Supplemental Materials

Efficacy and Safety of Esaxerenone (CS-3150) for the Treatment of Type 2 Diabetes with Microalbuminuria

A Randomized, Double-blind, Placebo-controlled, Phase II Trial

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Appendices

Appendix 1. Study sites and investigators participating in this study

Medical institution	Investigator
Shimizu-Naika Clinic; Social Medical Corporation	Noriyasu Taya
Sakajiri-Naika Clinic; Social Medical Corporation	Kazuo Yamagata
NTT-East Sapporo Hospital	So Nagai
Manda Memorial Hospital; Medical Corporation	Kazushi Misawa
Miyanomori Memorial Hospital; Medical Corporation Sanseikai	Itaru Maeda
Sapporo Ryokuai Hospital; Hokkaido Health Coop	Fumitaka Shinojima
Aoki-Naika Clinic; Social Medical Corporation	Shin Aoki
Onoyuri Clinic; Social Medical Corporation	Yuri Ono
Jiyugaoka YAMADA Clinic, Internal Medicine	Daishiro Yamada
Hasegawa-Naika Clinic; Social Medical Corporation Tousui-kai	Atsushi Hasegawa
Ato Internal Medicine Clinic	Keita Ato
Imamura Clinic	Kenichi Imamura
Minami Akatsuka Clinic; Medical Corporation Eiwa-kai	Hideo Takahashi
Kozawa Eye Hospital; Medical Corporation	Masakazu Mizutani
Naka Memorial Clinic; Medical Corporation Kensei-kai	Takeshi Osonoi
Itabashi Diabetic Medicine and Dermatology Clinic; Medical Corporation Kensei-kai	Naoki Itabashi
Oyama East Clinic; Medical Corporation	Hiroshi Ohashi
Onai-Naika Clinic; Social Medical Corporation Towa-kai	Toru Onai
Cardiovascular Hospital of Central Japan; Medical Corporation	Yoshiaki Takayama
Sugiura Clinic; Social Medical Corporation	Toshiyuki Sugiura
Shimizu Clinic Fusa; Social Medical Corporation Fusa-no-kai	Yukari Shimizu
Funabashi Municipal Medical Center	Hideaki Iwaoka

Medical institution	**Investigator**
Kashiwa Municipal Hospital; Public Interest Incorporated Foundation, Kashiwa City Medical Corporation	Takeshi Inazawa
Kobari General Hospital; Social Medical Corporation Keisyun-kai	Shuichi Watanabe
Tokyo Kamata Medical Center; Japan Community Health care Organization	Masato Kawaguchi Nobuyuki Sato Ikutaka Takemoto
Japanese Red Cross Medical Center	Toru Hiyoshi
Sugawara Clinic; Social Medical Corporation Kouken-kai	Masahiro Sugawara
Hino Municipal Hospital	Marohito Murakami
Kato Clinic; Social Medical Corporation Kouji-kai	Mitsutoshi Kato
Seiwa Clinic, Nishi-Arai Hospital; Social Medical Corporation Seiwa-kai Medical Group	Tatsushi Sugiura
Kitasato University Kitasato Institute Hospital	Noriaki Watanabe
Chiyoda Tomohito Clinic	Isao Uchimura
AGE Makita Medical Clinic	Zenji Makita
Tokyo Heart Center, Osaki Hospital; Social Medical Corporation Kanshin-kai	Masahiro Endo
P-one Clinic; Keiko-kai Medical Corporation	Kenichi Furihata
Tokyo Center Clinic; Social Medical Corporation Chisei-kai	Yumiko Ide
Tomonaga Clinic; Social Medical Corporation LifeStyle	Osamu Tomonaga
ToCROM Clinic; Medical Corporation Heishin-kai	Osamu Matsuoka
Shonan-Takai-Naika Clinic; Social Medical Corporation Shobi-kai	Katsumi Takai
Matoba Diabetes Clinic; Medical Corporation	Kiyokazu Matoba
Japanese Red Cross Kanazawa Hospital	Yasuyuki Nishimura
Okamoto-Naika Clinic; Seishin-kai Social Medical Corporation	Mitsuo Imura
Suruga Clinic; Social Medical Corporation Rikei-kai	Akira Yamauchi
ASO Clinic	Katsumi Aso

