## Supplementary material

**Table S1.** Search strategy performed on the following databases: PubMed, Embase, the

 Cochrane Central Register of Controlled Trials (CENTRAL).

1. Randomi*ed study OR random allocation OR Randomi*ed controlled trial OR Random*
Control* trial OR RCT Epidemiological study
2. sodium glucose cotransporter 2 OR sodium glucose cotransporter 2 inhibitor* OR sglt2
inhibitor* OR empagliflozin OR dapagliflozin OR canagliflozin OR ipragliflozin OR
tofogliflozin OR ertugliflozin OR sotagliflozin OR sergliflozin OR remogliflozin
3. 1 AND 2

Safety outcome	Comparator 1	<b>Comparator 2</b>	<b>I</b> <sup>2</sup>	RR [95% CI]						
	Number of events	Number of events /								
	/ total subjects	total subjects								
i. Empagliflozin + linagliptin vs empagliflozin monotherapy										
	Empagliflozin +	Empagliflozin								
	linagliptin	monotherapy								
$\geq 1 \text{ AE}(s)$	202/272	203/270	77% 0.99 [0.81, 1.21]							
≥1 drug-related	37/272	38/270	38/270 0% 0.97 [0.64, 1							
AE(s)										
$\geq$ 1 serious AE(s)	13/272	19/270	0%	0.68 [0.34, 1.35]						
Hypoglycaemia*	0/272	5/270	0%	0.18 [0.02, 1.56]						
UTI	32/272	25/270	29%	1.28 [0.70, 2.35]						
Events suggestive	12/272	13/270 9%		0.92 [0.40, 2.09]						
of genital infection										
i. E	mpagliflozin + linag	liptin vs linagliptin m	onother	ару						
	Empagliflozin +	Linagliptin	ətin							
	linagliptin	monotherapy								
$\geq 1 \text{ AE}(s)$	202/272	97/135	0%	1.03 [0.91, 1.17]						
≥1 drug-related	37/272	17/135	17/135 0%							
AE(s)										
$\geq$ 1 serious AE(s)	13/272	2/135	35 0% 3.22 [0.74,							
Hypoglycaemia*	0/272	1/135	NA 0.17 [0.01, 4.07]							
UTI	32/272	12/135	0%	1.32 [0.70, 2.49]						
Events suggestive	12/272	4/135	.35 0% 1.45 [0.47, 4.47]							
of genital infection										

**Table S2.** Safety outcomes of empagliflozin and linagliptin combination therapy compared with empagliflozin or linagliptin monotherapy in treatment naïve type 2 diabetes patients

RR, relative risk; AE, adverse event; UTI, urinary tract infection. \* Hypoglycaemia defined as plasma glucose  $\leq$  3.9 mmol/L and/or assistance required.



**Figure S1.** The mean change from baseline (pre-treatment) in diastolic BP (mmHg) between SGLT2 inhibitor and metformin combination therapy versus metformin monotherapy in treatment naïve type 2 diabetes patients. SGLT2I, SGLT2 inhibitor; Emp, empagliflozin; Met, metformin; Dap, dapagliflozin; Can, canagliflozin.

ence Mean Difference
95% CI IV, Random, 95% CI
100 C
0.30]
(,-U.45)
, -0.52]
.0.311
0.64]
,-0.37]
0.171
0.211
;-0.24j <b>•</b>
,-0.46]
-2 -1 0 1 Favours SGLT2I + Metformin Favours SGLT2I alone
nco Mann Diffarenco
95% CI IV. Random, 95% CI
-0.39]
, 0.42]
0.50
, 0.00
-0.37j 🍝
0.221
0.771
, 0.25]
. 0.53]
0.33]
0.191
(vite)
.0.25]
-4 -2 0 2 4
rerous course and and and a second course and the
ence Mean Difference
95% CI IV, Random, 95% CI
6, 2.26]
5, 2, 25]
5 3 0 51
0, 0.95]
-2574
6, 1.66]
3, 1.53]
3, 0.94]

	SGLT2I + Me	tformin	SGL	T2I Alo	ne		Mean Difference	Mean Difference
Study or Subgroup	Mean S	D Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Empagliflozin + Metformin vs SGLT2I Alone								
Emp 25 mg + Met 2000 mg vs Emp 25 mg	g -1.9 7.5	59 160	-1	7.18	71	9.3%	-0.90 [-2.94, 1.14]	
Emp 25 mg + Met 1000 mg vs Emp 25 mg	g -1.6 7.3	32 149	-1	7.18	72	9.3%	-0.60 [-2.63, 1.43]	
Emg 10 mg + Met 2000 mg vs Emg 10 mg	-1.9 7.3	84 150	-1.7	7.49	78	9.3%	-0.20 [-2.24, 1.84]	
Emp 10 mg + Met 1000 mg vs Emp 10 mg	s -1.6 7.4	7 155	-1.7	7.49	78	9.3%	0.10 [-1.94, 2.14]	
Subtotal (95% CI)		614			299	37.2%	-0.40 [-1.42, 0.62]	-
l² = 0%								
Canagliflozin + Metformin vs So	GLT2I Alon	2						
Can 300 mg + Met 2000 mg vs Can 300 mg	g -1.02 6.1	5 236	-1.7	6.15	236	31.4%	0.68 [-0.43, 1.79]	
Can 100 mg + Met 2000 mg vs Can 100 mg	·1.5 6.	6 237	-1.1	6.15	236	31.4%	-0.40 [-1.51, 0.71]	
Subtotal (95% CI)		473			472	62.8%	0.14 [-0.92, 1.20]	
l² = 45%								
		108			771	100%	-0.06 [-0.68,0.56	1
Total (95% CI)								•
I <sup>2</sup> = 0%								-4 -2 0 2 4
								Favours SGLT2I+Metformin Favours SGLT2I alone

**Figure S2.** The mean change from baseline (pre-treatment) in: (**A**) HbA1c (%) (**B**) body weight (kg) and (**C**) systolic BP (mmHg) (**D**) diastolic BP (mmHg) between SGLT2 inhibitor and metformin combination therapy versus SGLT2 inhibitor monotherapy in treatment naïve type 2 diabetes patients. SGLT2I, SGLT2 inhibitor; Emp, empagliflozin; Met, metformin; Dap, dapagliflozin; Can, canagliflozin.



**Figure S3.** The mean change from baseline (pre-treatment) in: (**A**) HbA1c (%) (**B**) body weight (kg) (**C**) systolic BP (mmHg) and (**D**) diastolic BP (mmHg) between combination high dose SGLT2 inhibitor and metformin versus combination low dose SGLT2 inhibitor and metformin in treatment naïve type 2 diabetes patients. Emp, empagliflozin; Met, metformin; Dap, dapagliflozin; Can, canagliflozin.



**Figure S4.** The mean change from baseline (pre-treatment) in: (**A**) HbA1c (%) (**B**) body weight (kg) between empagliflozin and linagliptin combination therapy versus empagliflozin monotherapy in treatment naïve type 2 diabetes patients. SGLT2I, SGLT2 inhibitor; Emp, empagliflozin; Lin, Linagliptin.



**Figure S5.** The mean change from baseline in: (A) HbA1c (%) (B) body weight (kg) between empagliflozin and linagliptin combination therapy versus linagliptin monotherapy in treatment naïve type 2 diabetes patients. SGLT2I, SGLT2 inhibitor; Emp, empagliflozin; Lin, Linagliptin.