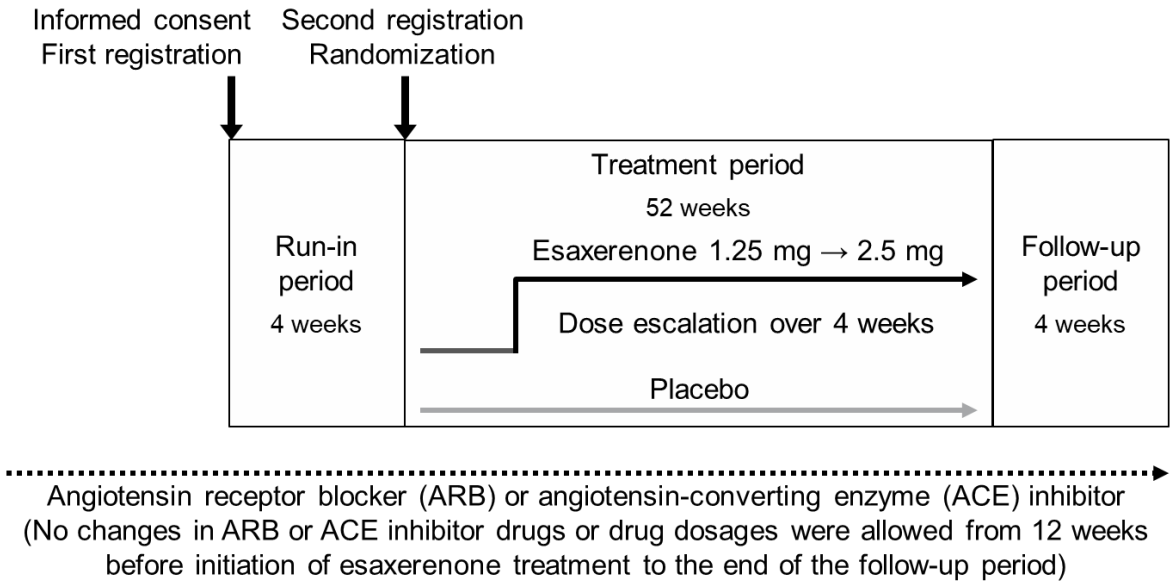
measured from the submitted samples and the UACR was calculated using the following formula:

UACR (mg/g creatinine) = urinary albumin concentration (μg/mL) / urine creatinine concentration (mg/dL) × 100

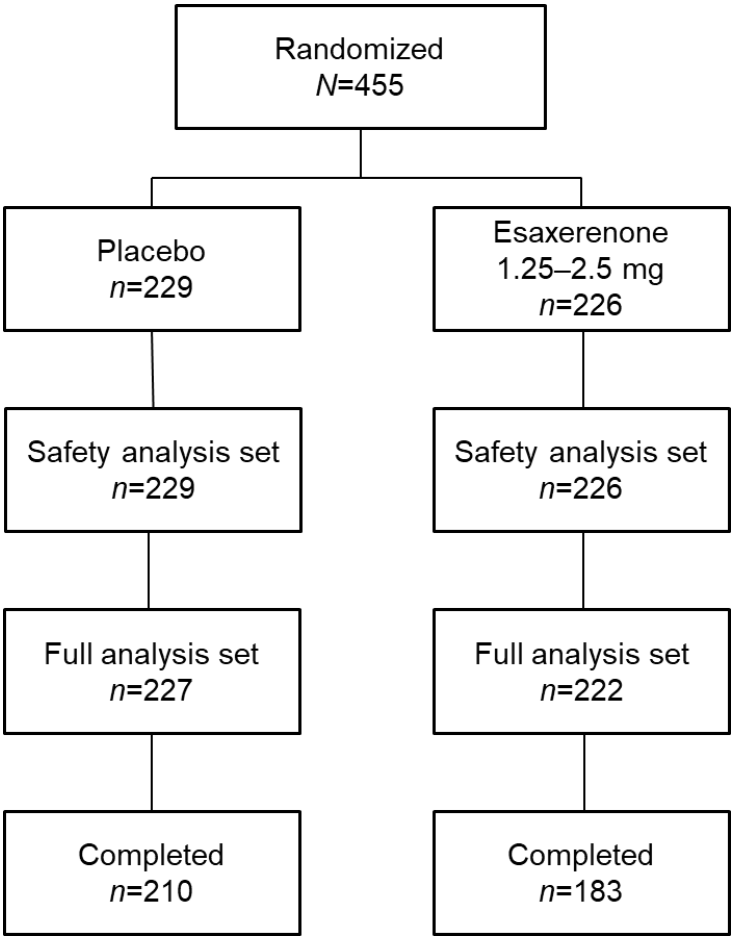
Test data and the date of collections were recorded by the investigators.

