Supplementary Material

Supplementary Table Legends

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Supplementary Figure Legends

Figure S1. Relative changes in eGFR (FAS) in (A) cohort G3 and (B) cohort G4

Data are mean (95% CI). *P* value: multiplicity-unadjusted *P* value by *t*-test and post hoc analyses.

CI, confidence interval; eGFR, estimated glomerular filtration rate; FAS, full analysis set.

Figure S2. Urinary ACR (FAS) in (A) cohort G3 and (B) cohort G4

Data are median (+/- IQR). P value: difference between treatment groups at week 16 were calculated by the Wilcoxon rank sum test and post hoc analyses.

ACR, albumin/creatinine ratio; IQR, interquartile range, FAS, full analysis set.

Figure S3. Change from baseline in ACR for individual patients at week 16 (safety analysis set) in (A) placebo-treated cohort G3, (B) bardoxolone methyl-treated cohort G3, (C) placebo-treated cohort G4, and (D) bardoxolone methyl-treated cohort G4

ACR, albumin/creatinine ratio.

Figure S4. BNP levels (safety analysis set) in (A) cohort G3 and (B) cohort G4

Data are median (+/- IQR). P value: difference between treatment groups at week 16 were calculated by the Wilcoxon rank sum test and post hoc analyses.

BNP, B-type natriuretic peptide; IQR, interquartile range.

Figure S5. Change from baseline in BNP for individual patients at week 16 (safety analysis set) in (A) placebo-treated cohort G3, (B) bardoxolone methyl-treated cohort G3, (C) placebo-treated cohort G4, and (D) bardoxolone methyl-treated cohort G4

BNP, B-type natriuretic peptide.

Figure S6. Change from baseline at week 16 in FS (safety analysis set) in (A) cohort G3 and (B) cohort G4

Data are mean (95% CI). *P* value: multiplicity-unadjusted *P* value by *t*-test and post hoc analyses.

CI, confidence interval; FS, fractional shortening.

Figure S7. Change from baseline at week 16 in CTR (safety analysis set) in (A) cohort G3 and (B) cohort G4

Data are mean (95% CI). P value: multiplicity-unadjusted P value by t-test and post hoc analyses.

CI, confidence interval; CTR, cardiothoracic ratio.

This supplementary material has been provided by the authors to give readers additional information about their work.

Table S1. TSUBAKI study inclusion/exclusion criteria and details of masking

Main inclusion criteria
1. CKD with type 2 diabetes mellitus 2. Age between ≥ 20 and < 80 years at the time of consent 3. Estimated glomerular filtration rate between ≥ 15 and < 60 ml/min/1.73 m^2 4. ACR < 300 mg/g for CKD stage G3 or ACR < 2000 mg/g for CKD stage G4 5. BNP < 200 pg/ml 6. Treatment with an angiotensin-converting enzyme inhibitor and/or an angiotensin II receptor blocker before screening, with no change in dosage or medication 7. Voluntary written informed consent to participate in the study
Main exclusion criteria
1. Type 1 diabetes mellitus 2. Nondiabetic renal disease 3. History of renal transplantation 4. Systolic blood pressure > 160 mmHg or diastolic blood pressure > 90 mmHg 5. Glycated hemoglobin > 10.0% (National Glycohemoglobin Standardization Program) 6. Cardiovascular disease defined as any of the following ・ Unstable angina pectoris ・ Myocardial infarction, coronary artery bypass graft surgery, or percutaneous transluminal

coronary angioplasty/stenting

- Cerebrovascular accident, including transient ischemic attack
- Valvular heart disease or hypertrophic cardiomyopathy requiring treatment
- Second- or third-degree atrioventricular block not improved by a pacemaker
- Class III or IV New York Heart Association congestive heart failure

7. History of heart failure
8. Onset or worsening of symptoms/signs of peripheral edema as an early manifestation of acute volume overload
9. Left ventricular fractional shortening < 22% on echocardiography
10. Abnormal hepatobiliary function defined as the following:
    - Total bilirubin level greater than the ULN
    - Aspartate aminotransferase or alanine aminotransferase level greater than the ULN
    - Alkaline phosphatase level greater than 2 times the ULN
11. Dialysis, acute kidney injury, or rapid improvement or worsening of CKD
12. Clinical symptoms of dysuria (excluding catheterized patients)
13. 100 ml or more of residual urine volume measured after complete voiding

