Supplementary Material

An exploratory randomized trial of SCO-792, an enteropeptidase inhibitor, in patients with type 2 diabetes and albuminuria

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Running title: Effect of SCO-792 in T2DM and albuminuria patients

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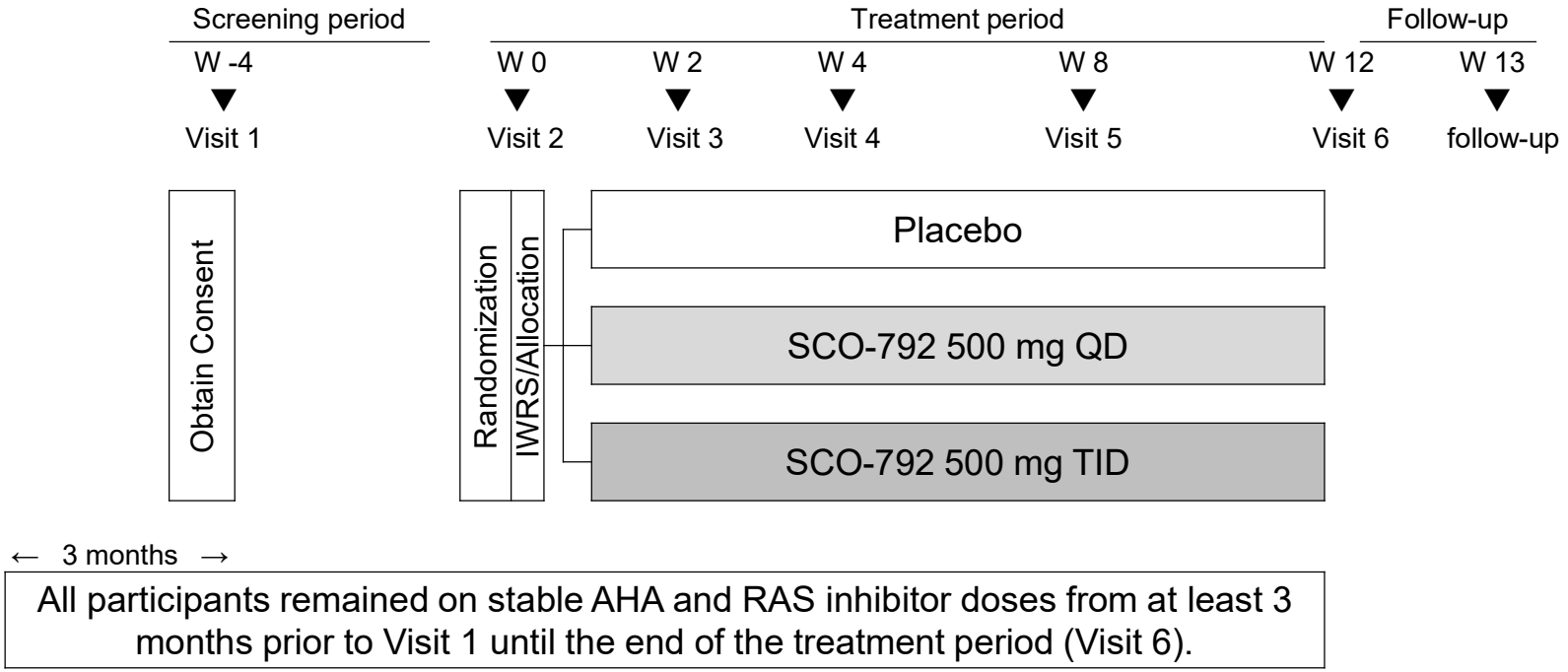


Supplementary Figure S1. Study design

After the screening period (-4 weeks), the enrolled subjects were randomized to either one of the three treatment groups. Stratification and randomization were performed via the Interactive Web Response System (IWRS). The study included a treatment period of 12 weeks and a follow-up period of one week. In addition to urine and blood collection, body weight, pulse rate, body temperature, 12-lead electrocardiograms (ECG), trough sitting diastolic blood pressure, and systolic blood pressure were measured at each visit.

