SUPPLEMENTARY DATA

Study investigators

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Exclusion criteria

Diabetes-related exclusion criteria included: type 1 diabetes; diabetes insipidus; corticosteroid-induced type 2 diabetes; a history of diabetic ketoacidosis or hyperosmolar non-ketotic coma; poorly controlled diabetes characterized by polyuria/polydipsia with >10% weight loss; use of insulin within 1 year of enrolment, except in the case of hospitalization or use in gestational diabetes.

General exclusion criteria included: body mass index (BMI) >45.0 kg/m^2; calculated creatinine clearance <60 mL/min; urine albumin:creatinine ratio >203.4 mg/mmol; aspartate aminotransferase and/or alanine aminotransferase and/or creatine kinase ≥3 × upper limit of normal range; serum total bilirubin >34 μmol/L; hemoglobin (Hb) ≤11 g/dL for men and ≤10 g/dL for women; abnormal thyroid stimulating hormone level; systolic blood pressure ≥180 mmHg and/or diastolic blood pressure ≥110 mmHg; cardiovascular event within 6 months of enrolment; congestive heart failure; congenital renal glycosuria; significant renal, hepatic, respiratory, haematological, oncological, endocrine, immunological (including hypersensitivity to study medications), and alcohol and/or substance misuse disorders; pregnancy and/or lactation; use of systemic corticosteroids equivalent to >10 mg of oral prednisolone within 30 days of enrolment; a history of bariatric surgery; and use of weight loss medication within 30 days of enrolment.

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Supplementary Table 1. Metformin dose adjustments during the 8-week stabilization period.

Metformin status during the 8 weeks prior to enrolment	Open-label metformin adaptation during 8-week dose stabilization	Open-label metformin during placebo lead-in
Metformin monotherapy		
If metformin dose was:		
<1500 mg/day	1500 mg/day	1500 mg/day
≥1500 mg/day, stable dose, and:	Skipped dose stabilization:	
≥1500 and <1750 mg/day	→	1500 mg/day
≥1750 and <2250 mg/day	→	2000 mg/day
≥2250 mg/day	→	2500 mg/day
≥1500 mg/day, unstable dose, and:		
≥1500 and <1750 mg/day	1500 mg/day	1500 mg/day
≥1750 and <2250 mg/day	2000 mg/day	2000 mg/day
≥2250 mg/day	2500 mg/day	2500 mg/day
Metformin plus ≤1 other OAD		
Discontinue other OAD		
If metformin dose was:		
<1500 mg/day	1500 mg/day	1500 mg/day
≥1500 and <2000 mg/day	2000 mg/day	2000 mg/day
≥2000 mg/day	2500 mg/day	2500 mg/day

OAD, oral antidiabetic drug

Sample size calculations

To demonstrate non-inferiority of dapagliflozin in comparison with glipizide as add-on therapy to metformin for changes from baseline to week 52 in HbA1C with a non-inferiority margin of 0.35 %, assuming a standard deviation (SD) of 1.25 %, and at a one-sided significance level of 0.025, 280 evaluable patients were needed in each treatment group to provide approximately 90% power (given a true difference of zero between the 2 treatment groups). Assuming a 5% exclusion rate from the full analysis set, 295 patients per treatment group are needed for the full analysis set. Additionally, to have 90% power for the per-protocol population and assuming a 25% exclusion rate from the per-protocol population, 373 patients per treatment group (746 patients in total) were planned for randomization.

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Supplementary Table 2. Demographic and baseline characteristics of the full analysis set.