Masking

Patients, investigators, site medical staff, and the sponsor were masked to the treatment assignment until the code was broken in each cohort, and to parameters that could vary by treatment with

bardoxolone methyl, ie, AST, ALT, creatinine clearance, serum creatinine, urine creatinine, serum inulin, urine inulin, GFR, eGFR, plasma bardoxolone methyl concentration, ACR, and urinary protein/creatinine ratio, until the observation was completed for the last patient in each cohort.

ACR, albumin/creatinine ratio; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BNP, B-type natriuretic peptide; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; GFR, glomerular filtration rate; ULN, upper limit of normal.

Table S2. Breakdown of reasons for discontinuation

Group	Reasons for discontinuation			
Placebo	Cohort G3	1	1 AE	・Angina pectoris
Bardoxolone methyl	Cohort G3	8	2 AE	・ALT increased (126 U/l) ・Worsening spinal osteoarthritis
			4 physician decision	・Difficulty in securing patient safety when traveling abroad ・AST/ALT increased (AST, 44 U/l; ALT, 61 U/l) ・Difficulty in maintaining ARB usage that was specified in the protocol ・Hospitalization due to tibia fracture (impossible to evaluate kidney function properly)
			2 withdrew consent	-
	Cohort G4	7	3 AE	・Pyelonephritis acute ・Influenza/pneumonia pneumococcal ・Diabetic gangrene (history of ASO and diabetic gangrene)
			4 withdrew	-

consent

AE, adverse event; ALT, alanine aminotransferase; ARB, angiotensin II receptor blocker;

ASO, arteriosclerosis obliterans; AST, aspartate aminotransferase.

Table S3. Baseline characteristics (interim PPS)

	Cohort G3	
	Bardoxolone methyl	**Placebo**
	(n = 17)	**(n = 23)**
Sex, n (%)		
Female	6 (35.3)	6 (26.1)
Male	11 (64.7)	17 (73.9)
Age, yr, mean (SD)	69.4 (8.5)	72.7 (4.6)
Weight, kg, mean (SD)	61.29 (9.68)	65.46 (10.59)
BMI, kg/m^2, mean (SD)	24.21 (3.59)	25.22 (3.17)
GFR, ml/min per 1.73 m^2, mean (SD)	48.95 (9.62)	48.13 (9.86)
eGFR, ml/min per 1.73 m^2, mean (SD)	48.89 (7.70)	45.03 (6.68)
Serum creatinine, mg/dl, mean (SD)	1.085 (0.227)	1.181 (0.224)
Urine creatinine, g/d, mean (SD)	1.081 (0.263)	1.110 (0.263)
ACR, mg/g, mean (SD)	77.94 (113.58)	36.20 (50.33)
BNP, pg/ml, mean (SD)	27.59 (37.36)	24.92 (22.32)

Blood pressure, mmHg, mean (SD)		
Systolic	127.3 (20.9)	122.2 (16.4)
Diastolic	73.8 (12.3)	67.0 (9.0)
HbA_{1c}, %, mean (SD)	6.89 (1.05)	6.91 (0.55)

ACR, albumin/creatinine ratio; BMI, body mass index; BNP, B-type natriuretic peptide; eGFR, estimated glomerular filtration rate; GFR, glomerular filtration rate; HbA_{1c}, glycated hemoglobin; PPS, per-protocol set; SD, standard deviation.