Medical institution	**Investigator**
Meitetsu Hospital; Nagoya Railroad Health Insurance Association	Hideki Okamoto
Chubu Rosai Hospital; Japan Labour Health and Welfare Organization	Eitaro Nakashima
Kasugai Municipal Hospital	Hiromitsu Sasaki
Toyota Memorial Hospital	Jyunji Shinoda
Nakayama Clinic	Mikihiro Nakayama
TOSAKI Clinic for Diabetes and Endocrinology; Medical Corporation TDE	Takahiro Tosaki
Yokkaichi Hazu Medical Center; Japan Community Health care Organization	Yasuhiro Sumida
Yokkaichi Diabetes Clinic; To-cli Medical Corporation	Ryuichi Mizubayashi
Kyoto City Hospital; Local Incorporated Administrative Agency Kyoto City Hospital Organization	Akinori Kogure
Takeda General Hospital; Medical Corporation Ijin-kai	Nobuyuki Azuma
Takatsuki Red Cross Hospital	Shizuka Kaneko
Osak Saiseikai Tondabayashi Hospital; Social Welfare Organization Saiseikai Imperial Gift Foundation, Inc.	Takeshi Kubota
OCROM Clinic; Medical Corporation Heishin-kai	Shigeto Kaneda
Nishi-Umeda Clinic for Asian Medical Collaboration near JR	Naohiko Ueda
Osaka station; Medical Corporation Kyoso-kai	Yoshimitsu Yamasaki
Ikeda Hospital; Social Medical Corporation Seimei-kai	Hiroki Ikeda
The Veritas Hospital; Shinshin-kai Medical Corporation	Keiichiro Tanigawa
	Mitsuru Tsujimoto
Kawanishi City Hospital	Masafumi Koga
	Yuko Nakamura
Japanese Red Cross Society Matsue Hospital	Toshiaki Sato

Medical institution	**Investigator**
Sanuki Municipal Hospital	Toshihiko Inoue
Fukuoka Wajiro Hospital; Social Medical Corporation, the Chiyu-kai Foundation	Masao Ishii
Sugimoto Clinic	Hidekatsu Sugimoto
Shin Koga Clinic; Tenjin-kai Social Medical Corporation	Shoichi Akazawa Eiji Kawasaki
Hirohata Naika Clinic; Medical Corporation	Yoshihide Hirohata
Jinnouchi Hospital Diabetes Care Center; Social Medical Corporation Jinnouchi-kai	Hideaki Jinnouchi
Naika-Abe Clinic; Social Medical Corporation Nobunari-kai	Nobuyuki Abe
Tenpozan Naika; Medical Corporation Shoju-kai	Yasuhiro Hashiguchi
Fukumoto Clinic; Medical Corporation Kashiwagi-kai	Yoshihide Fukumoto

Supplemental Table

Supplemental Table 1. Proportion of participants with missing data

		Esaxerenone				
	Placebo	0.625 mg	1.25 mg	2.5 mg	5 mg	All
	n=73	*n*=73	*n*=73	*n*=72	*n*=74	*N*=365
	n (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)
No primary efficacy data	7 (10)	4 (5)	8 (11)	4 (6)	15 (20)	38 (10)

Supplemental Table 2. Sensitivity analyses for the missing data in the primary endpoint analysis

						Treatment difference		
			n	Geometric LS mean ratio to baseline	95% CI	Geometric LS mean ratio to placebo	95% CI	*P* value
Primary analysis (FAS)	Placebo	*n*=73	71	0.931	0.807–1.074	-	-	-
	Esaxerenone 0.625 mg	*n*=71	70	0.790	0.684–0.913	0.848	0.692–1.040	0.113
	Esaxerenone 1.25 mg	*n*=72	71	0.616	0.533–0.711	0.661	0.539–0.810	<0.001
	Esaxerenone 2.5 mg	*n*=70	69	0.501	0.433–0.579	0.537	0.439–0.659	<0.001
	Esaxerenone 5 mg	*n*=72	69	0.443	0.383–0.512	0.475	0.388–0.583	<0.001
Complete case only analysis (PPS)	Placebo	*n*=61	61	0.927	0.794–1.082	-	-	-
	Esaxerenone 0.625 mg	*n*=64	64	0.782	0.673–0.909	0.844	0.680–1.047	0.123
	Esaxerenone 1.25 mg	*n*=61	61	0.638	0.546–0.745	0.688	0.553–0.857	<0.001
	Esaxerenone 2.5 mg	*n*=64	64	0.497	0.428–0.578	0.537	0.432–0.666	<0.001

	Esaxerenone 5 mg	*n*=55	55	0.449	0.382–0.529	0.485	0.388–0.606	<0.001
MMRM	Placebo	*n*=73	73	0.917	0.793–1.062	-	-	-
analysis	Esaxerenone 0.625 mg	*n*=71	71	0.792	0.685–0.917	0.864	0.703–1.062	0.164
(FAS)	Esaxerenone 1.25 mg	*n*=72	72	0.624	0.538–0.723	0.680	0.552–0.837	<0.001
	Esaxerenone 2.5 mg	*n*=70	70	0.498	0.430–0.577	0.543	0.442–0.668	<0.001
	Esaxerenone 5 mg	*n*=72	72	0.435	0.373–0.507	0.474	0.383–0.585	<0.001