Supplemental Figures

Supplemental Figure 1. Study design

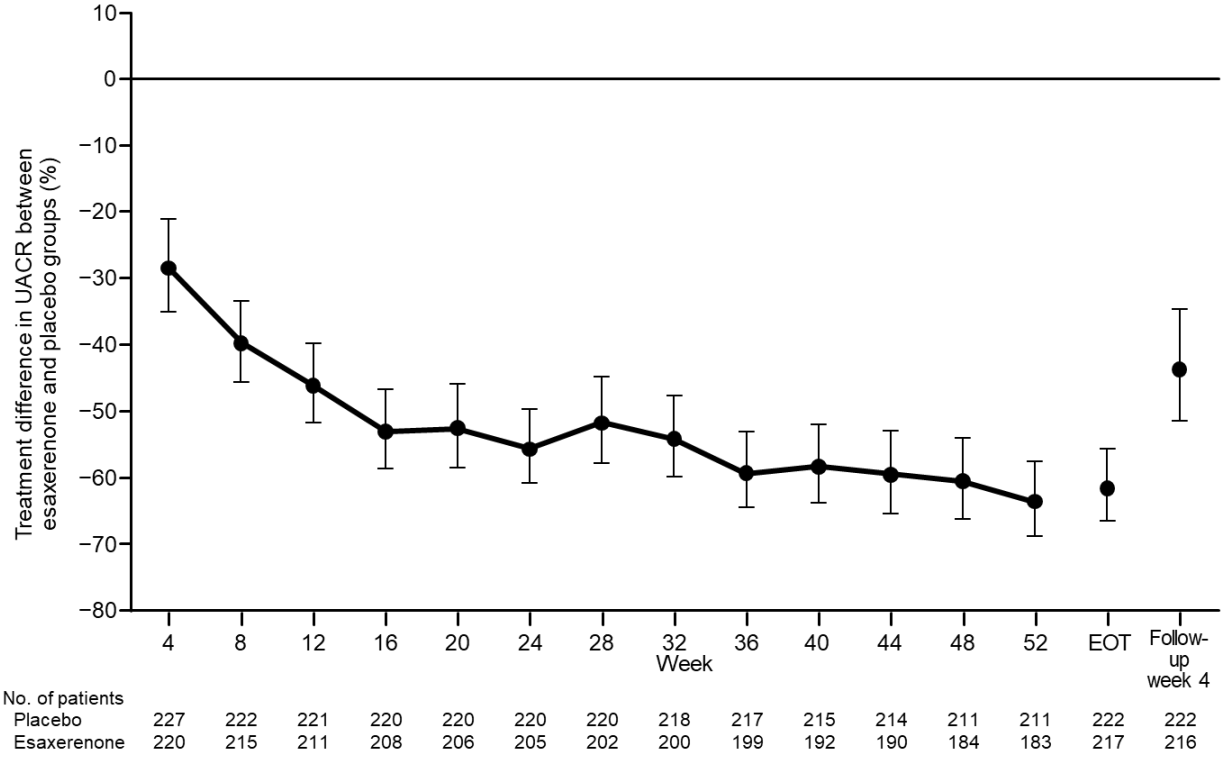


Supplemental Figure 2. Patient disposition



Supplemental Figure 3. Time course indicating treatment difference in the urinary albumin-creatinine ratio (UACR) change from baseline between the esaxerenone and placebo groups Data are shown as least-squares mean ± 95% confidence intervals.