Table S4. Baseline characteristics (final PPS)

	Cohort G3	
	Bardoxolone methyl	**Placebo**
	(n = 19)	**(n = 25)**
Sex, n (%)		
Female	7 (36.8)	6 (24.0)
Male	12 (63.2)	19 (76.0)
Age, yr, mean (SD)	69.3 (8.0)	72.2 (5.1)
Weight, kg, mean (SD)	62.35 (10.45)	65.65 (10.47)
BMI, kg/m^2, mean (SD)	24.62 (3.61)	25.12 (3.06)
GFR, ml/min per 1.73 m^2, mean (SD)	48.51 (9.60)	47.92 (9.47)
eGFR, ml/min per 1.73 m^2, mean (SD)	48.09 (8.52)	45.28 (6.60)
Serum creatinine, mg/dl, mean (SD)	1.101 (0.225)	1.183 (0.215)
ACR, mg/g, mean (SD)	71.26 (108.96)	48.43 (76.74)
BNP, pg/ml, mean (SD)	26.22 (35.50)	23.80 (21.84)

Blood pressure, mmHg, mean (SD)		
Systolic	125.6 (21.0)	121.4 (16.0)
Diastolic	72.7 (11.6)	67.4 (8.8)
HbA_{1c}, %, mean (SD)	6.97 (1.01)	7.01 (0.64)

ACR, albumin/creatinine ratio; BMI, body mass index; BNP, B-type natriuretic peptide; eGFR, estimated glomerular filtration rate; GFR, glomerular filtration rate; HbA_{1c}, glycated hemoglobin; PPS, per-protocol set; SD, standard deviation.

Table S5. Adverse events of special interest

	Cohort G3		**Cohort G4**	
	Bardoxolone methyl	**Placebo**	**Bardoxolone methyl**	**Placebo**
	(n = 41)	**(n = 41)**	**(n = 24)**	**(n = 14)**
Any adverse event, n (%)				
Muscle spasms*	5 (12.2)	1 (2.4)	1 (4.2)	0 (0)
Weight decreased	0 (0)	0 (0)	1 (4.2)	0 (0)
Urine protein/creatinine ratio increased	2 (4.9)	0 (0)	2 (8.3)	0 (0)
Urine ACR increased	2 (4.9)	0 (0)	2 (8.3)	0 (0)
Hypomagnesemia	0 (0)	0 (0)	0 (0)	0 (0)

*All the muscle spasm events observed were mild events

ACR, albumin/creatinine ratio

Table S6. TSUBAKI study groups

Independent data monitoring committee:
Yuzo Watanabe (Kasugai Municipal Hospital; Chair), Yoshiharu Tsubakihara (Graduate School of Health Care Sciences, Jikei Institute), Makoto Akaishi (Tokai University School of Medicine), Hajime Takikawa (Teikyo University), Satoshi Morita (Kyoto University Graduate School of Medicine).
Sites and principal investigators:
Shinshu University Hospital: Yuji Kamijo Japanese Red Cross Society Suwa Hospital: Naoki Tachibana Matsumoto City Hospital: Shinji Ako Ina Central Hospital: Wataru Yumita Tsuchiura Kyodo General Hospital: Takayuki Toda JA Toride Medical Center: Yoshitaka Maeda Moriya Keiyu Hospital: Tokuro Kobayashi/Akira Imamura Ibaraki Seinan Medical Center Hospital: Tadashi Iitsuka Japanese Red Cross Koga Hospital: Yasushi Asano Mito Kyodo General Hospital: Hiroaki Yagyu Taga General Hospital: Soichi Hotta Showa University Northern Yokohama Hospital: Eriko Kinugasa/Masahiro Yamamoto