AHA, antihyperglycemic agent; RAS, renin-angiotensin system; QD, once a day; TID, thrice a day; W, week.

Supplementary Table S1. Concomitant medications in AHA

ATC Level 2 Preferred Term	Placebo (*N* = 15) *n* (%)	SCO-792 500 mg QD (*N* = 29) *n* (%)	SCO-792 500 mg TID (*N* = 28) *n* (%)	All SCO-792 (*N* = 57) *n* (%)	All Participants (*N* = 72) *n* (%)
DRUGS USED IN DIABETES	15 (100.0)	29 (100.0)	28 (100.0)	57 (100.0)	72 (100.0)
Metformin hydrochloride	11 (73.3)	18 (62.1)	21 (75.0)	39 (68.4)	50 (69.4)
Gliclazide	3 (20.0)	3 (10.3)	9 (32.1)	12 (21.1)	15 (20.8)
Insulin Glargine	4 (26.7)	5 (17.2)	4 (14.3)	9 (15.8)	13 (18.1)
Empagliflozin	3 (20.0)	3 (10.3)	2 (7.1)	5 (8.8)	8 (11.1)
Metformin hydrochloride; Vildagliptin	1 (6.7)	4 (13.8)	3 (10.7)	7 (12.3)	8 (11.1)
Insulin	1 (6.7)	4 (13.8)	2 (7.1)	6 (10.5)	7 (9.7)
Insulin aspart	0	3 (10.3)	2 (7.1)	5 (8.8)	5 (6.9)
Insulin aspart; Insulin aspart protamine (crystalline)	4 (26.7)	1 (3.4)	0	1 (1.8)	5 (6.9)
Dulaglutide	1 (6.7)	3 (10.3)	0	3 (5.3)	4 (5.6)
Glipizide	2 (13.3)	2 (6.9)	0	2 (3.5)	4 (5.6)
Dapagliflozin propanediol monohydrate	1 (6.7)	1 (3.4)	1 (3.6)	2 (3.5)	3 (4.2)
Insulin aspart; Insulin degludec	1 (6.7)	2 (6.9)	0	2 (3.5)	3 (4.2)
Insulin Glulisine	0	3 (10.3)	0	3 (5.3)	3 (4.2)
Insulin human injection, isophane	0	0	3 (10.7)	3 (5.3)	3 (4.2)
Empagliflozin; Metformin hydrochloride	0	2 (6.9)	0	2 (3.5)	2 (2.8)
Exenatide	0	2 (6.9)	0	2 (3.5)	2 (2.8)
Insulin Lispro	0	0	2 (7.1)	2 (3.5)	2 (2.8)
Insulin lispro; Insulin lispro protamine suspension	0	2 (6.9)	0	2 (3.5)	2 (2.8)
Linagliptin	1 (6.7)	0	1 (3.6)	1 (1.8)	2 (2.8)
Metformin hydrochloride; Sitagliptin phosphate monohydrate	0	1 (3.4)	1 (3.6)	2 (3.5)	2 (2.8)
Sitagliptin	1 (6.7)	0	1 (3.6)	1 (1.8)	2 (2.8)
Sitagliptin Phosphate	0	1 (3.4)	1 (3.6)	2 (3.5)	2 (2.8)
Vildagliptin	1 (6.7)	0	1 (3.6)	1 (1.8)	2 (2.8)
Alogliptin benzoate; Metformin hydrochloride	0	1 (3.4)	0	1 (1.8)	1 (1.4)
Dapagliflozin propanediol monohydrate; Metformin hydrochloride	1 (6.7)	0	0	0	1 (1.4)
Dapagliflozin; Metformin	0	0	1 (3.6)	1 (1.8)	1 (1.4)
Insulin human	0	0	1 (3.6)	1 (1.8)	1 (1.4)
Insulin isophane bovine	0	1 (3.4)	0	1 (1.8)	1 (1.4)
Semaglutide	0	0	1 (3.6)	1 (1.8)	1 (1.4)

Concomitant medication is defined as any medication taken at least once on or after the first IP administration. Medications were coded using WHODRUG GLOBAL C3 September 1, 2019.