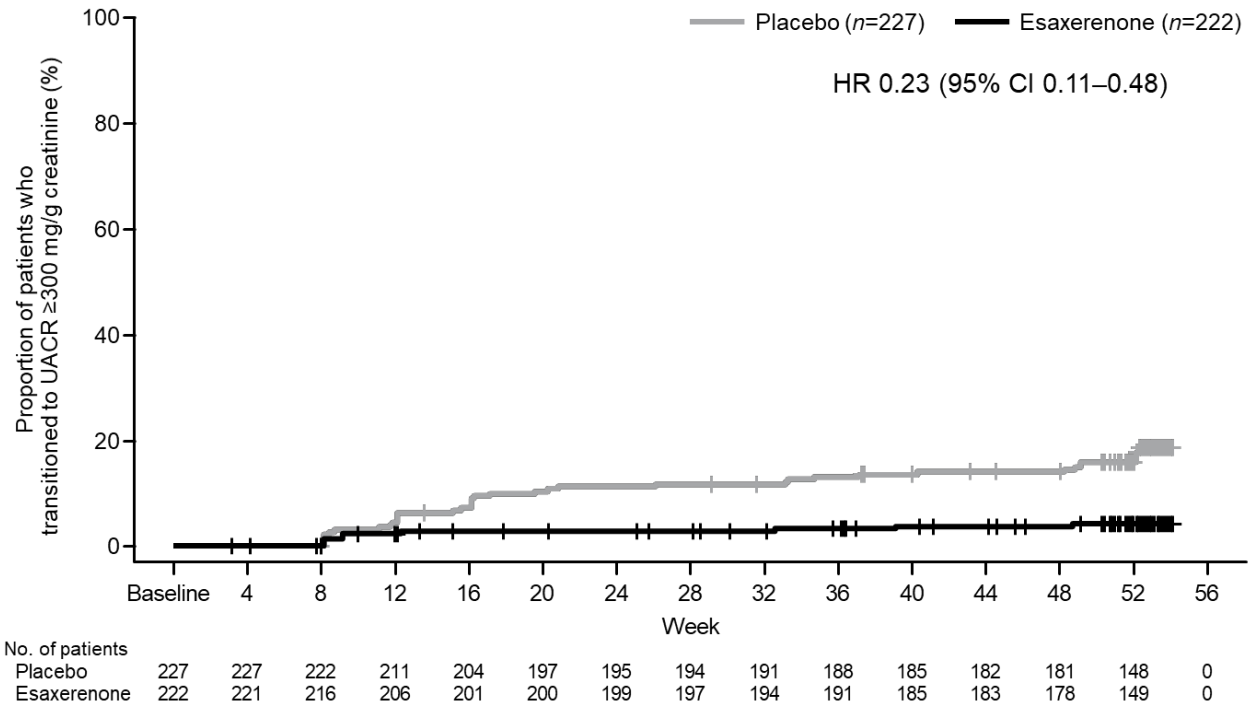
EOT, end of treatment.



No. of patients															
Placebo	227	222	221	220	220	220	220	218	217	215	214	211	211	222	222
Esaxerenone	220	215	211	208	206	205	202	200	199	192	190	184	183	217	216

Supplemental Figure 4. Kaplan–Meier curve for time to first transition to UACR ≥300 mg/g creatinine.

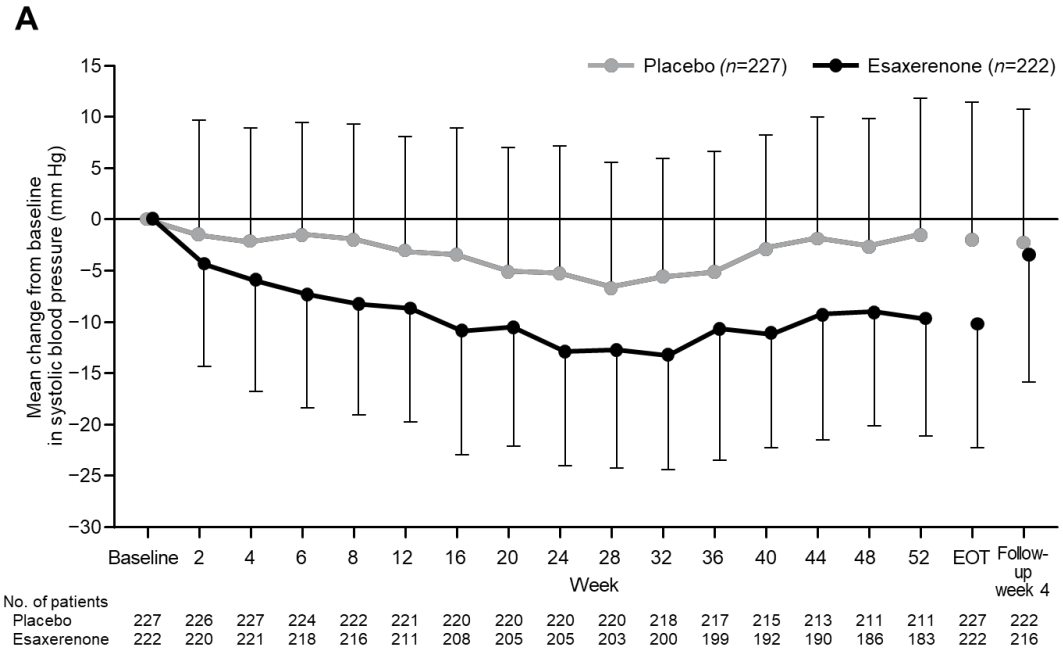
CI, confidence interval; HR, hazard ratio