Tokyo Teishin Hospital: Hideki Takano

Dokkyo Medical University Koshigaya Hospital: Tetsuro Takeda

Chubu-Rosai Hospital: Nakashima Eitaro

Daiyukai Daiichi Hospital: Masanobu Horie

Meitetsu Hospital: Hideki Okamoto

Kamiiida Daiichi General Hospital: Yukiko Yamamoto

Kodama Hospital: Naoya Kodama

Shigei Medical Research Hospital: Masaki Fukushima

Japanese Red Cross Society Azumino Hospital: Masuo Tokoo

Maruko Central Hospital: Shigetoshi Tsuzuki

Nagano Chuo Hospital: Teruki Kondou

Nagoya Kyoritsu Hospital: Hirotake Kasuga

Jyousai Hospital: Hachiro Seno

Narita Memorial Hospital: Takaaki Ohbayashi

Shirasagi Hospital: Shigeichi Shoji

Matsumoto Medical Center: Makoto Higuchi

New Tokyo Hospital: Yusuke Fujino

Edogawa Hospital: Hiroyuki Ito

Okayama Saiseikai General Hospital: Makoto Hiramatsu

Japanese Red Cross Fukuoka Hospital: Koji Mitsuiki

Japanese Red Cross Nagoya Daini Hospital: Daijyo Inaguma/Asami Takeda

Osaka General Medical Center: Terumasa Hayashi

Kokura Kinen Hospital: Hidetoshi Kanai

Daido Hospital: Yasuhiro Terashima

Figure S1. Relative changes in eGFR (FAS) in (A) cohort G3 and (B) cohort G4

Data are mean (95% CI). *P* value: multiplicity-unadjusted *P* value by *t*-test and post hoc analyses.

CI, confidence interval; eGFR, estimated glomerular filtration rate; FAS, full analysis set.

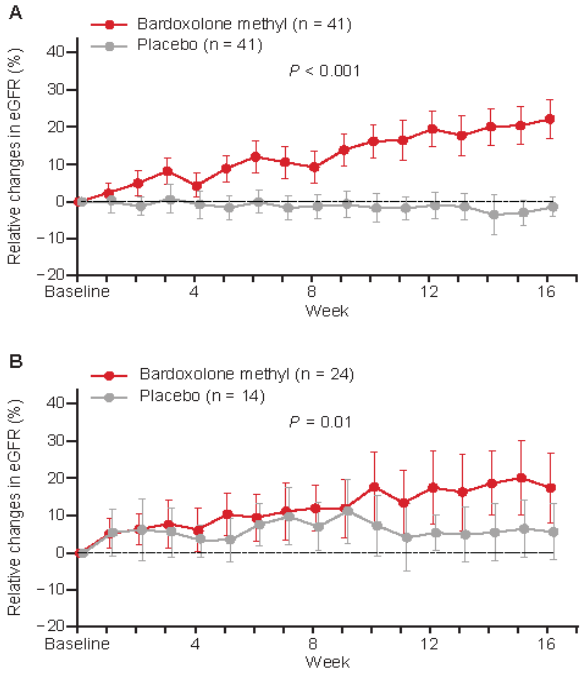


Figure S2. Urinary ACR (FAS) in (A) cohort G3 and (B) cohort G4

Data are median (+/- IQR). P value: difference between treatment groups at week 16 were calculated by the Wilcoxon rank sum test and post hoc analyses.

ACR, albumin/creatinine ratio; IQR, interquartile range, FAS, full analysis set.

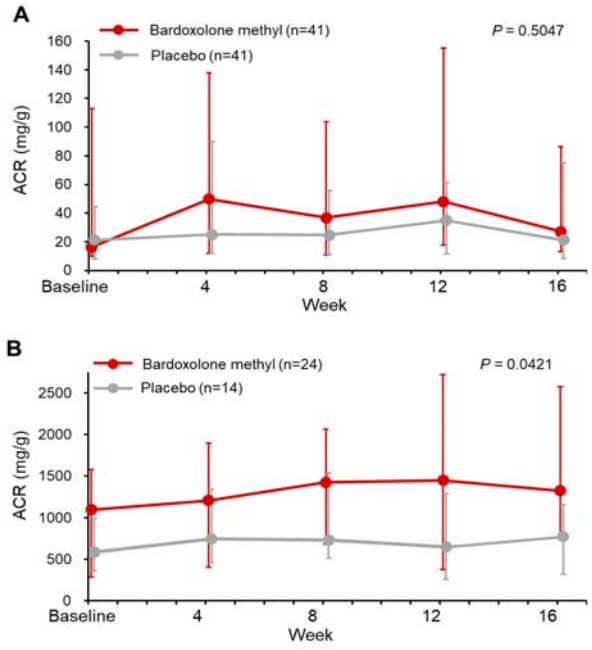


Figure S3. Change from baseline in ACR for individual patients at week 16 (safety analysis set) in (A) placebo-treated cohort G3, (B) bardoxolone methyl-treated cohort G3, (C) placebo-treated cohort G4, and (D) bardoxolone methyl-treated cohort G4

ACR, albumin/creatinine ratio.