	Dapagliflozin + metformin	Glipizide + metformin
Number of patients	400	401
Age, years, mean ± SD	58 ± 9	59 ± 10
Gender, n (%)		
Male	221 (55.3)	220 (54.9)
Female	179 (44.8)	181 (45.1)
Race, n (%)		
White	327 (81.8)	323 (80.5)
Black	26 (6.5)	24 (6.0)
Asian	27 (6.8)	34 (8.5)
Other	20 (5.0)	20 (5.0)
Body mass index		
Kg/m^2, mean ± SD	31.7 ± 5.1	31.2 ± 5.1
≥ 25 kg/m^2, n (%)	380 (95.0)	364 (90.8)
≥ 30 kg/m^2, n (%)	228 (57.0)	222 (55.4)
Duration of type 2 diabetes, years, mean ± SD	6 ± 5	7 ± 6
HbA1C, percent, mean ± SD	7.7 ± 0.9	7.7 ± 0.9
FPG, mmol/L, mean ± SD	9.0 ± 2.1	9.1 ± 2.3
Fasting C-peptide, nmol/L, mean ± SD	1.00 ± 0.43	0.95 ± 0.44
OAD use at enrolment*, n (%)		
Metformin monotherapy < 1500 mg/day	34 (8.4)	37 (9.1)
Metformin monotherapy ≥ 1500 mg/day	231 (56.9)	238 (58.3)
OAD and metformin < 1500 mg/day	19 (4.7)	28 (6.9)
OAD and metformin ≥ 1500 mg/day	122 (30.0)	104 (25.5)
No OAD	0	1 (0.2)
Metformin dose, median		
At enrolment	1700	1700
At randomization	2000	2000
Diabetes-related diseases, n (%)		
Neuropathy	23 (5.8)	23 (5.7)
Retinopathy	22 (5.5)	24 (6.0)
Nephropathy	15 (3.8)	10 (2.5)
Microalbuminuria	42 (10.5)	39 (9.7)
Prior history of CVD†, n (%)	72 (18.0)	78 (19.5)
Hypertension, n (%)	282 (70.5)	282 (70.3)
Dyslipidemia, n (%)	245 (61.3)	239 (59.6)
Estimated GFR‡, n (%)		
< 30 $mL/min/1.73m^2$	1 (0.3)	1 (0.2)

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≥ 40 and < 60 mL/min/1.73m^2	18 (4.5)	23 (5.7)
≥ 60 and < 90 mL/min/1.73m^2	198 (49.5)	181 (45.1)
≥ 90 mL/min/1.73m^2	183 (45.8)	196 (48.9)

BMI, Body Mass Index; CVD, cardiovascular disease; GFR, glomerular filtration rate; FPG, fasting plasma glucose; HbA1C, hemoglobin A1C; OAD, oral antidiabetic drug; type 2 diabetes, type 2 diabetes mellitus; SD, standard deviation. *Patient numbers based on safety analysis set. †Does not include patients with a cardiovascular history of hypertension only. ‡Calculation of GFR based upon the Modification of Diet in Renal Disease formula; eGFR (mL/min/1.73m^2) = 186 × (serum creatinine[mg/dL])$^{-1.154}$ × (Age)$^{-0.203}$ × (0.742 if female) × (1.21 if black).

Supplemenatry Table 3. Proportion of patients reaching each dose level at the end of the titration period and down-titrated within the titration and double-blind treatment periods.

	Number (percent) of patients	
	Dapagliflozin + metformin	**Glipizide + metformin**
	(n=406)	**(n=408)**
Dose at end of titration period		
DAPA 0 mg / GLIP 0 mg	0	7 (1.7)
DAPA 2.5 mg / GLIP 5 mg (Level 1)	19 (4.7)	54 (13.2)
DAPA 5 mg / GLIP 10 mg (Level 2)	34 (8.4)	51 (12.5)
DAPA 10 mg / GLIP 20 mg (Level 3)	353 (86.9)	296 (72.5)
Mean dose	Dapagliflozin 9.2 mg	Glipizide 16.4 mg
Down-titration		
Within titration period	9 (2.2)	41 (10.0)
After titration period	2 (0.5)	21 (5.1)
Within and after the titration period	0	3 (0.7)
Neither within nor after titration period	395 (97.3)	343 (84.1)

DAPA, dapagliflozin; GLIP, glipizide

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Supplementary Table 4, Exploratory endpoints at week 52

