Appendix – Detailed study data

Dapagliflozin

Bailey CJ, Gross JL, Pieters A, Bastien A, List JF. **Effect of dapagliflozin in patients with type 2 diabetes who have inadequate glycaemic control with metformin: a randomised, double-blind, placebo-controlled trial.** Lancet 2010; 375: 2223-2233[8]				**Funding source:** Astra-Zeneca and Bristol-Myers-Squibb
				SGLT2 inhibitor (2.5, 5 or 10 mg dapagliflozin) + metformin versus placebo + metformin
Aim: to determine the efficacy and safety of dapagliflozin in type 2 diabetes in patients with inadequate HbA1c control with metformin alone				
Study quality	High – see quality table for further information			
Study particulars	**Multi-centre:** 80 (USA, Canada, Argentina, Mexico, Brazil) **Duration of intervention**: 24 weeks **Duration of run in**: 2 weeks **Follow-up:** on completion of 24 weeks, a 102 week long-term study **Design:** 4-arm parallel-group RCT, double blind, placebo controlled **Primary outcome:** change from baseline in HbA1c at week 24 **Secondary outcomes:** At 24 weeks changes in: - Fasting plasma glucose - Proportion of patients achieving HbA1c <7%, number with HbA1c of 9% or more - Total bodyweight, change from baseline in bodyweight, and decreases in bodyweight of 5% or more - Laboratory tests, adverse events			
Participant criteria	**N:** 534 analysed **Inclusion criteria:** participants aged between 18 and 77 years; type 2 diabetes; BMI ≤45 kg/m^2; HbA1c 7 to 10.0%; fasting C-peptide ≥0.34 ng/ml; taking stable dose metformin ≥1500 mg per day **Exclusion criteria:** serum creatinine ≥133 µmol/L for men or ≥124 µmol/L for women (consistent with metformin labelling); urine albumin/creatinine ratio >203.4 mg/mmol; AST or ALT >three times the upper limit of normal; creatine kinase >three times the upper limit of normal, symptoms of poorly controlled diabetes (including marked polyuria and polydipsia with >10% weight loss during the 3 months before enrolment); systolic blood pressure ≥180 mmHg or diastolic blood pressure ≥110 mmHg; any significant other systemic disease			
Interventions	**Intervention 1:** 2.5 mg dapagliflozin + metformin **Intervention 2:** 5 mg dapagliflozin + metformin **Intervention 3:** 10 mg dapagliflozin + metformin **Intervention 4:** matching placebo + metformin **OAD schedule:** metformin at pre-study dose (≥1500 mg/day; mean dose 1792 to 1861 mg/day); dapagliflozin once daily before morning meal **All groups:** diet and exercise counselling **Lead in period:** 2 weeks, single blind, to assess compliance with placebo, patients randomised after successful completion; metformin dose (open label 500 mg tablets) continued at pre-study levels			
Participant baseline data	**Group 1 (n analysed=134):** Placebo OD + metformin	**Group 2 (n=135):** 2.5 mg dapagliflozin OD + metformin	**Group 3 (n=133):** 5 mg dapagliflozin OD + metformin	**Group 4 (n=132):** 10 mg dapagliflozin OD + metformin
	Age: 53.7 SD10.3 years **Sex:** 55% male	**Age:** 55.0 SD9.3 years **Sex:** 51% male	**Age:** 54.3 SD9.4 years **Sex:** 50% male	**Age:** 52.7 SD9.9 years **Sex:** 57% male