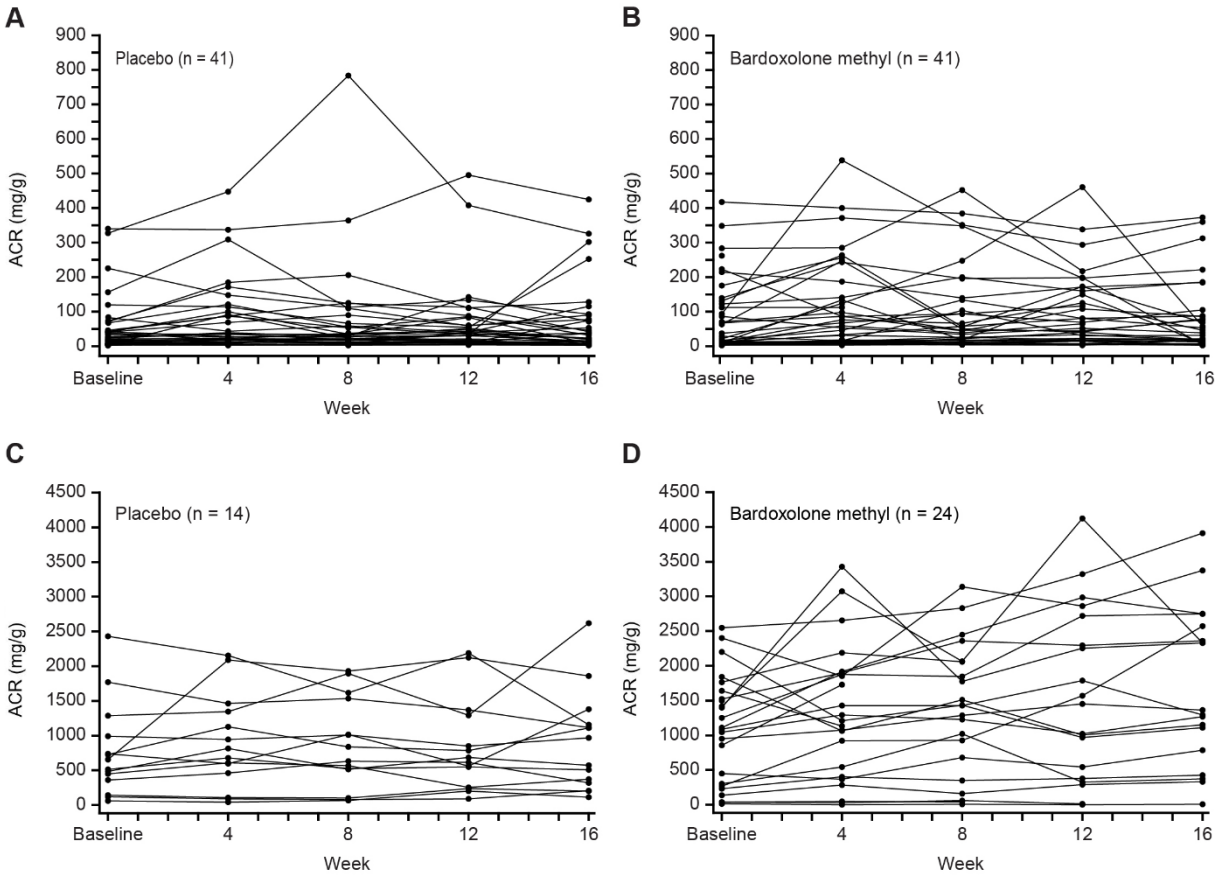


Figure S4. BNP levels (safety analysis set) in (A) cohort G3 and (B) cohort G4

Data are median (+/- IQR). P value: difference between treatment groups at week 16 were calculated by the Wilcoxon rank sum test and post hoc analyses.

BNP, B-type natriuretic peptide; IQR, interquartile range.