CI, confidence interval; FAS, full analysis set; LS, least square; MMRM, mixed effect model repeat measurement; PPS, per protocol set

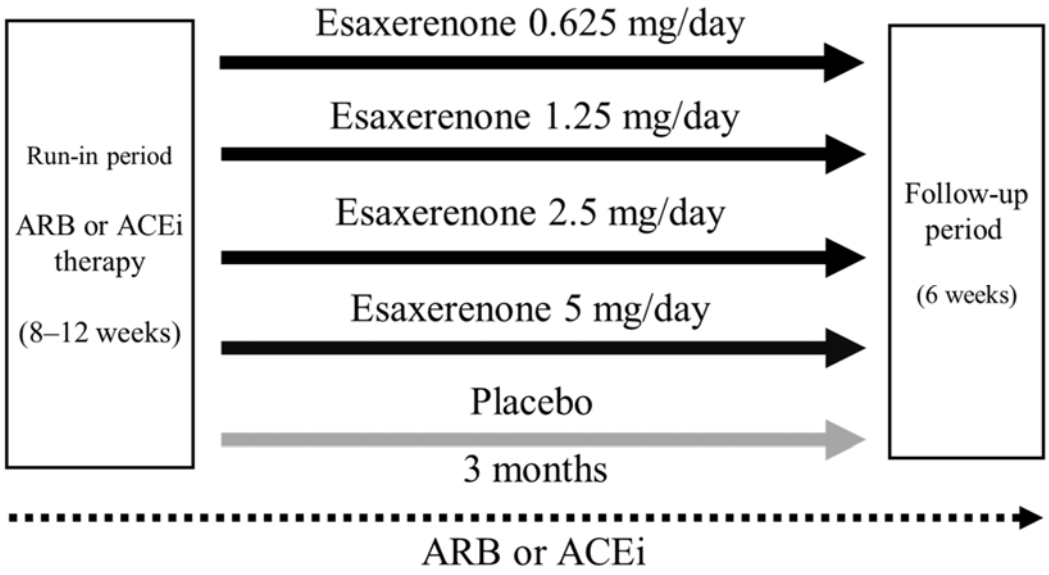
Supplemental Table 3. Plasma esaxerenone concentrations

Esaxerenone dosage		Esaxerenone concentration (ng/mL)	
		Week 4	Week 12
0.625 mg/day	*n*	70	67
	Mean (SD)	4.29 (1.88)	4.43 (1.99)
	Median (min–max)	4.02 (0.0–9.8)	4.00 (0.0–12.8)
1.25 mg/day	*n*	69	64
	Mean (SD)	9.33 (3.55)	9.46 (3.60)
	Median (min–max)	8.91 (3.8–20.2)	9.06 (2.4–20.6)
2.5 mg/day	*n*	68	65
	Mean (SD)	18.28 (7.02)	19.41 (8.94)
	Median (min–max)	17.50 (4.8–39.0)	18.50 (0.3–47.1)
5 mg/day	*n*	68	58
	Mean (SD)	36.80 (15.82)	37.94 (13.02)
	Median (min–max)	34.10 (13.9–84.6)	34.35 (16.1–84.8)

SD, standard deviation.

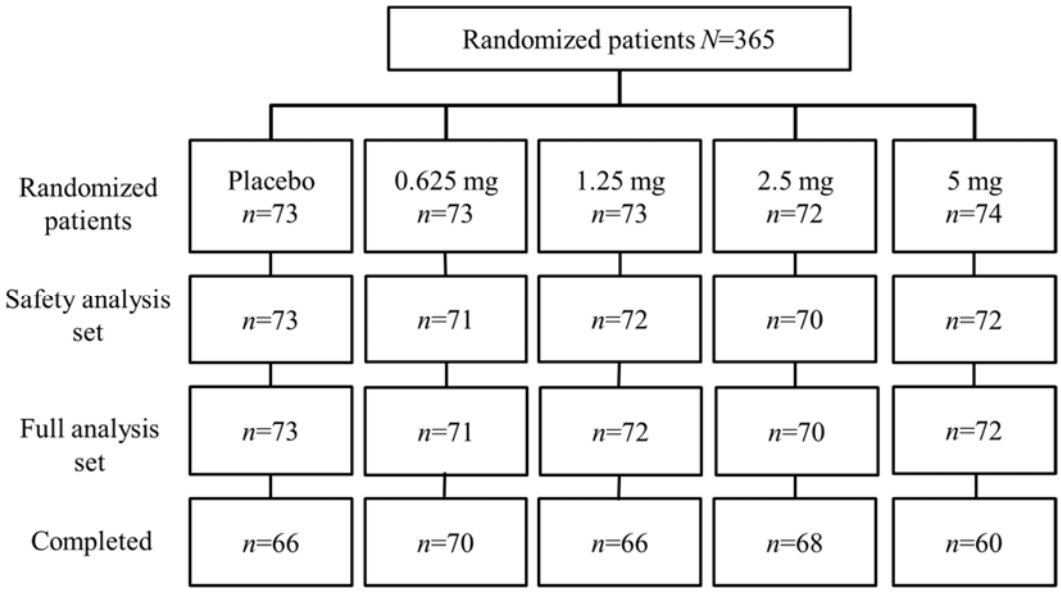
Supplemental figures

Supplemental Figure 1.