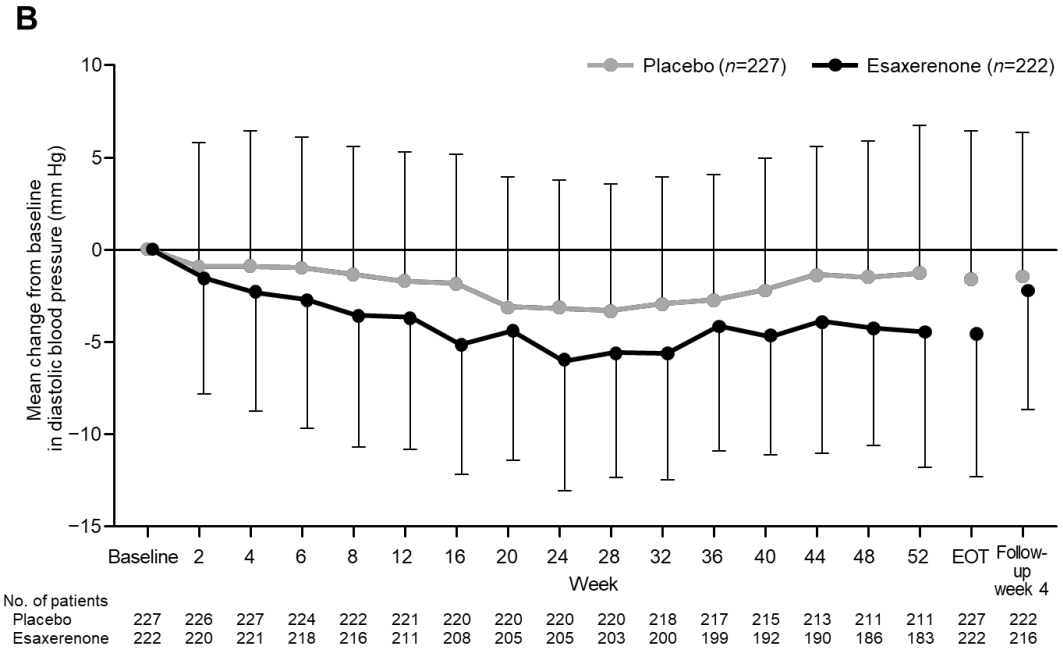


Supplemental Figure 5. Mean change from baseline at the end of treatment in sitting systolic blood pressure (**A**) and sitting diastolic blood pressure (**B**)

Data are shown as mean ± standard deviation.