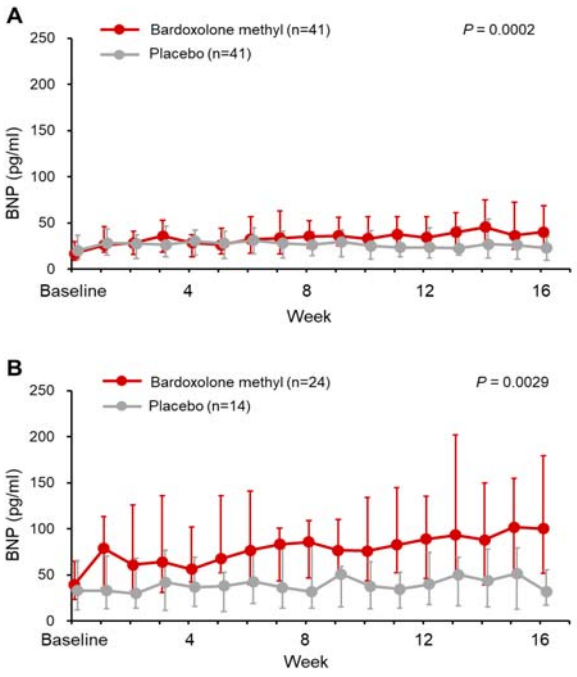


Figure S5. Change from baseline in BNP for individual patients at week 16 (safety analysis set) in (A) placebo-treated cohort G3, (B) bardoxolone methyl-treated cohort G3, (C) placebo-treated cohort G4, and (D) bardoxolone methyl-treated cohort G4

BNP, B-type natriuretic peptide.

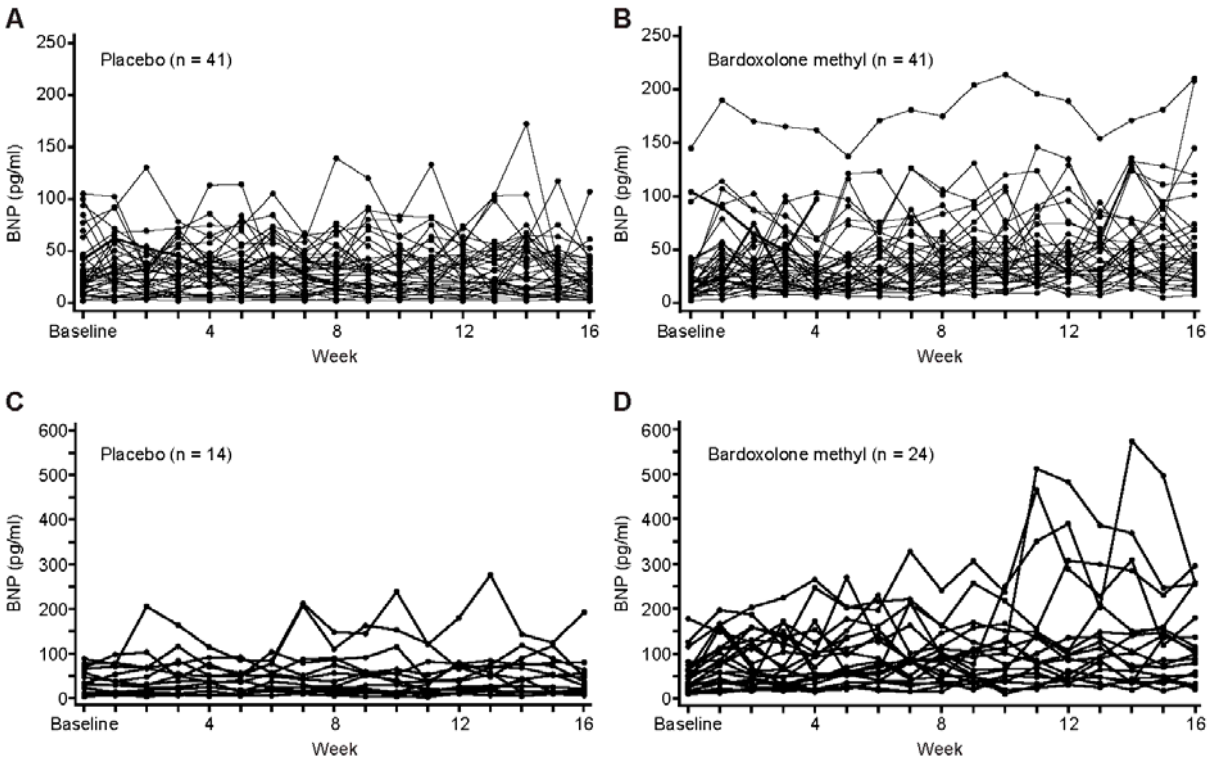


Figure S6. Change from baseline at week 16 in FS (safety analysis set) in (A) cohort G3 and (B) cohort G4

Data are mean (95% CI). *P* value: multiplicity-unadjusted *P* value by *t*-test and post hoc analyses.