Study design. ACEi, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers.

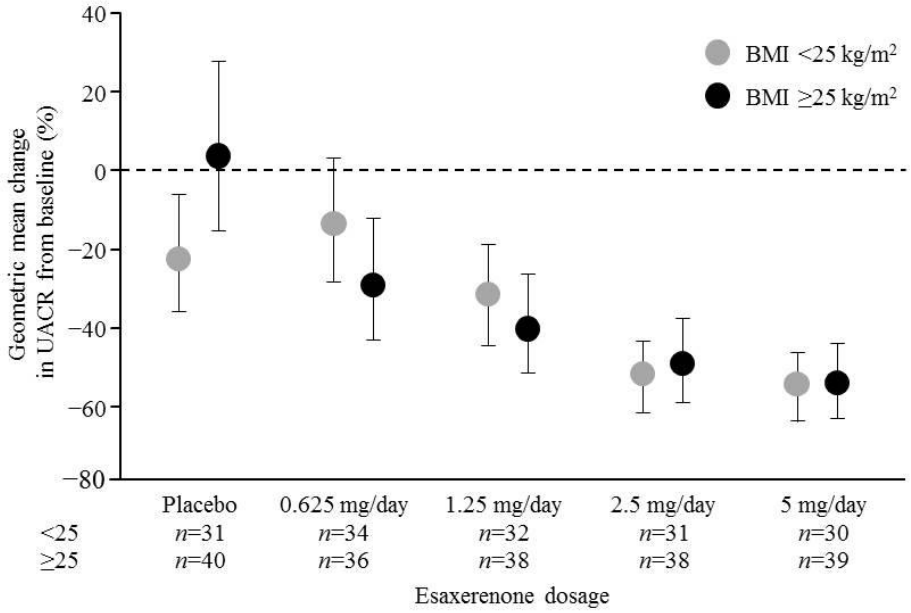
Supplemental Figure 2.



Participant disposition.

Supplemental Figure 3.

a)