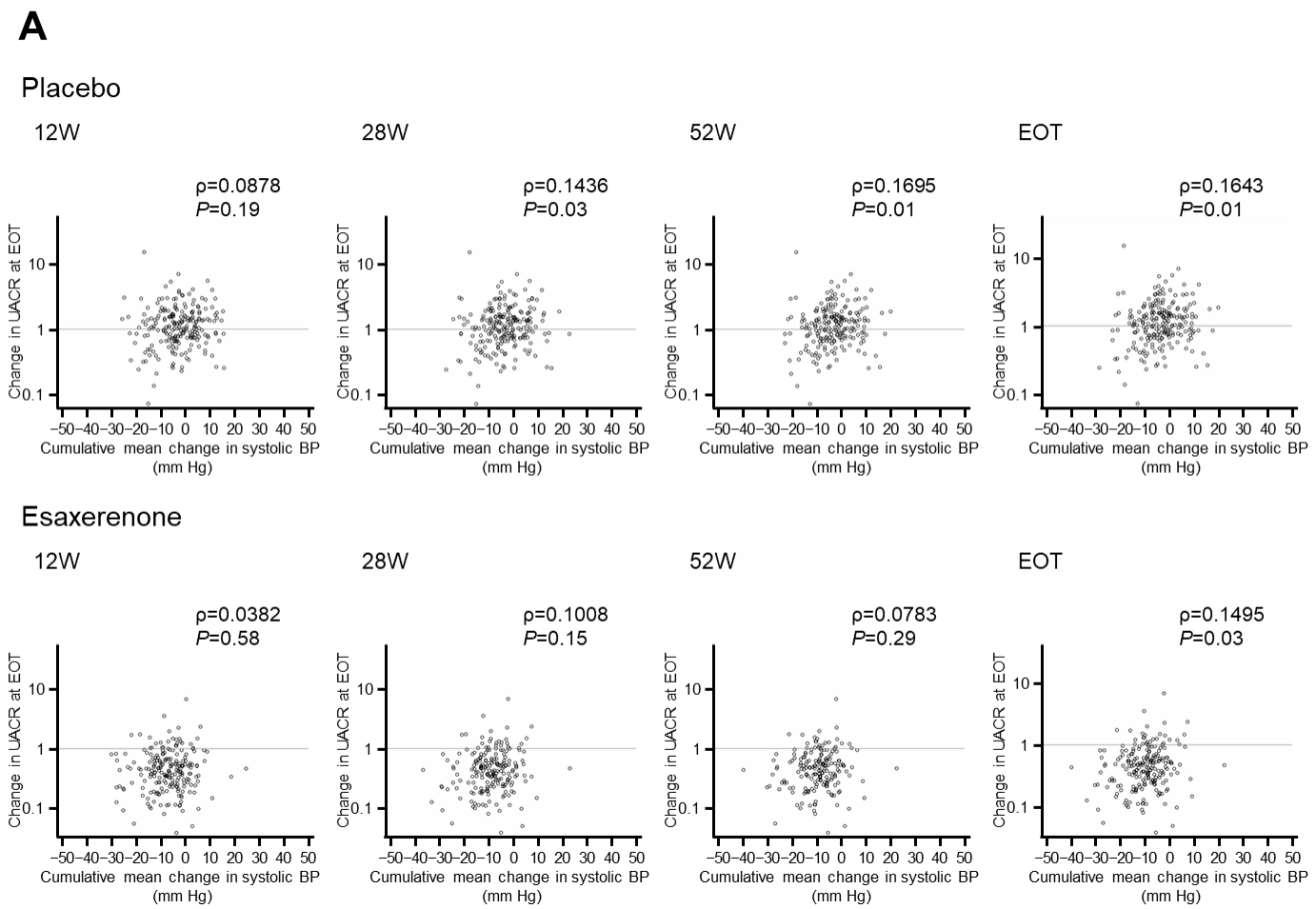
EOT, end of treatment.



