SUPPLEMENTARY DATA

Supplementary Table 1. Changes of insulin sensitivity from 0 to 24 weeks of treatment

	EMPA	n	PLAC	n
Whole-body insulin sensitivity				
Rd_LC[§] at week 0 (mg/kg/min)	2.1[1.9;2.4]	24	2.1[1.8;2.5]	25
Change from week 0 (%)	**21.9[7.7;37.9]***		-5.6[-17.1;6.6]	
Rd_HC[§] at week 0 (mg/kg/min)	3.6[3.0;4.2]	28	3.7[3.0;4.4]	26
Change from week 0 (%)	11.7[1.3;23.2]		3.2[-10.9;19.5]	
M-value_LC[§] at week 0 (mg/kg/min)	1.0[0.8;1.4]	23	1.0[0.7;1.5]	22
Change from week 0 (%)	26.6[-5.2;69.0]		-15.8[-36.6;11.9]	
M-value_HC[§] at week 0 (mg/kg/min)	3.2[2.6;3.9]	28	3.3[2.7;4.1]	26
Change from week 0 (%)	9.9[-3.9;25.7]		-1.6[-18.9;19.5]	
Hepatic insulin sensitivity				
HIR[§] at week 0 (AU)	24.0[19.2;29.9]	22	28.4[21.3;37.9]	17
Change from week 0 (%)	0.3[-17.0;21.2]		-11.2[-31.9;15.7]	
EGP_suppr_LC at week 0 (%)	50[45.;56]	24	47[41;54]	25
Change from week 0 (%)	-0.05[-5.31;5.22]]		-3.41[-7.86;1.05]	
EGP_suppr_HC at week 0 (%)	88[81;96]	28	93[85;101]	26
Change from week 0 (%)	-1.8[-7.2;3.6]		-5.5[-12.4;1.5]	
Adipose tissue insulin sensitivity				
Adipo-IR[§] at week 0 (AU)	6894[5682;8365]	22	8003[5825;10994]	18
Change from week 0 (%)	-17.7[-31.6;-1.0]		-12.1[-30.9;11.9]	
FFA_suppr_LC[§] at week 0 (%)	66[61;72]	27	59[49;70]	27
Change from week 0 (%)	6.9[0.0;14.2]		4.7[-5.7;16.1]	
FFA_suppr_HC[§] at week 0 (%)	88[86;91]	28	87[84;90]	27
Change from week 0 (%)	-0.04[-2.40;2.37]		-1.80[-5.64;2.19]	

Values at week 0 are shown as means for normally distributed and geometric means (median) for log-normally ([§]) distributed data with 95% confidence intervals, respectively, of those patients in EMPA and PLAC for whom also 24-week values were obtained. Changes from week 0 are compared using ANCOVA adjusted for age, sex, BMI and respective value at week 0. Asterisks indicate $p<0.05$ for placebo-corrected changes from week 0 to week 24 based on ANCOVA adjusted for age, sex, BMI and respective value at week 0.

AU, arbitrary units, HIR, fasting hepatic insulin resistance; Rd_HC, rate of disappearance during high clamp conditions; M-value_HC, whole-body insulin sensitivity during high insulin conditions; HIR, hepatic insulin resistance index; EGP, endogenous glucose production; EGP_suppr_LC; insulin-stimulated suppression of EGP during low insulin conditions; EGP_suppr_HC, insulin-stimulated suppression of EGP during high insulin conditions; Adipo-IR, adipose tissue insulin resistance index; FFA_suppr_HC, insulin-stimulated free fatty acid suppression during high insulin conditions.

SUPPLEMENTARY DATA

Supplementary Table 2. Changes of metabolic parameters from 0 to 24 weeks of treatment

	EMPA	n	PLAC	n
Body weight and fat distribution				
Body weight at week 0 (kg)	94.7[90.0;99.5]	32	98.0[92.2;103.8]	32
Change from week 0 (kg)	**-2.7[-3.4;-1.9]***		-0.1[-1.0;0.8]	
Liver fat[§] at week 0 (%)	9.6[7.3;12.7]	31	11.3[8.6;14.7]	31
Change from week 0 (%)	**-34[-43;-23]***		-15[-24;-4]	
SCAT[§] at week 0 (cm^3)	11962[10460;13679]	21	14144[12223;16369]	29
Change from week 0 (%)	-2.8[-7.8;2.4]		-0.5[-6.0;5.3]	
VAT at week 0 (cm^3)	6216[5478;6954]	22	6563[5749;7377]	29
Change from week 0 (cm^3)	-251[-533;51]		39[-222;300]	
Glycemia				
HbA1c at week 0 (%)	6.7[6.5;6.9]	32	6.5[6.3;6.7]	31
Change from week 0 (%)	-0.06[-0.19;0.07]		0.13[-0.04;0.30]	
Insulin[§] at week 0 (mU/L)	2.6[2.4;2.8]	22	2.7[2.4;3.0]	18
Change from week 0 (%)	-7[-20;8]		-12[-29;10]	
C-peptide[§] at week 0 (ng/ml)	3.0[2.6;3.4]	29	3.0[2.5;3.6]	24
Change from week 0 (%)	-4[-12;5]		-3[-14;9]	
Lipidemia				
Fasting FFA[§] at week 0 (µmol/L)	505[445;573]	29	519[458;587]	27
Change from week 0 (%)	-11[-23;3]		-1[-11;11]	