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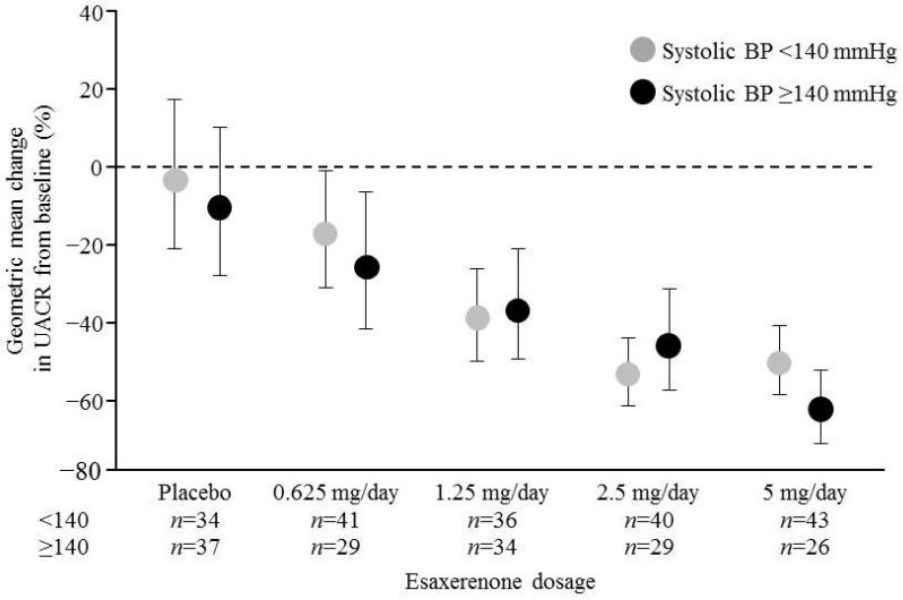
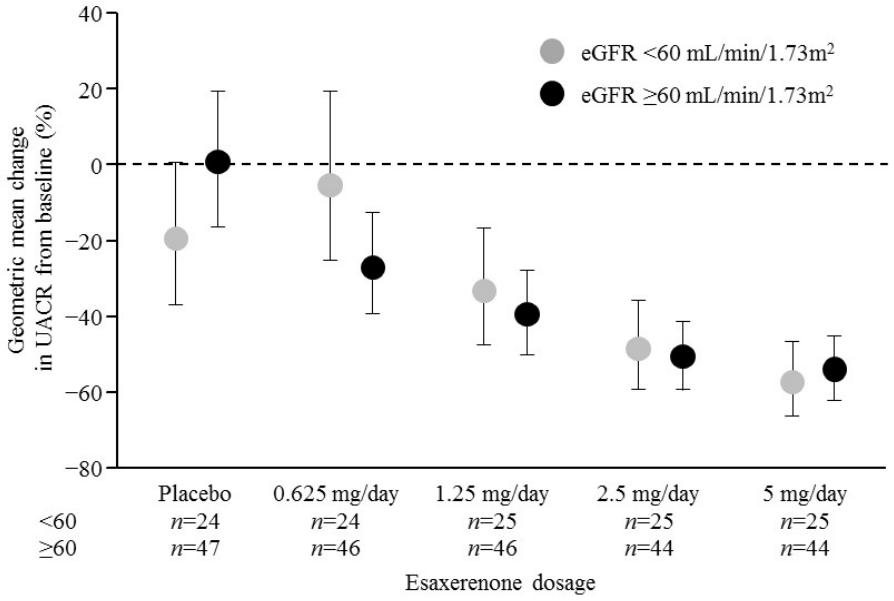
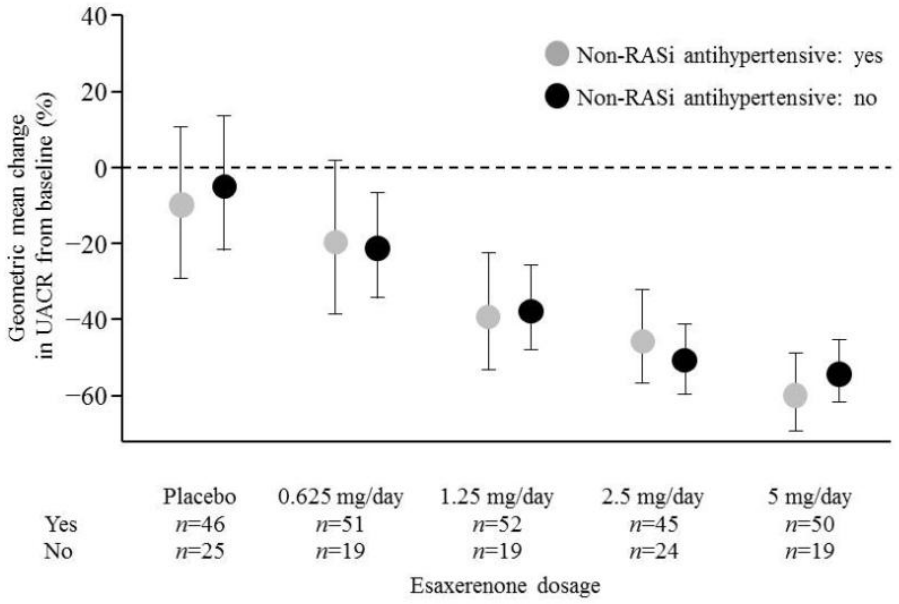

40
20
0
−20
−40
−60
−80
Geometric mean change in UACR from baseline (%)
Systolic BP <140 mmHg
Systolic BP ≥140 mmHg
Placebo
0.625 mg/day
1.25 mg/day
2.5 mg/day
5 mg/day
<140 n=34 n=41 n=36 n=40 n=43
≥140 n=37 n=29 n=34 n=29 n=26
Esaxerenone dosage

c)



d)