CI, confidence interval; FS, fractional shortening.

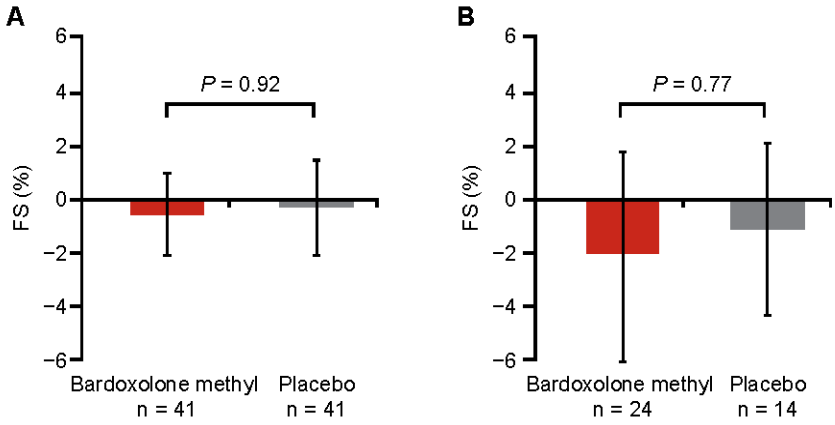
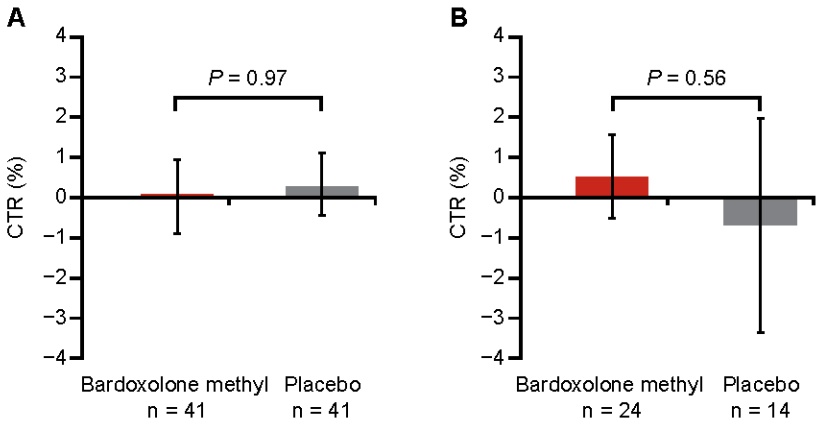


Figure S7. Change from baseline at week 16 in CTR (safety analysis set) in (A) cohort G3 and (B) cohort G4

Data are mean (95% CI). P value: multiplicity-unadjusted P value by t-test and post hoc analyses.

CI, confidence interval; CTR, cardiothoracic ratio.



CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	3-4
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	5-6
	2b	Specific objectives or hypotheses	5-6
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	6-7
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	6
Participants	4a	Eligibility criteria for participants	6
	4b	Settings and locations where the data were collected	6
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	6-7
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	7-9
	6b	Any changes to trial outcomes after the trial commenced, with reasons	NA
Sample size	7a	How sample size was determined	9
	7b	When applicable, explanation of any interim analyses and stopping guidelines	8
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	6-7
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	6-7
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	6-7
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	6-7
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	6-7

		assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	NA
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	9
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	9
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	10
	13b	For each group, losses and exclusions after randomisation, together with reasons	10
Recruitment	14a	Dates defining the periods of recruitment and follow-up	10
	14b	Why the trial ended or was stopped	NA
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	11
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	10
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	11
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	NA
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	11-12
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	NA
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	18-19
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	18-19
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	14-19
Other information			
Registration	23	Registration number and name of trial registry	4
Protocol	24	Where the full trial protocol can be accessed, if available	Other file
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	19

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.