	Dapagliflozin + metformin	Glipizide + metformin
Absolute change in body weight (kg) in patients with baseline BMI ≥30 kg/m^2		
n	228	222
Baseline mean body weight	96.4	96.5
Adjusted mean change from baseline (95% CI)	−3.60 (−4.12, −3.09)	1.55 (1.03, 2.07)
Difference (95% CI) vs glipizide	−5.15 (−5.8, −4.42)	
Absolute change in body weight (kg) in patients with baseline BMI ≥27 kg/m^2		
n	331	317
Baseline mean body weight	91.8	92.3
Adjusted mean change from baseline (95% CI)	−3.35 (−3.75, −2.95)	1.41 (1.00, 1.81)
Difference (95% CI) vs glipizide	−4.76 (−5.3, −4.19)	
Change in waist circumference (cm)		
n	368	379
Baseline mean waist circumference	105.6	104.8
Adjusted mean change from baseline (95% CI)	−2.33 (−2.85, −1.81)	1.09 (0.58, 1.60)
Difference (95% CI) vs glipizide	−3.42 (−4.14, −2.69)	
Change in HbA1C (%) in patients with baseline HbA1C ≥7%		
n	316	323
Baseline mean HbA1C	7.96	8.01
Adjusted mean change from baseline (95% CI)	−0.65 (−0.74, −0.56)	−0.63 (−0.73, −0.54)
Difference (95% CI) vs glipizide	−0.02 (−0.15, 0.11)	
Proportion of patients (%) achieving HbA1C <7% at week 52 in patients with baseline HbA1C ≥7%		
Baseline mean HbA1C	7.69	7.74
x/n	110/400	128/401
Adjusted proportion (95% CI)	27.4% (23.0%, 31.8%)	32.0% (27.4%, 36.6%)
Difference (95% CI) vs glipizide	−4.6% (−10.9%, 1.7%)	
Proportion of patients (%) with HbA1C ≤6.5% at week 52 (%)		
Baseline mean HbA1C	7.69	7.74
x/n	67/400	109/401
Adjusted proportion (95% CI)	16.5% (13.0%, 20.1%)	27.5% (23.3%, 31.7%)
Difference (95% CI) vs glipizide	−11.0% (−16.6%, −5.3%)	
Change in FPG (mmol/L)		
n	399	394
Baseline mean FPG	9.01	9.12
Adjusted mean change from baseline (95% CI)	−1.24 (−1.42, −1.07)	−1.04 (−1.22, −0.98)
Difference (95% CI) vs glipizide	−0.20 (−0.44, 0.05)	

n=the number of patients in the full analysis set with non-missing baseline and week 52 LOCF values. x=number of patients responding. BMI, body mass index; CI, confidence interval; FPG, fasting plasma glucose; HbA1C, hemoglobin A1C.

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Supplementary Table 5. Selected laboratory values of interest and vital signs: change from baseline at week 52 using the safety analysis set.

	Dapagliflozin + metformin (n=406)		Glipizide + metformin (n=408)	
	Baseline mean	Mean change at week 52	Baseline mean	Mean change at week 52
Serum creatinine (µmol/L)	74.2 (23.8)	−0.18 [1.11]	72.8 (17.5)	3.62 [0.63]
Calculated creatinine renal clearance with current weight (mL/min)*	118.5 (38.5)	−6.2 [0.9]	117.5 (39.6)	−4.6 [0.9]
Calculated creatinine renal clearance using baseline weight (mL/min)†	118.7 (38.6)	−0.1 [0.9]	117.8 (39.7)	−5.5 [0.9]
Estimated GFR (mL/min/1.73m^2)‡	89.6 (21.4)	−0.5 [0.8]	90.5 (22.6)	−5.4 [0.8]
Cystatin-C (nmol/L)	54.3 (12.2)	5.7 [0.5]	53.8 (12.3)	6.4 [0.4]
Serum uric acid (µmol/L)	336.1 (86.7)	−45.2 [3.4]	323.6 (82.3)	16.1 [3.4]
Blood urea nitrogen (mmol/L)	5.5 (1.8)	0.5 [0.08]	5.5 (1.7)	0.1 [0.07]
Urine glucose (mmol/L)	9.3 (27.1)	141.2 [5.4]	8.4 (23.2)	−4.1 [1.4]
Urinary glucose:creatinine ratio (g/g)	1.89 (5.97)	32.49 [1.25]	2.25 (12.92)	−1.60 [0.87]
Urine albumin:creatinine ratio (mg/g)	65.1 (215.6)	−19.0 [6.6]	51.0 (340.4)	−0.8 [7.1]
Sodium (mmol/L)	139.8 (2.9)	0.5 [0.17]	139.7 (3.0)	0.5 [0.16]
Potassium (mmol/L)	4.47 (0.44)	−0.08 [0.02]	4.47 (0.43)	0.02 [0.03]
Calcium (mmol/L)	2.40 (0.11)	−0.02 [0.01]	2.38 (0.13)	−0.02 [0.01]
Magnesium (mmol/L)	1.68 (0.26)	0.08 [0.01]	1.68 (0.23)	0.00 [0.01]
Inorganic phosphorus	1.14 (0.16)	0.03 [0.01]	1.13 (0.17)	0.01 [0.01]
Haematocrit (%)	41.25 (3.61)	2.86 [0.14]	40.99 (3.38)	0.39 [0.13]
Aspartate aminotransferase (U/L)	24.1 (11.1)	−1.7 [0.5]	23.2 (10.5)	1.6 [0.5]
Alanine aminotransferase (U/L)	29.7 (16.8)	−5.0 [0.6]	29.3 (16.0)	0.8 [0.8]
Alkaline phosphatase (U/L)	80.1 (26.1)	−4.9 [0.7]	78.6 (23.2)	−3.7 [0.7]
Total bilirubin (µmol/L)	8.2 (4.1)	0.0 [0.2]	7.9 (3.5)	−0.3 [0.2]
Parathyroid hormone (ng/L)	33.4 (17.1)	3.2 [0.73]	33.5 (16.9)	2.8 [0.79]
25-hydroxy vitamin D (nmol/L)	56.7 (22.1)	−4.2 [0.9]	55.2 (20.3)	−5.7 [0.8]
Seated heart rate (bpm)	74.1 (10.9)	−0.1 [0.5]	73.7 (10.3)	0.3 [0.5]
	Baseline	Week 52	Baseline	Week 52
	x/n (%)	x/n (%)	x/n (%)	x/n (%)
Proportion with orthostatic hypotension	15/294 (3.8%)	15/312 (4.8%)	20/391 (5.1%)	15/299 (5.0%)