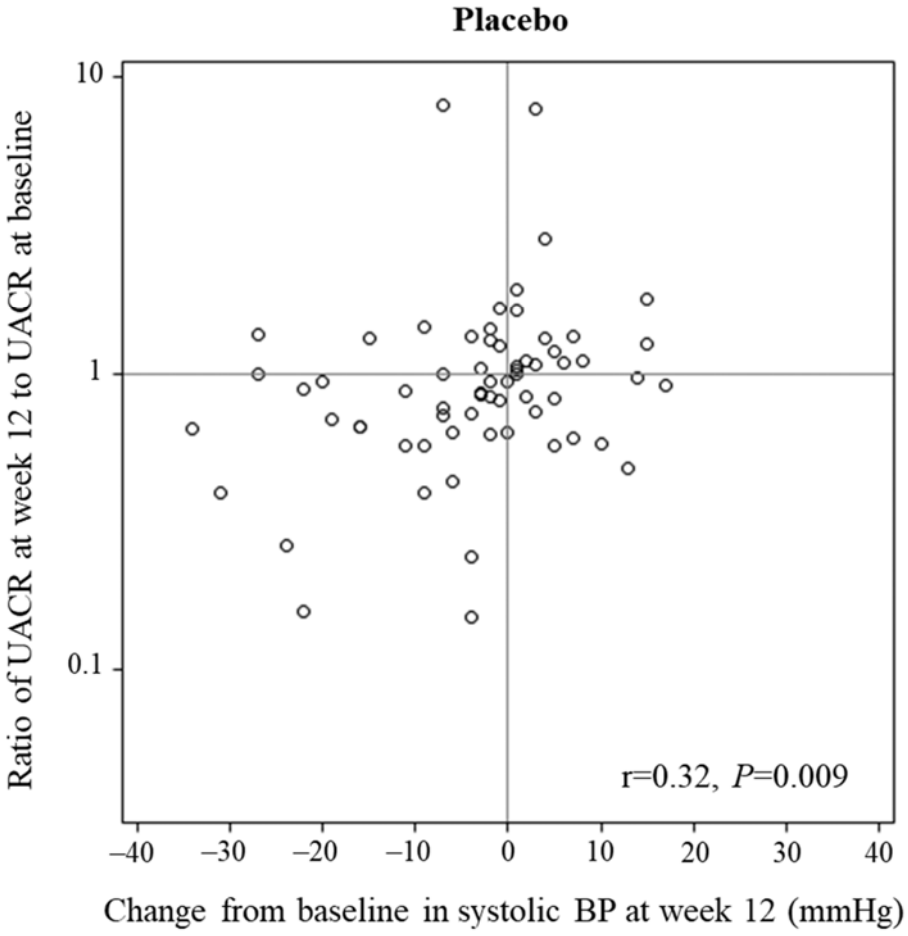


Change in UACR from baseline stratified by (a) BMI, (b) systolic BP, (c) eGFR, and (d) concurrent use of non-RASi antihypertensive drugs.

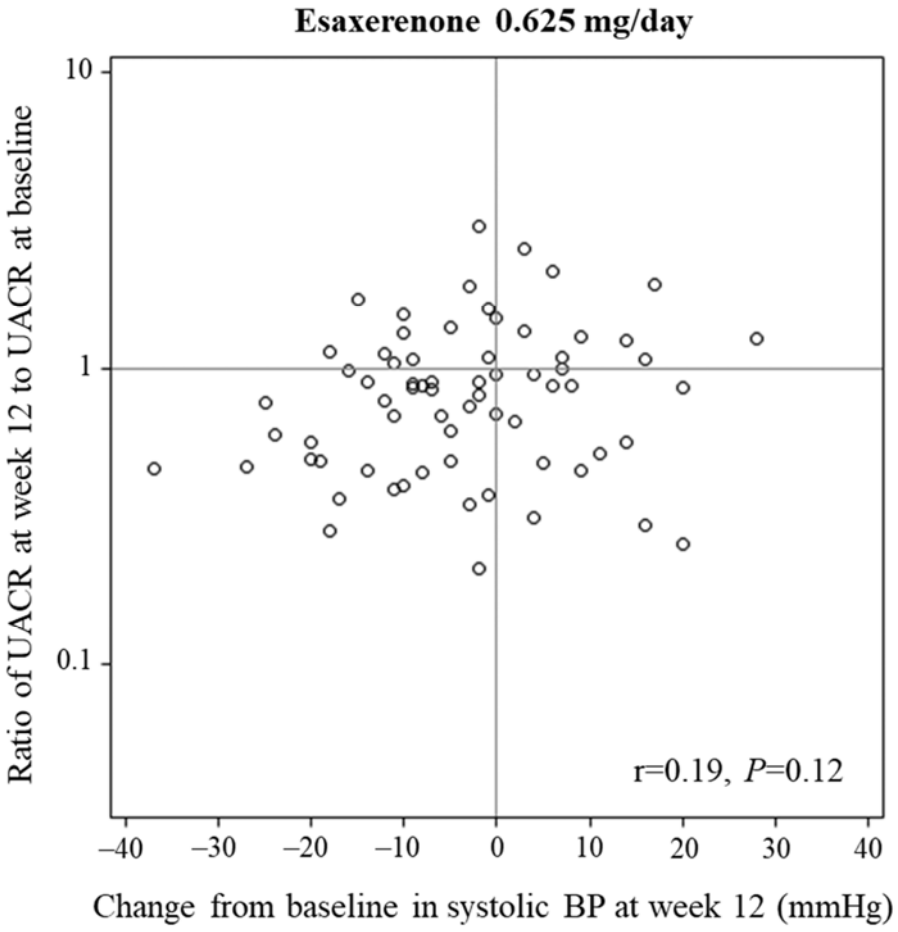
BMI, body mass index; BP, blood pressure; eGFR, estimated glomerular filtration rate; RASi, renin-angiotensin system inhibitors; UACR, urinary albumin/creatinine ratio

Supplemental Figure 4.