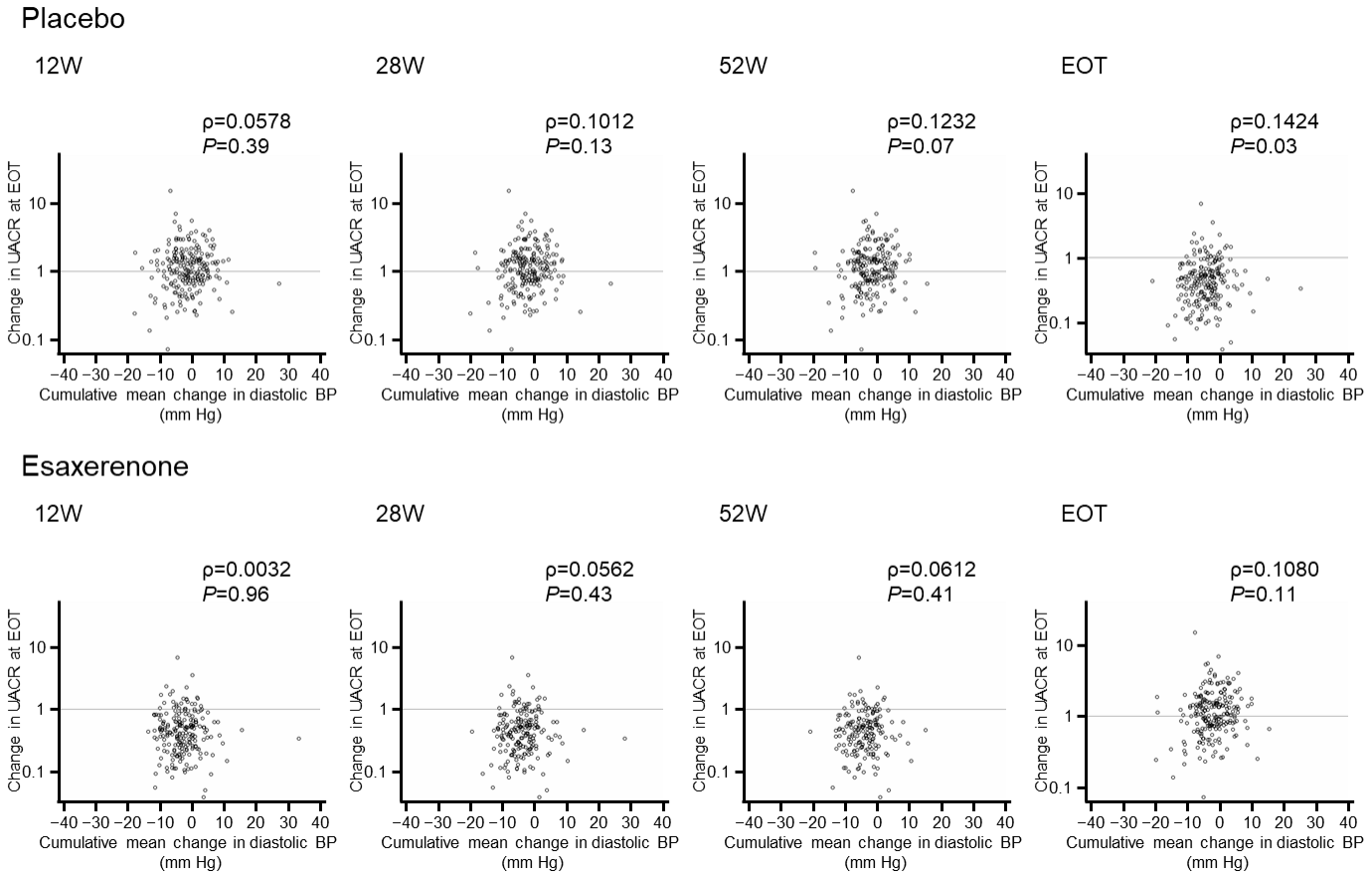


Supplemental Figure 6. Scatter plot showing the relationship between changes in the urinary albumin-to-creatinine ratio (UACR) at the EOT and cumulative mean change in systolic blood pressure (⊿systolic BP) (**A**) or diastolic blood pressure (⊿diastolic BP) (**B**)

EOT, end of treatment; W, week.