AHA, antihyperglycemic agents; ATC, anatomical therapeutic chemical (class); QD, once a day; TID, thrice a day; WHO, World Health Organization; *N*, total number of participants in the relevant group; *n*, number of participants in each category (participants with multiple medications in each category were counted only once in each category); % = percentage of participants in each category calculated relative to the total number of participants in the relevant group.

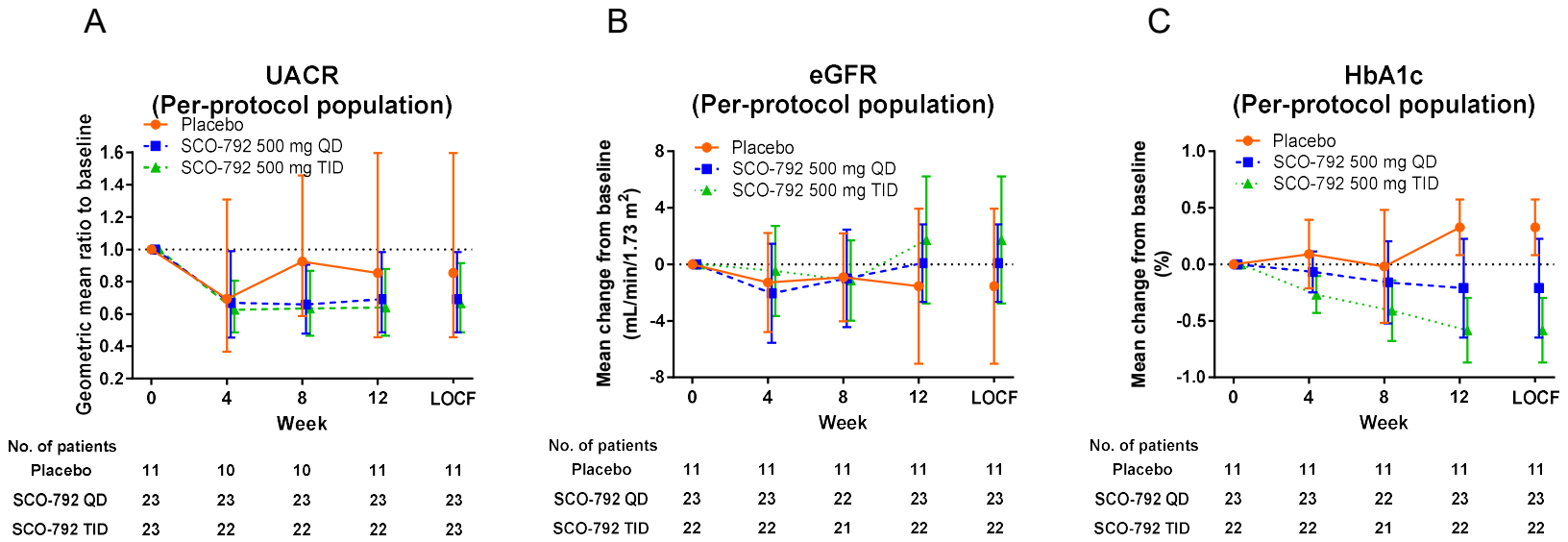
Supplementary Table S2. Concomitant medications in RAS inhibitors