Values at week 0 are shown as means for normally distributed and geometric means (median) for log-normally ([§]) distributed data with 95% confidence intervals, respectively, of those patients in EMPA and PLAC for whom also 24-week values were obtained. Changes from week 0 are based on ANCOVA adjusted for age, sex, BMI and the respective value at week 0. Asterisks indicate p-value < 0.05 for placebo-corrected changes from week 0 to week 24 based on ANCOVA adjusted for age, sex, BMI and the respective value at week 0.

AU, arbitrary units; SCAT, subcutaneous adipose tissue; VAT, visceral adipose tissue; FFA, free fatty acids.

SUPPLEMENTARY DATA

Supplementary Table 3. Changes in inflammation- and liver-related parameters from 0 to 24 weeks of treatment

	EMPA	n	PLAC	n
Inflammation-related parameters				
IL-6[§] at week 0 (pg/ml)	2.2[1.9;2.7]	31	2.5[1.9;3.1]	30
Change from week 0 (%)	-8[-22;8]		-3[-15;10]	
TNFα[§] at week 0 (pg/ml)	1.4[1.2;1.5]	31	1.4[1.3;1.6]	30
Change from week 0 (%)	1[-10;13]		3[-8;14]	
IL1-RA[§] at week 0 (pg/ml)	538[457;634]	31	533[440;646]	30
Change from week 0 (%)	-3[-13;9]		-11[-20;-0.1]	
Liver-related parameters				
ALT[§] at week 0 (mol/s/l)	0.57[0.48;0.67]	32	0.61[0.52;0.73]	32
Change from week 0 (%)	-20[-26;-14]		-13[-22;-4]	
GGT[§] at week 0 (mol/s/l)	0.64[0.54;0.77]	31	0.64[0.49;0.84]	30
Change from week 0 (%)	-15[-20;-9]		-8[-17;3]	
FGF-21[§] at week 0 (pg/ml)	257[213;311]	31	308[236;403]	30
Change from week 0 (%)	-3[-17;20]		-13[-28;5]	
CK18-M30[§] at week 0 (U/l)	135[104;175]	31	130[104;163]	30
Change from week 0 (%)l	-22[-31;-11]		-10[-25;7]	
CK18-M65[§] at week 0 (U/l)	372[310;447]	31	332[272;406]	30
Change from week 0 (%)l	-19[-28;-8]		-8[-19;5]	

Values at week 0 are shown as means for normally distributed and geometric means (median) for log-normally ([§]) distributed data with 95% confidence intervals, respectively, of those patients in EMPA and PLAC for whom also 24-week values were obtained. Changes from week 0 are based on ANCOVA adjusted for age, sex, BMI and the respective value at week 0. Asterisks indicate p-value < 0.05 for placebo-corrected changes from week 0 to week 24 based on ANCOVA adjusted for age, sex, BMI and the respective value at week 0.

AU, arbitrary units; IL-6, interleukin-6; TNFα, tumor necrosis factor α; IL1-RA, interleukin-1 receptor antagonist; ALT, alanine aminotransferase; GGT, gamma-glutamyl transferase, FGF-21, fibroblast growth factor-21; CK18-M65, cytokeratin 18-M65 fragment.

SUPPLEMENTARY DATA

Supplementary Material

Inclusion and exclusion criteria

To be considered eligible to participate in this trial, volunteers had to meet all of the inclusion criteria listed below:

- Age between 18 and 75 years
- Obtained written informed consent
- 6%≤HbA1c≤8%
- BMI<45 kg/m^2
- Drug naïve - no previous antihyperglycemic treatment or one-month washout period of treatment with oral glucose lowering drugs (no previous treatment with thiazolidinedione (TZD) drugs allowed)
- Known diabetes duration up to 7 years

In addition, to be eligible for enrolment in the trial, volunteers must not meet any of the exclusion criteria listed below:

- Participation in other interventional trials
- Uncontrolled hyperglycemia at screening (glucose level ≥240 mg/dl after an overnight fast)
- Acute coronary syndrome, stroke or transient ischemic attack within 3 months prior to consent
- Previous lower limb amputation
- Severe lower limb infection/ulceration within 3 months prior to consent
- Evidence for liver disease (other than NAFLD) including chronic viral hepatitis (B or C), alcohol abuse, hemochromatosis, alpha-1 antitrypsin deficiency, autoimmune hepatitis, Wilson's disease, primary sclerosing cholangitis or primary biliary cirrhosis, or liver cirrhosis of any etiology
- AST or ALT >3times ULN
- Positive result on hepatitis B (HBs-AG), hepatitis C (HCV-AB) or HIV-1 and -2 tests
- Impaired kidney function (estimated glomerular filtration rate [eGFR] <60 mL/min/1.73m^2) during screening
- Structural or functional urogenital abnormalities, that predispose to urogenital infections
- Gastrointestinal surgeries that induce chronic malabsorption
- History of cancer (except basal cell carcinoma) or treatment for cancer within 5 years prior to screening
- Blood dyscrasias or any disorders causing hemolysis or unstable erythrocytes
- Treatment with antiobesity drugs 3 months prior to consent
- Treatment with immunomodulatory drugs (oral steroids, antihistamines)
- Change in dosage of thyroid hormones within 6 weeks of consent
- Pregnancy, lactation period
- Metal or magnetic implants, devices or objects inside of or on the body, which are not MRI compatible
- Claustrophobia
- Cigarette smoking (non-smoker <1year), alcohol consumption (male >30 g/d, female >20 g/d)
- Drug abuse or psychiatric disease
- Night-worker or circumstances not allowing normal day-night rhythm
- Hypersensitivity to empagliflozin or any of the drug compounds (galactose intolerance, Lapp-lactase deficiency, glucose-galactose malabsorption)
- Pharmaceutical preparations with which interactions can be expected – amiloride, furosemide, indapamide, spironolactone, torasemide, triamterene
- Use of anti-NASH drugs (vitamin E, ursodeoxycholic acid, S-adenosylmethionine, betaine, silymarin, gemfibrozil, anti-TNF therapies, probiotics) in the 3 months prior to randomization
- Women of childbearing potential not using two adequate methods of contraception, including a barrier method and a highly efficacious non-barrier method

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- Persons with any kind of dependency on the investigator or employed by the sponsor or investigator
- Persons held in an institution by legal or official order
- Legally incapacitated persons

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Table of assessments

	Screen	Baseline		Treatment period										
Visit	**1**	**2.1**	**2.2**	**3**	**3.1**	**4**	**4.1**	**5**	**6**	**7**	**8**	**9.1**	**9.2**	**10**
Study week	**≤ 6 w**	**0 (Day -1)**	**0 (Day 0)**	**1**	**2**	**4**	**6**	**8**	**12**	**16**	**20**	**24 (Day 1)**	**24 (Day 2)**	**2 w ±3 d after last dose**
Informed consent	x													
Demography & smoking	x													
Telephone visit	x				x		x							
Medical history	x													
Assessment of changes in diet and exercise		x				x		x	x	x	x	x		
Physical examination	x	x		x		x		x	x	x	x	x		x
Vital signs and anthropometry	x	x		x		x		x	x	x	x	x		x
12-lead ECG	x	x							x			x		x
Bioimpedance analysis	x	x							x			x		
Diet counselling[#]		x												
Blood chemistry, hematology,liver parameters, renal function, glycemia, urine analysis[*,**]	x	x		x		x		x	x	x	x	x		x
Coagulation, serology, autoantibodies, blood alcohol, drugs of abuse, 17-β-estradiol, Follicle-stimulating hormone (females only)	x													
Markers of liver steatosis/inflammation/genetic markers		x							x			x		
Lipids	x	x							x			x		
Thyroid function	x											x		
Randomization[##]		x												
Specific exams														
MRI/MRS		x							x			x		
Hyperinsulinemic euglycemic clamp			x										x	
Assessment of concomitant treatment	x	x	x	x		x		x	x	x	x	x	x	x
Assessment of adverse events	x	x	x	x		x		x	x	x	x	x	x	x
Drug dispensing[***]			x			x		x	x	x	x			

*No pregnancy test on visit 3 and 9.2

**No glucose in urine measurement on visit 3, 4 , 5, 6, 7, 8 and 9.1

***First drug dispensing at visit 2.2 after end of clamp test

[#]Diet counselling will be done during drug wash-out phase in patients on antihyperglycemic medication

[##]Randomisation upon completion of baseline visit 2.1

SUPPLEMENTARY DATA

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
	2b	Specific objectives or hypotheses	5
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	6
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	n.a.
Participants	4a	Eligibility criteria for participants	6; suppl.
	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	7-9
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	9
	6b	Any changes to trial outcomes after the trial commenced, with reasons	n.a.
Sample size	7a	How sample size was determined	9-10
	7b	When applicable, explanation of any interim analyses and stopping guidelines	n.a.
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	7
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	10
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	10
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 1
	13b	For each group, losses and exclusions after randomisation, together with reasons	Figure 1
Recruitment	14a	Dates defining the periods of recruitment and follow-up	11
	14b	Why the trial ended or was stopped	n.a.
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	Table 1, Figures 2,3
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)	11-12 Figure 2, Supplementary table 1
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	done
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	n.a.
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	n.a.
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	18
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	18
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	14-18
Other information			
Registration	23	Registration number and name of trial registry	6
Protocol	24	Where the full trial protocol can be accessed, if available	n.a.
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	19-20

*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.