	BMI (kg/m^2): 31.8 SD5.3 **HbA1c (%):** 8.11% SD0.96 **Duration of diabetes:** 5.8 SD5.1 years **FPG (mmol/L):** 9.19 SD2.57 **Systolic BP (mmHg):** 127.7 SD14.6		**BMI (kg/m^2):** 31.6 SD4.8 **HbA1c (%):** 7.99% SD0.90 **Duration of diabetes:** 6.0 SD6.2 years **FPG (mmol/L):** 8.96 SD2.39 **Systolic BP (mmHg):** 126.6 SD14.5		**BMI (kg/m^2):** 31.4 SD5.0 **HbA1c (%):** 8.17% SD0.96 **Duration of diabetes:** 6.4 SD5.8 years **FPG (mmol/L):** 9.39 SD2.72 **Systolic BP (mmHg):** 126.9 SD14.3		**BMI (kg/m^2):** 31.2 SD5.1 **HbA1c (%):** 7.92% SD0.82 **Duration of diabetes:** 6.1 SD5.4 years **FPG (mmol/L):** 8.66 SD2.15 **Systolic BP (mmHg):** 126.0 SD15.9	
Outcome (change from baseline to study end (week 24))								
	Group 1 (n=134): Placebo OD + metformin		**Group 2 (n=135):** 2.5 mg dapagliflozin OD + metformin		**Group 3 (n=133):** 5 mg dapagliflozin OD + metformin		**Group 4 (n=132):** 10 mg dapagliflozin OD + metformin	
	Mean	**95% CI**	**Mean**	**95% CI**	**Mean**	**95% CI**	**Mean**	**95% CI**
ΔHbA1c (%)	-0.3	-0.44 to -0.16	-0.67	-0.81 to -0.53 p=0.0002 vs placebo	-0.70	-0.85 to -0.56 p<0.0001 vs placebo	-0.84	-0.98 to -0.70 p<0.0001 vs placebo
ΔWeight (kg)	-0.9	-1.4 to -0.4	-2.2	-2.7 to -1.8 p<0.0001 vs placebo	-3.0	-3.5 to -2.6 p<0.0001 vs placebo	-2.90	-3.3 to -2.4 p<0.0001 vs placebo
ΔFPG (mmol/L)	-0.33	-0.62 to -0.04	-0.99	-1.28 to -0.69 p=0.0019 vs placebo	-1.19	-1.49 to -0.90 p<0.0001 vs placebo	-1.3	-1.60 to -1.00 p<0.0001 vs placebo
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
ΔSBP (mmHg)	-0.2	1.20	-2.10	1.10	-4.3	1.30	-5.10	1.30
HbA1c (%)	7.79	1.18	7.34	0.93	7.42	0.94	7.13	0.94
Adverse events **Safety assessment**: assessed via adverse events from the Medical Dictionary or Regulatory Activities (MedDRA v12.1) via patient questionnaire and active questioning during visits								
	Minor hypoglycaemia = symptomatic episode, capillary glucose <3.5mmol/L **Major hypoglycaemia =** symptomatic episode, needing external assistance with following recovery, capillary glucose <3.0mmol/L				**General events – where frequency is >5%** UTI = Urinary Tract Infection GTI = Genital Tract Infection HypoT = Hypotension HypoG = Hypoglycaemia		**At least one or more adverse event** **Group 1 =** n=88 **Group 2 =** n=89 **Group 3 =** n=95 **Group 4 =** n=98	
	Group 1 (n analysed=134): Placebo OD + metformin		**Group 2 (n= 135):** 2.5 mg dapagliflozin OD + metformin		**Group 3 (n= 133):** 5 mg dapagliflozin OD + metformin		**Group 4 (n= 132):** 10 mg dapagliflozin OD + metformin	
Specific events	UTI n=11, GTI n=7 HypoT n=1, HypoG n=4 Events leading to discontinuation n=5		UTI n= 6, GTI n=11 HypoT n=0, HypoG n=3 Events leading to discontinuation n=3		UTI n=10, GTI n=18 HypoT n=2, HypoG n=5 Events leading to discontinuation n=3		UTI n=16, GTI n=12 HypoT n=0, HypoG n=5 Events leading to discontinuation n=4	
	Diarrhoea n=7 Back pain n=7 Nasopharyngitis n=11 Cough n=7 Influenza n=10 Hypertension n=6 Upper resp. tract Infection n=10 Headache n=6		Diarrhoea n=3 Back pain n=5 Nasopharyngitis n=12 Cough n=4 Influenza n=13 Hypertension n=9 Upper resp. tract Infection n=5 Headache n=4		Diarrhoea n=5 Back pain n=3 Nasopharyngitis n=4 Cough n=4 Influenza n=13 Hypertension n=4 Upper resp. tract Infection n=4 Headache n=1		Diarrhoea n=10 Back pain n=10 Nasopharyngitis n=8 Cough n=1 Influenza n=8 Hypertension n=5 Upper resp. tract Infection n=3 Headache n=11	