Data are mean (standard deviation) or mean [standard error]; x=number of patients with orthostatic hypotension at baseline or week 52 defined as decrease from supine to standing of >20 mm Hg in systolic blood pressure or >10 mm Hg in diastolic blood pressure. n=number of patients with non-missing baseline or week 52 values in the safety analysis set.*Calculated using the Cockcroft-Gault equation (14) with current values for body weight at each study visit; †Calculated *post hoc* using baseline body weight for all study visits. Cockcroft-Gault equation: eCC = ((140−Age) × Weight in kg × (1.23 if male, 1.04 if female)) / serum creatinine in µmol per L. ‡Calculation of glomerular filtration rate based upon the Modification of Diet in Renal Disease formula; eGFR (mL/min/1.73m^2) = 186 × (serum creatinine[mg/dL])$^{-1.154}$ × (Age)$^{-0.203}$ × (0.742 if female) × (1.21 if black).

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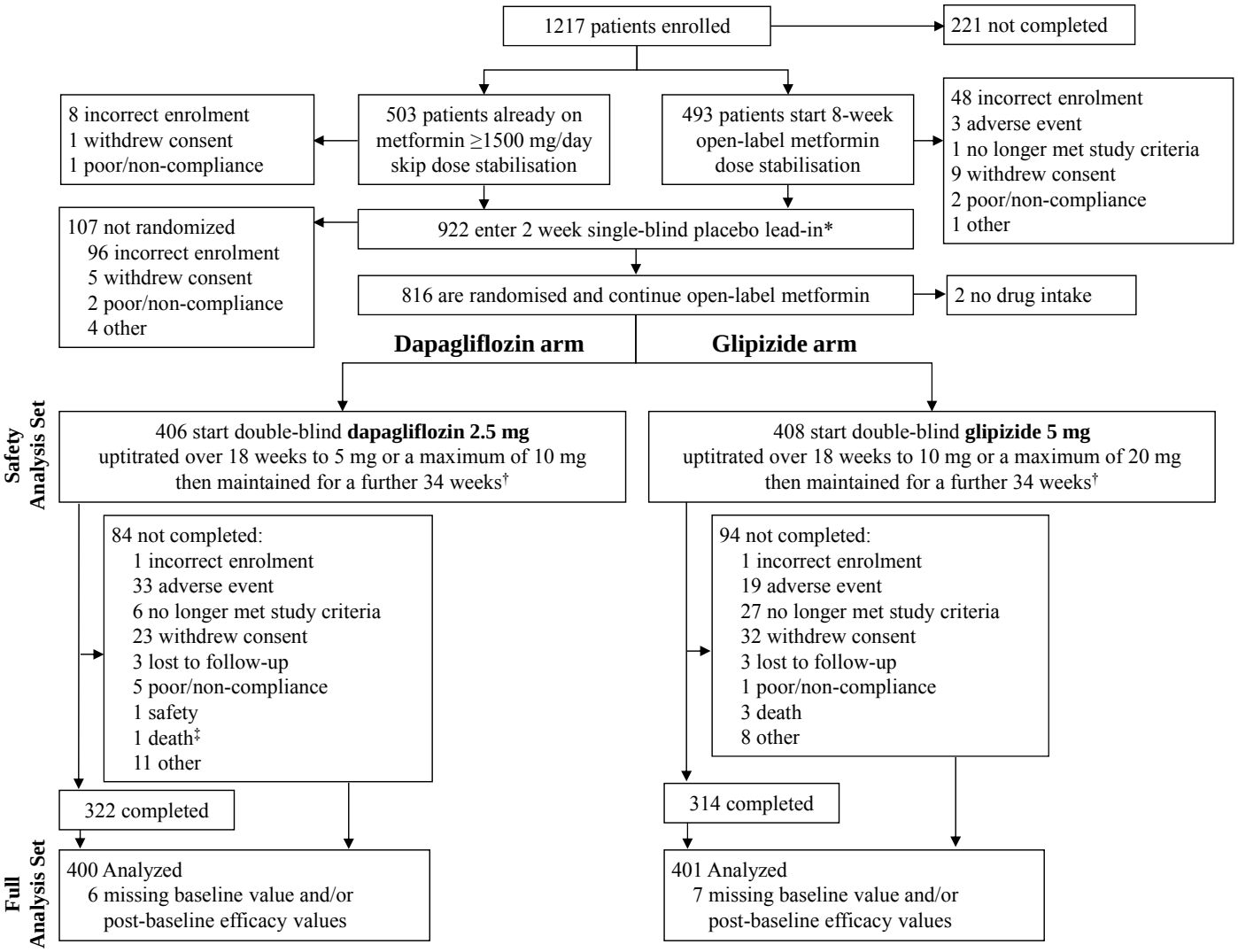
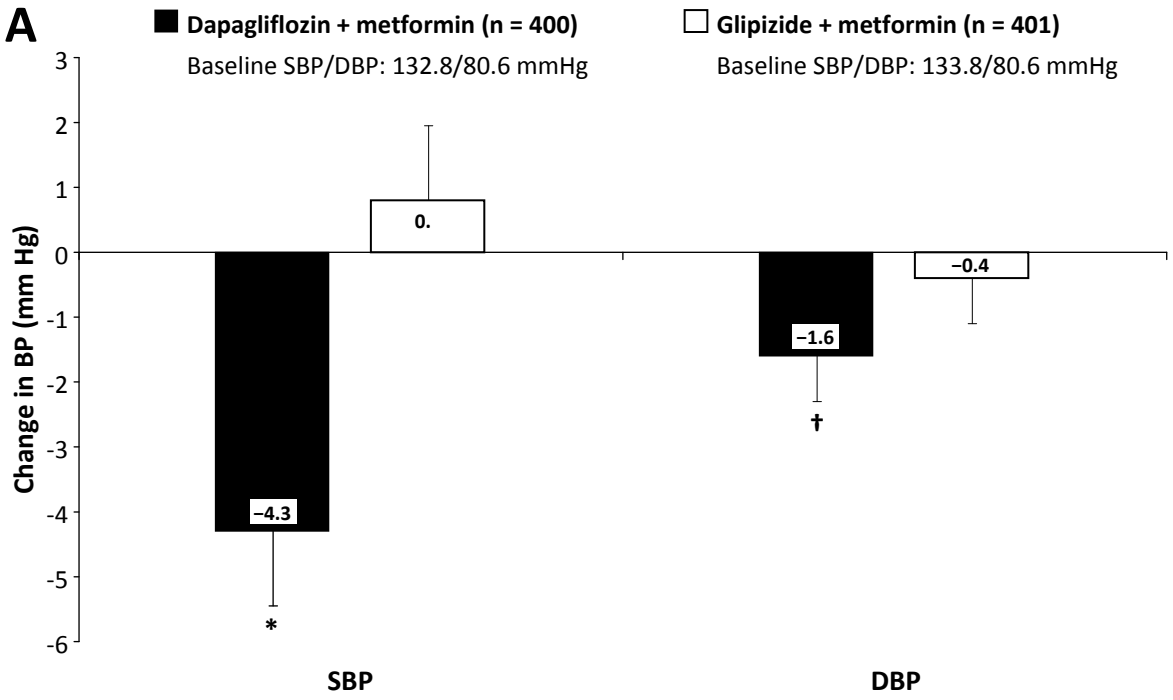
Supplementary Figure 1. Trial profile. The term 'incorrect enrollment' was defined as patients not meeting inclusion criteria or meeting exclusion criteria. *One patient took no placebo medication but was randomized. †down titration was permitted in the event of hypoglycemia. ‡Included in the listing of deaths because the patient died before the scheduled follow-up visit but was not included in the analysis of adverse events during the 52-week double-blind treatment period (Table 2) because the patient died >30 days after the last dose of double-blind study medication.