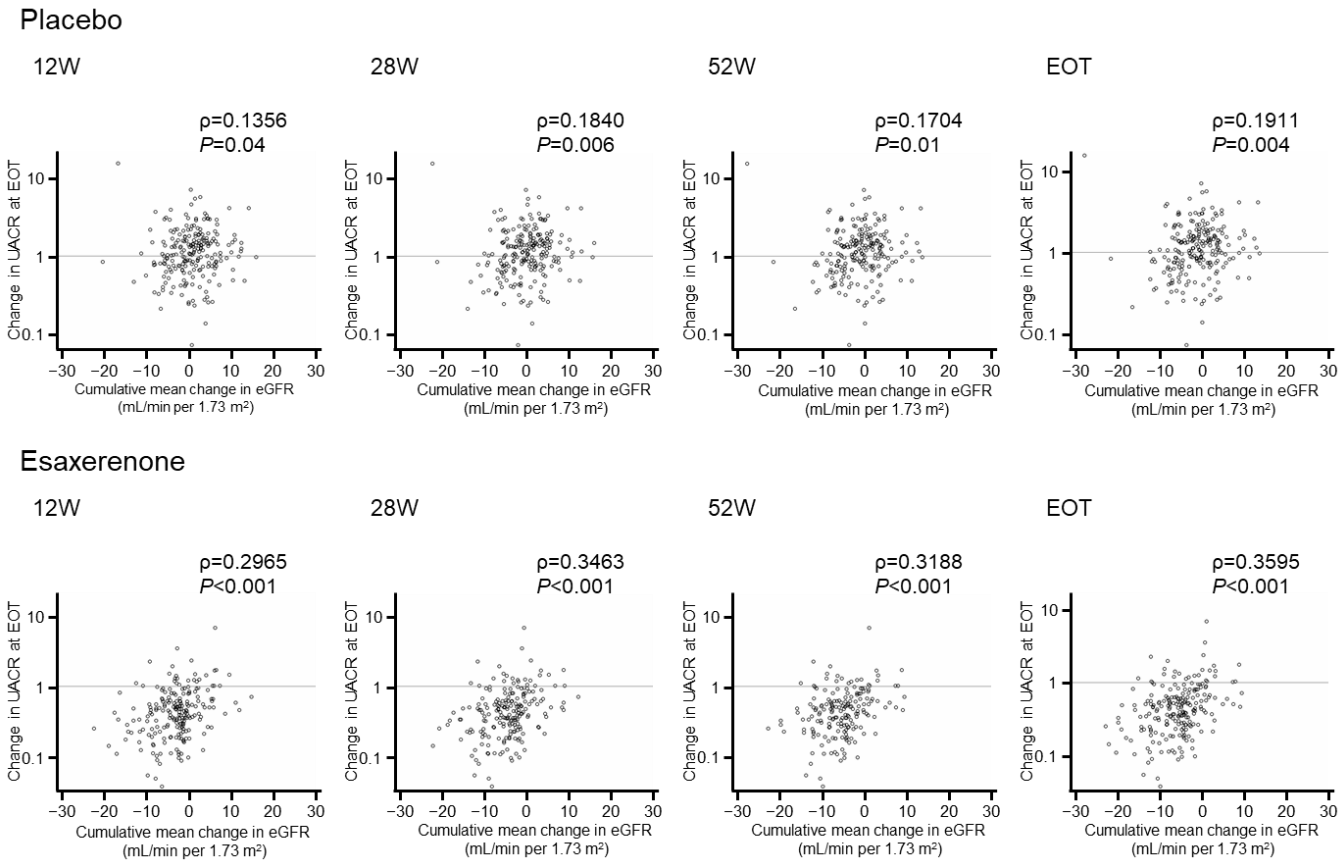


B


Placebo
12W
ρ=0.0578
P=0.39
28W
ρ=0.1012
P=0.13
52W
ρ=0.1232
P=0.07
EOT
ρ=0.1424
P=0.03
Esaxerenone
12W
ρ=0.0032
P=0.96
28W
ρ=0.0562
P=0.43
52W
ρ=0.0612
P=0.41
EOT
ρ=0.1080
P=0.11
Change in UACR at EOT
10
1
0.1
−40 −30 −20 −10 0 10 20 30 40
Cumulative mean change in diastolic BP (mm Hg)

Supplemental Figure 7. Scatter plot showing the relationship between changes in the urinary albumin-to-creatinine ratio (UACR) at the EOT and cumulative mean change in estimated glomerular filtration rate up to each visit (⊿eGFR)

EOT, end of treatment; W, week.



Supplemental tables

Supplemental Table 1. Schedule of study assessments

	Run-in period			Treatment period																		Follow-up period
Timing of visit (weeks)	**Start**	**2**	**3[a]**	**Start**	**2**	**4**	**6**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52 (EOT)**	**2 weeks after dose increase**	**After visits where serum potassium ≥5.5 mEq/L**	**Treatment discontinuation**	**4 weeks after EOT**
Urine sampling																							
UACR	X	X	X[a]			X		X	X	X	X	X	X	X	X	X	X	X	X			X	X
Blood sampling																							
Hematology,		X				X			X				X						X			X	
Biochemistry		X				X			X				X						X			X	
Potassium		X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[b]	X	X
Creatinine		X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[b]	X	X
Vital signs																							
BP, pulse	X	X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X
Adverse events				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

[a]Assessed at week 3 if urinary albumin-to-creatinine ratio criteria were not met at week 2.

[b]Serum potassium and creatinine measurement only.

BP, blood pressure; EOT, end of treatment; UACR, urinary albumin-to-creatinine ratio.

Supplemental Table 2. Reasons for discontinuation

	Placebo (*n*=229)	Esaxerenone (*n*=226)	All (*n*=455)
Completed	210 (91.7)	183 (81.0)	393 (86.4)
Discontinued[a]	19 (8.3)	43 (19.0)	62 (13.6)
Withdrawal by subject	6 (2.6)	4 (1.8)	10 (2.2)
Adverse event[a]	8 (3.5)	21 (9.3)	29 (6.4)
Did not fulfil inclusion criteria or met exclusion criteria	1 (0.4)	4 (1.8)	5 (1.1)
Lost to follow-up	0 (0.0)	1 (0.4)	1 (0.2)
Death	0 (0.0)	0 (0.0)	0 (0.0)
Study terminated by sponsor	0 (0.0)	0 (0.0)	0 (0.0)
Enrollment closed by sponsor	0 (0.0)	0 (0.0)	0 (0.0)
Other[a]	4 (1.7)	13 (5.8)	17 (3.7)
Serum potassium increase[b]	0	1	1
eGFR decrease[c]	3	9	12
Withdrawal by investigator or prioritizing other treatments	1	3	4

Data are presented as *n*/*N* (%).