Bolinder J, Ljunggren Ö, Kullberg J, Johansson L, Wilding J, Langkilde AM, Sugg J, Parikh S. **Effects of dapagliflozin on body weight, total fat mass, and regional adipose tissue distribution in patients with type 2 diabetes mellitus with inadequate glycemic control on metformin.** Journal of Clinical Endocrinology and Metabolism 2012; 97(3): 1020-1031[9] Ljunggren Ö, Bolinder J, Johansson L, Langkilde AM, Sjöström CD, Sugg J, Parikh S. **Dapagliflozin has no effect on markers of bone formation and resorption or bone mineral density in patients with inadequately controlled type 2 diabetes mellitus on metformin.** Diabetes, Obesity and Metabolism 2012 [E-publication ahead of print][10]	**Funding source:** Astra-Zeneca and Bristol-Myers-Squibb **SGLT2 inhibitor (10 mg dapagliflozin) + metformin versus placebo + metformin**
Aim: to confirm weight loss with dapagliflozin, and establish effect on body composition and bone metabolism in patients with type 2 diabetes with inadequate glucose control with metformin	
Study quality	High – see quality table for further information
Study particulars	**Multi-centre:** 40 (Bulgaria, Czech Republic, Hungary, Poland, Sweden) **Duration of intervention**: 24 weeks **Duration of run in**: 2 weeks **Follow-up:** 78 week extension period **Design:** 2-arm parallel group RCT, double blind, placebo controlled **Primary outcome:** change from baseline in total body weight at week 24 **Secondary outcomes:** At week 24: - Change in waist circumference and total fat mass - Proportion achieving weight reduction of >5% - HbA1c, fasting plasma glucose - Markers of bone formation and resorption - DXA assessment of bone mineral density and body composition - Systolic and diastolic blood pressure - Adverse events, laboratory values
Participant criteria	**N:** 180 analysed **Inclusion criteria:** participants with type 2 diabetes; postmenopausal women aged 55 to 75 years or men aged 30 to 75 years; HbA1C 6.5 to 8.5%; FPG ≤13.2 mmol/L; BMI ≥25 kg/m^2; weight ≤120 kg; treatment exclusively with a stable dose of metformin ≥1500 mg/day for at least 12 weeks before enrolment **Exclusion criteria:** men <30 years, perimenopausal women, HbA1c >8.5%, use of insulin within 6 months (except temporary ≤7 days); body weight change >5% within 3 months; calculated creatinine clearance <60 mL/min; urine albumin:creatinine ratio >1800 mg/g (>203.4 mg/mmol); ASP and/ALT and/or creatine kinase ≥3 times upper limit of normal range; serum total bilirubin >34 µmol/L; haemoglobin (Hb) ≤105 g/L (10.5 g/dL) for men and ≤95 g/L (9.5 g/dL) for women; abnormal thyroid stimulating hormone level; 25-hydroxyvitamin D level <12 ng/mL (<30 nmol/L); history of osteoporotic fracture, and other skeletal problems; metabolic bone disease or similar within 6 months of enrolment; SBP ≥180 mmHg and/or DBP ≥110 mmHg; congenital renal glycosuria; significant cardiac, renal, hepatic, respiratory, haematological, oncological, endocrine, immunological (including hypersensitivity to study medications), and alcohol and/or substance misuse disorders; pregnancy and/or lactation; a history of bariatric surgery; use of weight loss medication within 30 days of enrolment