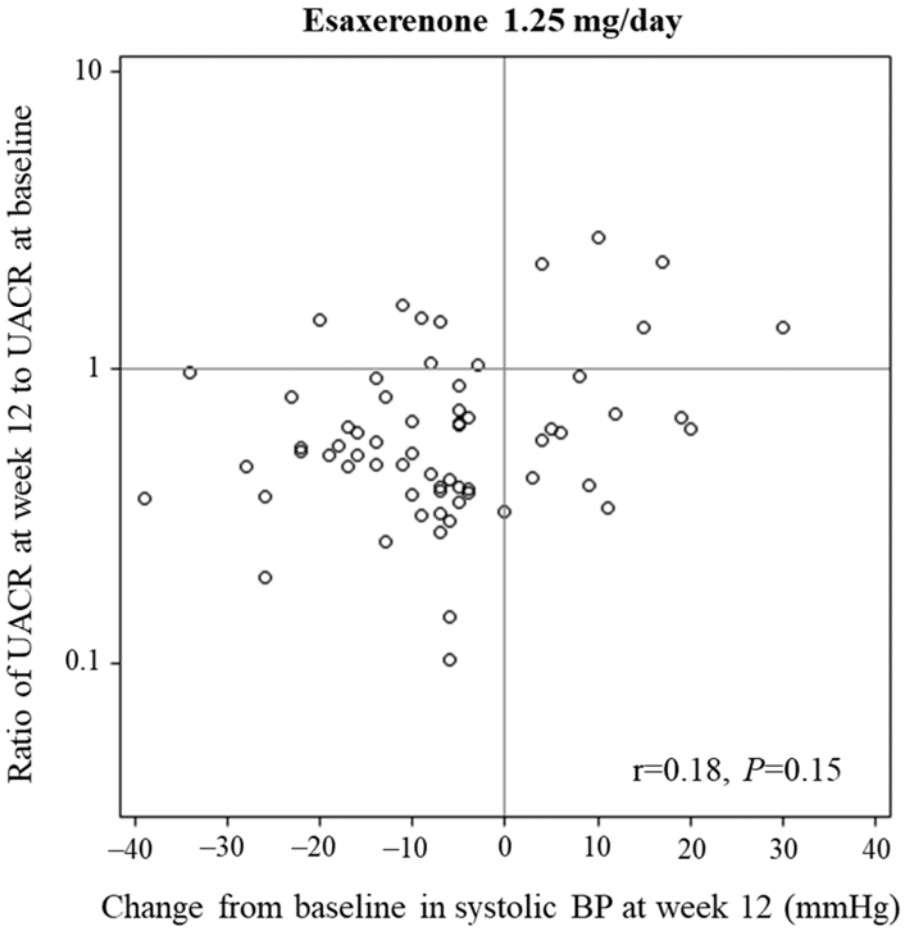
a)



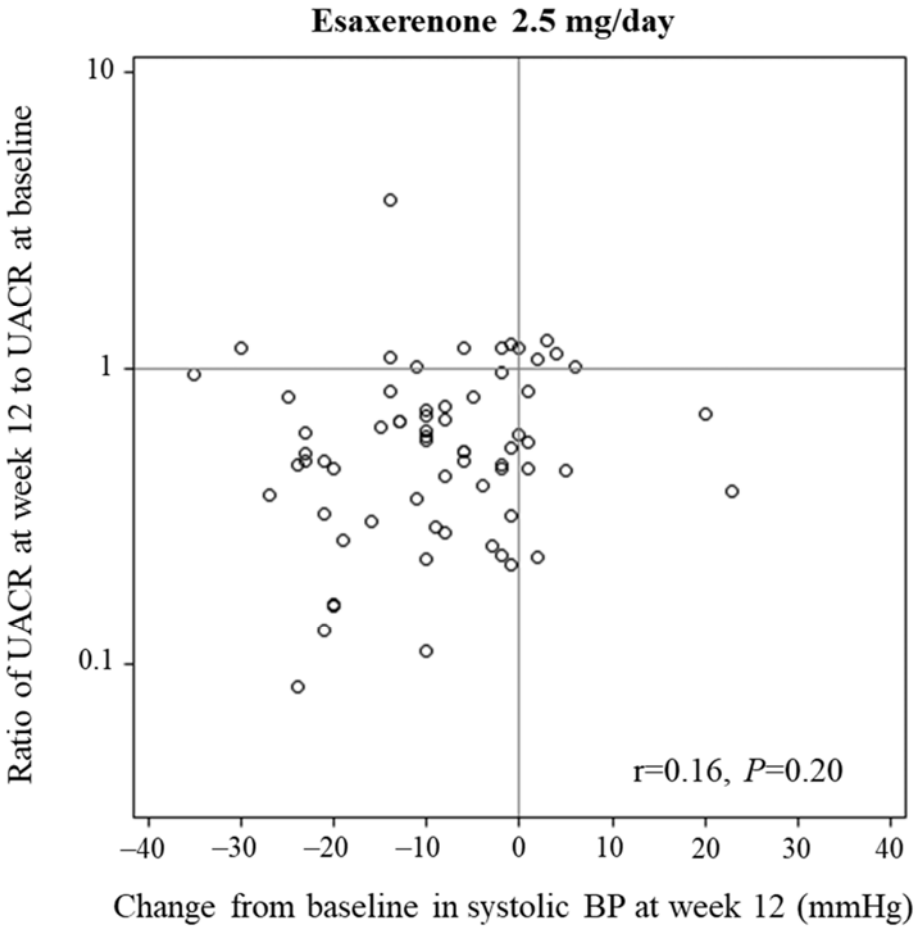
b)