[a]*P*<0.005 (esaxerenone vs. placebo)

[b]Discontinuation criteria were having a serum potassium level ≥6.0 mEq/L or ≥5.5 mEq/L on two consecutive occasions during the treatment with esaxerenone 1.25 mg/d; serum potassium level ≥6.0 mEq/L at the first measurement and ≥5.5 mEq/L at second measurement, or serum

potassium level 5.5 to <6.0 mEq/L at the first measurement and ≥5.5 mEq/L at second measurement during the treatment with esaxerenone 2.5 mg/d.
[c]eGFR ≥30% reduction compared with the measurement during the run-in period.

Supplemental Table 3. Proportion of patients achieving remission of UACR 45–<300 mg/g creatinine (defined as two consecutive urinary albumin-to-creatinine ratio [UACR] values <30 mg/g creatinine at the end of treatment and ≥30% reduction in UACR from baseline to the end of treatment) in patient subgroups

Concomitant treatment	Placebo	Esaxerenone	Treatment difference [95% confidence interval]	*P* value
Remission of UACR 45–<300 mg/g creatinine				
Baseline UACR, mg/g creatinine				
<100	8/97 (8)	36/95 (38)	30 [17–41]	<0.001
≥100	1/130 (1)	13/127 (10)	10 [4–16]	<0.001
Baseline eGFR, mL/min per 1.73 m^2				
<60	4/74 (5)	16/71 (23)	17 [5–29]	0.003
≥60	5/153 (3)	33/151 (22)	19 [11–26]	<0.001
Baseline blood pressure, mm Hg				
<140/<90	1/83 (1)	22/90 (24)	23 [14–34]	<0.001
≥140/≥90	8/144 (6)	27/132 (21)	15 [7–24]	<0.001
Dipeptidyl peptidase 4 inhibitor				
No	5/75 (7)	16/78 (21)	14 [2–25]	0.01
Yes	4/152 (3)	33/144 (23)	20 [13–28]	<0.001

Sodium-glucose transport protein 2 inhibitor				
No	7/171 (4)	38/172 (22)	18 [11–26]	<0.001
Yes	2/56 (4)	11/50 (22)	18 [5–33]	0.004

Data are presented as *n*/*N* (%).

eGFR, estimated glomerular filtration rate; UACR, urinary albumin-to-creatinine ratio.

Supplemental Table 4. Changes in UACR, BP, and eGFR from baseline to the end of treatment in patients according to presence or absence of concomitant treatment with DPP-4 or SGLT2 inhibitors

	Least-square mean change from baseline to the end of treatment in UACR[a]		Change from baseline to the end of treatment in sitting systolic BP (mm Hg)		Change from baseline to the end of treatment in sitting diastolic BP (mm Hg)		Geometric mean change from baseline to the end of treatment in eGFR (mL/min per 1.73 m^2)	
	Yes	No	Yes	No	Yes	No	Yes	No
Dipeptidyl peptidase 4 inhibitor								
Placebo, (n)	1.1 (150)	1.1 (72)	–2 (152)	–2 (75)	–2 (152)	–1 (75)	1.0 (152)	1.0 (75)
Esaxerenone, (n)	0.4 (140)	0.4 (77)	–10 (144)	–11 (78)	–4 (144)	–5 (78)	1.0 (144)	1.0 (78)
***P* value**	<0.001	<0.001	<0.001	<0.001	<0.001	0.002	<0.001	<0.001
Sodium-glucose transport protein 2 inhibitor								
Placebo, (n)	1.0 (56)	1.1 (166)	0.2 (56)	–3 (171)	–1 (56)	–2 (171)	1.0 (56)	1.0 (171)
Esaxerenone, (n)	0.4 (50)	0.4 (167)	–12 (50)	–10 (172)	–6 (50)	–5 (172)	0.9 (50)	1.0 (172)
***P* value**	<0.001	<0.001	<0.001	<0.001	<0.001	0.001	<0.001	<0.001

[a]Least-squares means of the change from baseline log-transformed values at the end of treatment, based on the ANCOVA model with treatment group as a factor and log-transformed baseline values as covariates. The estimates are back-transformed, and expressed as the ratio in the original scale.

DPP-4, dipeptidyl peptidase 4 inhibitor; eGFR, estimated glomerular filtration rate; SGLT2, sodium-glucose transport protein 2 inhibitor; UACR, urinary albumin-to-creatinine ratio