ATC Level 2 Preferred Term	Placebo (*N* = 15) *n* (%)	SCO-792 500 mg QD (*N* = 29) *n* (%)	SCO-792 500 mg TID (*N* = 28) *n* (%)	All SCO-792 (*N* = 57) *n* (%)	All Participants (*N* = 72) *n* (%)
AGENTS ACTING ON THE RENIN-ANGIOTENSIN SYSTEM	15 (100.0)	29 (100.0)	27 (96.4)#	56 (98.2)	71 (98.6)
Cilazapril	4 (26.7)	9 (31.0)	7 (25.0)	16 (28.1)	20 (27.8)
Candesartan cilexetil	1 (6.7)	4 (13.8)	4 (14.3)	8 (14.0)	9 (12.5)
Quinapril hydrochloride	2 (13.3)	4 (13.8)	3 (10.7)	7 (12.3)	9 (12.5)
Losartan potassium	1 (6.7)	4 (13.8)	3 (10.7)	7 (12.3)	8 (11.1)
Irbesartan	1 (6.7)	1 (3.4)	2 (7.1)	3 (5.3)	4 (5.6)
Amlodipine besilate; Telmisartan	0	3 (10.3)	0	3 (5.3)	3 (4.2)
Perindopril Erbumine	1 (6.7)	0	2 (7.1)	2 (3.5)	3 (4.2)
Telmisartan	0	2 (6.9)	1 (3.6)	3 (5.3)	3 (4.2)
Cilazapril;Hydrochlorothiazide	1 (6.7)	0	1 (3.6)	1 (1.8)	2 (2.8)
Olmesartan Medoxomil	1 (6.7)	0	1 (3.6)	1 (1.8)	2 (2.8)
Perindopril Arginine	0	1 (3.4)	1 (3.6)	2 (3.5)	2 (2.8)
Amlodipine besilate; Perindopril Arginine	0	1 (3.4)	0	1 (1.8)	1 (1.4)
Amlodipine besilate; Valsartan	1 (6.7)	0	0	0	1 (1.4)
Hydrochlorothiazide; Irbesartan	1 (6.7)	0	0	0	1 (1.4)
Hydrochlorothiazide; Quinapril hydrochloride	0	0	1 (3.6)	1 (1.8)	1 (1.4)
Lisinopril dihydrate	1 (6.7)	0	0	0	1 (1.4)
Ramipril	0	1 (3.4)	0	1 (1.8)	1 (1.4)
Valsartan	0	0	1 (3.6)	1 (1.8)	1 (1.4)

Concomitant medication is defined as any medication taken at least once on or after the first IP administration. Medications were coded using WHODRUG GLOBAL C3 September 1, 2019.

#: Participant 201-013 in the SCO-792 500 mg TID group was not reported on the electronic case report form page as having received an RAS inhibitor; however, all participants received RAS inhibitors throughout the study, in line with inclusion criterion #5 of the protocol.

RAS, renin-angiotensin system; ATC, anatomical therapeutic chemical (class); QD, once a day; TID, thrice a day; WHO, World Health Organization; *N*, total number of participants in the relevant group; *n*, number of participants in each category (participants with multiple medications in each category were counted only once in each category); % = percentage of participants in each category calculated relative to the total number of participants in the relevant group.



Supplementary Figure S2. UACR, eGFR, and HbA1c (per-protocol population)

Geometric mean ratio in UACR from baseline (A), mean change in eGFR from baseline (B), and Mean change in HbA1c from baseline (C). Values are presented as mean ± 95% CI. The number of patients is indicated in the figure.

UACR, urine albumin-creatinine ratio; eGFR, estimated glomerular filtration rate; QD, once a day; TID, thrice a day; LOCF, last observation carried forward; CI, confidence interval.

Supplementary Table S3. Treatment differences in change in UACR from baseline to end of treatment (per-protocol population)

	Per-protocol population		
	Placebo	SCO-792 500 mg QD	SCO-792 500 mg TID
n	11	23	23
Geo LS Mean	0.85	0.65	0.68
(95% CI)	(0.53, 1.36)	(0.46, 0.90)	(0.49, 0.94)
p-value[a]	0.4839	0.0114	0.0218
Geo LS Mean Ratio (ref. placebo)		0.76	0.80
(95% CI)		(0.43, 1.36)	(0.45, 1.42)
p-value[b]		0.3495	0.4411

a. value of the adjusted geometric least squares (LS) mean of each treatment group against 1 using *t*-test.
b. *p*-value of geometric LS mean ratio of each treatment group to placebo.
Geometric mean, geometric LS mean diff, 95% CI, and *p*-value were determined using the ANCOVA model of log-transformed UACR values.

UACR, urine albumin-creatinine ratio; QD, once a day; TID, thrice a day; *n* = number of participants in each category; Geo, geometric; CI, confidence interval.