Esaxerenone 0.625 mg/day
10
1
0.1
Ratio of UACR at week 12 to UACR at baseline
r=0.19, P=0.12
–40
–30
–20
–10
0
10
20
30
40
Change from baseline in systolic BP at week 12 (mmHg)

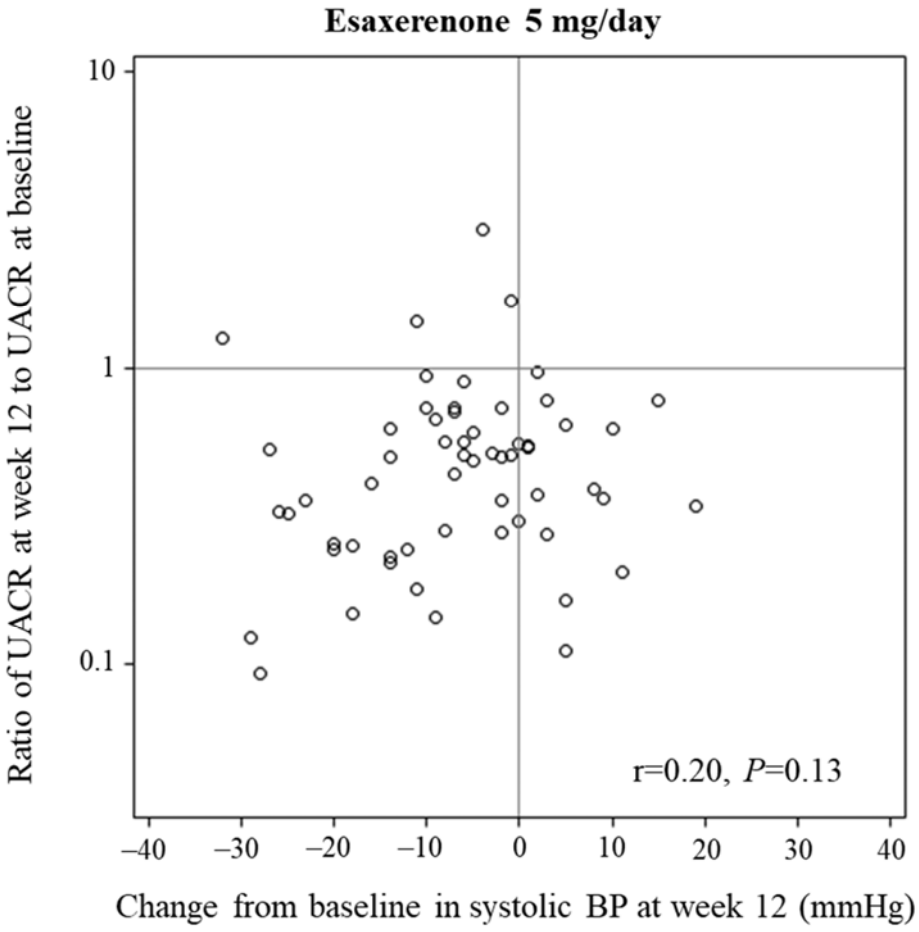
c)


Esaxerenone 1.25 mg/day
Ratio of UACR at week 12 to UACR at baseline
10
1
0.1
r=0.18, P=0.15
–40
–30
–20
–10
0
10
20
30
40
Change from baseline in systolic BP at week 12 (mmHg)

d)


Esaxerenone 2.5 mg/day
Ratio of UACR at week 12 to UACR at baseline
10
1
0.1
r=0.16, P=0.20
–40
–30
–20
–10
0
10
20
30
40
Change from baseline in systolic BP at week 12 (mmHg)

e)



Association between the ratio to baseline in urinary albumin-creatinine ratio (UACR) and the change from baseline in systolic blood pressure at week 12.