SUPPLEMENTARY DATA

Supplementary Figure 2. Change in (A) blood pressure (BP, mmHg) and (B) cholesterol, triglycerides and free fatty acids (%) over the 52-week double-blind treatment period. Data are adjusted mean change from baseline and 95% confidence intervals (CI) based upon ANCOVA with treatment group as effect and baseline value as covariate using the full analysis set and LOCF values. Lipid data are adjusted percent change from baseline based upon ANCOVA of log-transformed data with treatment group as effect and log (baseline value) as covariate using the full analysis set and LOCF values. *Difference vs glipizide + metformin −5.0 mmHg (95% CI of difference −6.7, −3.4); †−1.2 mmHg (95% CI of difference −2.3, −0.2); #0.156 mmol/L (95% CI of difference 0.104, 0.210). DBP, diastolic blood pressure; FFA, free fatty acids; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SBP, systolic blood pressure, TC, total cholesterol, TG, triglycerides.



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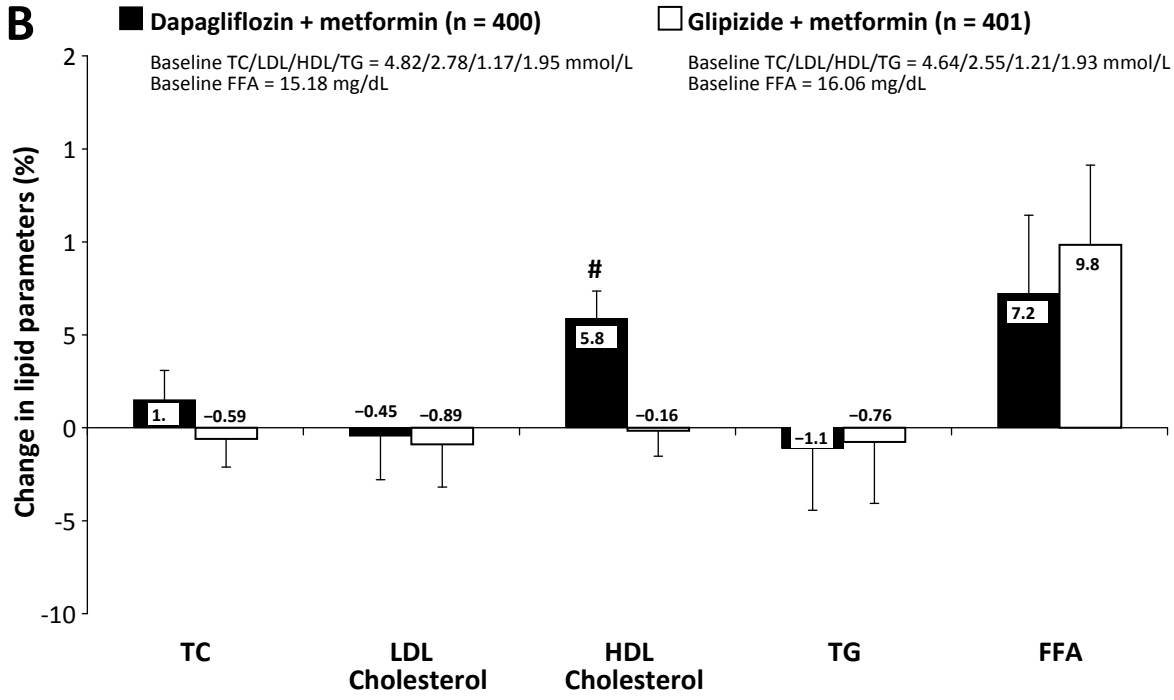