Supplementary Table S4. Changes in UACR from baseline to end of treatment (pre-defined setting)

	Intent-to-treat population			Per-protocol population		
	Placebo	SCO-792 500 mg QD	SCO-792 500 mg TID	Placebo	SCO-792 500 mg QD	SCO-792 500 mg TID
n	14	29	26	11	23	22
Geo LS Mean	0.86	0.76	0.80	0.85	0.68	0.77
(95% CI)	(0.60, 1.23)	(0.59, 0.98)	(0.62, 1.04)	(0.55, 1.31)	(0.50, 0.92)	(0.56, 1.04)
p-value[a]	0.4069	0.0323	0.0957	0.4435	0.0140	0.0903
Geo LS Mean Ratio (ref. placebo)		0.88	0.93		0.80	0.91
(95% CI)		(0.57, 1.36)	(0.60, 1.45)		(0.47, 1.36)	(0.53, 1.54)
p-value[b]		0.5627	0.7438		0.4059	0.7114

This analysis was conducted using the pre-defined setting for UACR analysis, which excluded urinary albumin values that exceeded the lower limit of assay detection. Analysis using lower limit urinary albumin value (when the value shown was below the lower limit) and upper limit urinary albumin value (when the value shown was over the upper limit) was conducted for the analysis of UACR changes, and the results are presented in Table 3.

a. value of the adjusted geometric least squares (LS) mean of each treatment group against 1 using *t*-test.
b. *p*-value of geometric LS mean ratio of each treatment group to placebo.
Geometric mean, geometric LS mean diff, 95% CI, and *p*-value were determined using the ANCOVA model of log-transformed UACR values.

UACR, urine albumin-creatinine ratio; QD, once a day; TID, thrice a day; *n* = number of participants in each category; Geo, geometric; CI, confidence interval.

Supplementary Table S5. Changes in secondary and exploratory endpoints (per-protocol population)

	Per-protocol population		
	Placebo (*N* = 11)	SCO-792 500 mg QD (*N* = 23)	SCO-792 500 mg TID (*N* = 22)
eGFR (mL/min/1.73 m^2)			
Change to week 12			
n	11	23	22
Mean	–1.5	0.1	1.7
(95% CI)	(–7.0, 4.0)	(–2.7, 2.8)	(–2.8, 6.2)
SD	8.19	6.35	10.14
Urinary albumin-to-creatinine ratio response rate ≥ 30% reduction			
n	2	7	7
%	18.2	30.4	31.8
(95% CI)	(2.28, 51.78)	(13.21, 52.92)	(13.86, 54.87)
Hemoglobin A1c (%)			
Change to week 12			
n	11	23	22
Mean	0.33	–0.21	–0.58
(95% CI)	(0.08, 0.57)	(–0.65, 0.23)	(–0.87, –0.30) *
SD	0.366	1.011	0.644
Fasting plasma glucose (mmol/L)			
Change to week 12			
n	10	21	21
Mean	0.69	–0.80	–1.33
(95% CI)	(–2.90, 4.28)	(–1.95, 0.34)	(–2.45, –0.21) *
SD	5.022	2.523	2.458
Fasting insulin (mU/L)			
Change to week 12			
n	10	19	21
Mean	3.04	–7.45	3.39
(95% CI)	(–22.18, 28.26)	(–19.87, 4.98)	(–1.11, 7.88)
SD	35.252	25.782	9.880
HOMA-IR			
Change to week 12			
n	11	21	22
Mean	3.475	–4.897	–0.690
(95% CI)	(–19.991, 26.942)	(–12.314, 2.520)	(–2.933, 1.552)
SD	34.9297	16.2945	5.0574
Body weight (kg)			
% change to week 12			
n	11	23	22
Mean	1.240	–0.319	–0.060
(95% CI)	(–0.209, 2.689)	(–1.490, 0.852)	(–1.143, 1.023)
SD	2.1567	2.7078	2.4432
Urinary protein-to-creatinine ratio (mg/gCr)			
Week 12			
n	11	23	21
Geo Mean	0.900	0.778	0.844
(95% CI)	(0.541, 1.498)	(0.578, 1.048)	(0.688, 1.036)
Geo SD	2.1347	1.9897	1.5660
Systolic blood pressure (mmHg)			
Change to week 12			
n	11	23	22
Mean	7.5	0.1	–3.7
(95% CI)	(–0.5, 15.4)	(–4.6, 4.8)	(–8.0, 0.6)
SD	11.83	10.80	9.65