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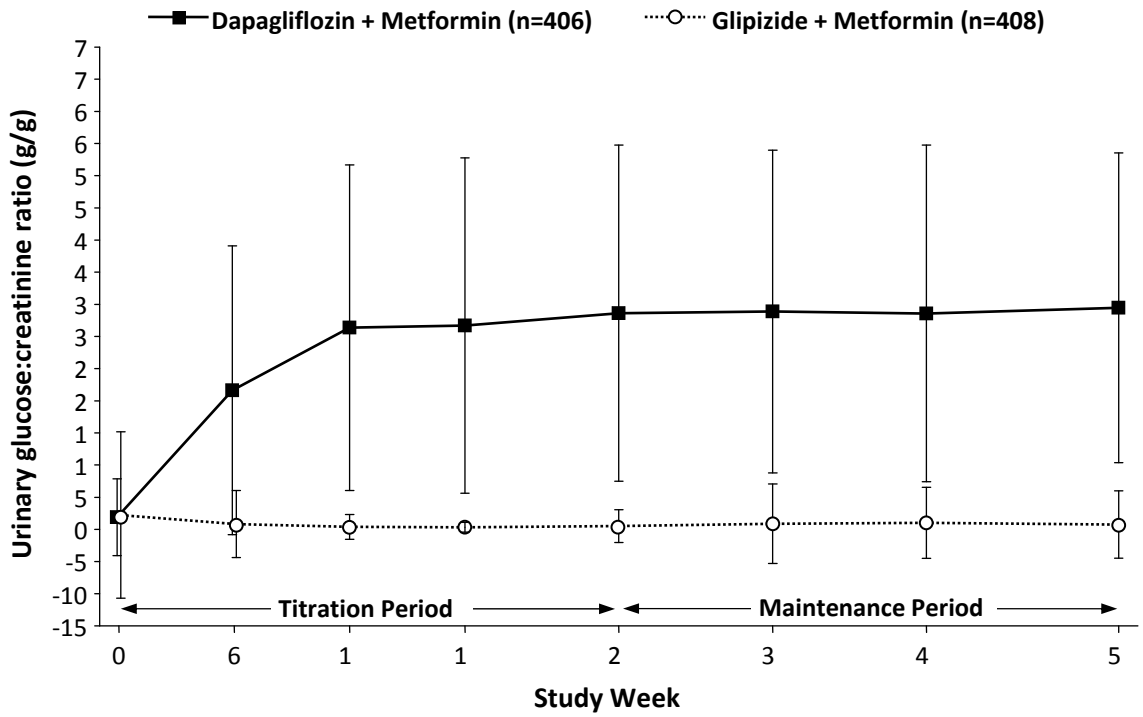
Supplementary Figure 3. Urinary glucose:creatinine ratio (g/g) during the 52-week double-blind treatment period. Data are mean ± standard deviation, obtained from morning spot urine checks in the fasting state and using the safety analysis set.



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

Section/Topic	Item No	Checklist item	Reported on page No (paragraph)
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	3
	2b	Specific objectives or hypotheses	3(4)–4(1)
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	4(2), 6(2)
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	Not applicable
Participants	4a	Eligibility criteria for participants	4(3) Online Appendix
	4b	Settings and locations where the data were collected	4(2)
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	5
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	6(3)
	6b	Any changes to trial outcomes after the trial commenced, with reasons	Not applicable
Sample size	7a	How sample size was determined	Online Appendix
	7b	When applicable, explanation of any interim analyses and stopping guidelines	Not applicable
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	6(2)
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	6(2)
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(2)
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	6(2)
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	6(2)

	11b	If relevant, description of the similarity of interventions	6(2)
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	7(3 onwards)
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	8(3)
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	Figure A1
	13b	For each group, losses and exclusions after randomisation, together with reasons	Figure A1
Recruitment	14a	Dates defining the periods of recruitment and follow-up	4(2)
	14b	Why the trial ended or was stopped	Not applicable
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	Table A2
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	Figures 1 & 2
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)	Figures 1 & 2
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	Not applicable
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	Table 1, Tables A4 & A5, Figures A2 & A3
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	10–12, Table 1
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	13
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	13
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	13
Other information			
Registration	23	Registration number and name of trial registry	2(2), 4(2)
Protocol	24	Where the full trial protocol can be accessed, if available	Available on request
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