Diastolic blood pressure (mmHg)			
Change to week 12			
n	11	23	22
Mean	–0.4	–1.1	–1.6
(95% CI)	(–7.7, 7.0)	(–4.1, 1.9)	(–4.0, 0.8)
SD	10.96	6.97	5.50
High-sensitivity C-reactive protein (mg/L)			
Change to week 12			
n	11	23	22
Mean	2.992	–4.187	1.870
(95% CI)	(–3.822, 9.805)	(–10.869, 2.494)	(–1.886, 5.627)
SD	10.1420	15.4507	8.4726
Triglycerides (mmol/L)			
% change to week 12			
n	11	23	22
Mean	24.967	17.013	17.082
(95% CI)	(–14.307, 64.240)	(–7.743, 41.769)	(–1.861, 36.024)
SD	58.4589	57.2489	42.7228
Low-density lipoproteins (mmol/L)			
% change to week 12			
n	11	23	22
Mean	6.553	–1.859	34.523
(95% CI)	(–5.994, 19.100)	(–9.972, 6.253)	(–15.871, 84.917)
SD	18.6770	18.7602	113.6607
High-density lipoprotein (mmol/L)			
% Change to week 12			
n	11	23	22
Mean	1.585	1.694	–2.569
(95% CI)	(–6.868, 10.038)	(–6.085, 9.472)	(–7.376, 2.238)
SD	12.5822	17.9876	10.8409
Valine (µmol/L)			
Change to week 12			
n	6	18	21
Mean	12.8	4.4	–7.7
(95% CI)	(–58.7, 84.3)	(–32.7, 41.5)	(–39.1, 23.7)
SD	68.13	74.59	68.97
Leucine (µmol/L)			
Change to week 12			
n	6	18	21
Mean	11.2	–7.7	–8.0
(95% CI)	(–39.4, 61.7)	(–28.2, 12.9)	(–22.6, 6.6)
SD	48.18	41.35	32.04
Isoleucine (µmol/L)			
Change to week 12			
n	6	18	21
Mean	8.5	0.6	–0.9
(95% CI)	(–26.3, 43.3)	(–11.0, 12.2)	(–10.4, 8.6)
SD	33.12	23.35	20.80

QD, once a day; TID, thrice a day; *N*, total number of participants in the relevant group; eGFR, estimated glomerular filtration rate; *n*, number of participants in each category; CI, confidence interval; SD, standard deviation; Geo, geometric.

HOMA-IR = fasting insulin level (µU/mL) × fasting blood glucose level (mg/dL) / 405.

*95% CI did not cross zero at the indicated measurement.

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)	2
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	4-5
	2b	Specific objectives or hypotheses	4-5
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	NA
Participants	4a	Eligibility criteria for participants	7
	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	8
	6b	Any changes to trial outcomes after the trial commenced, with reasons	NA
Sample size	7a	How sample size was determined	6, 9
	7b	When applicable, explanation of any interim analyses and stopping guidelines	NA
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 assessing outcomes) and how	6-7

	11b	If relevant, description of the similarity of interventions	NA
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	9-10
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	NA
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 Figure 1
	13b	For each group, losses and exclusions after randomisation, together with reasons	10 Figure 1
Recruitment	14a	Dates defining the periods of recruitment and follow-up	6
	14b	Why the trial ended or was stopped	NA
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	Table 1
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	6 Figure 1
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)	10-13 Table 2 Table 3 Table 4 Figures 2,3,4
	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	NA
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	15
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	13-15
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	13-15
Other information			
Registration	23	Registration number and name of trial registry	6, 16
Protocol	24	Where the full trial protocol can be accessed, if available	NA
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	16

*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.