Interventions	**Intervention 1:** 10 mg dapagliflozin + metformin **Intervention 2:** placebo + metformin **OAD schedule:** metformin at pre-study dose (≥1500 mg/day, mean dose 1901 mg SD430 in Group 1, 1989 mg SD477 in Group 2); dapagliflozin once daily before or with morning meal; in case of inadequate glycaemic control, sitagliptin 100 mg used as rescue medication **All groups:** diet, lifestyle, exercise counselling **Lead in period:** 2 weeks, single blind, placebo lead in

Participant baseline data	**Group 1 (start n= 91, analysed n=91):** Placebo + metformin		**Group 2 (start n= 91, analysed n= 89):** 10 mg dapagliflozin + metformin	
	Age: 60.8 SD6.9 years **Sex:** 56% male **BMI (kg/m^2):** 31.7 SD3.9 **HbA1c (%):** 7.16% SD0.53 **Duration of diabetes:** 5.5 SD5.3 years **FPG (mmol/L):** 8.3 SD1.4		**Age:** 60.6 SD8.2 years **Sex:** 55.1% male **BMI (kg/m^2):** 32.1 SD3.9 **HbA1c (%):** 7.19% SD0.44 **Duration of diabetes:** 6.0 SD4.5 years **FPG (mmol/L):** 8.2 SD1.4	
Outcome (change from baseline to study end (24 weeks))				
	Group 1 (n=91): Placebo + metformin		**Group 2 (n= 89):** 10 mg dapagliflozin + metformin	
	Mean	**95% CI**	**Mean**	**95% CI**
ΔHbA1c (%)	-0.10	-0.01 to -0.19 [from graph]	-0.39	-0.29 to -0.49 [from graph] , p<0.0001 vs placebo
ΔWeight (kg)	-0.88	-1.43 to -0.34	-2.96	-3.51 to -2.41, p<0.0001 vs placebo
ΔFPG (mmol/L)	+0.13	NR	-0.82	NR, p<0.0001 vs placebo
	Mean	**SD**	**Mean**	**SD**
ΔSBP (mmHg)	0.1	NR	-2.7	NR
Adverse events **Safety assessment:** assessed via adverse events from the Medical Dictionary or Regulatory Activities (MedDRA v12.1) via patient questionnaire and active questioning during visits, laboratory tests and vital signs				
	Minor hypoglycaemia (HypoM) = symptomatic episode, capillary glucose <3.5mmol/L, asymptomatic episode with glucose <3.5 mmol/L **Severe hypoglycaemia** (HypoS) = symptomatic episode needing external assistance with capillary glucose <3.0mmol/L, recovery following glucose or glucagon administration **Other hypoglycaemia** (HypoO) = symptoms, but without confirmative measurement		**General events – where frequency is >2%** UTI = Urinary Tract Infection GTI = Genital Tract Infection HypoS = Hypoglycaemia (severe) HypoM = Hypoglycaemia (mild) HypoO = Hypoglycaemia other HypoT = Hypotension	**At least one or more adverse event** **Group 1 =** 42.9% **Group 2 =** 39.6% 1 death in dapagliflozin group, no deaths in placebo group No significant effect on bone formation and resorption or bone mineral density
	Group 1 (n=91): Placebo + metformin		**Group 2 (n= 89):** 10 mg dapagliflozin + metformin	
Specific events	UTI n=2, GTI n=0 HypoM n=2, HypoS n=0, HypoO n=1 HypoT n=0 Events leading to discontinuation n=0		UTI n=6, GTI n=3 HypoM n=2, HypoS n=0, HypoO n=0 HypoT n=1 Events leading to discontinuation n=5	
	Nasopharyngitis n=5 Hypertension n=4 Pneumonia n=0 Angina pectoris n=0 Cystitis n=1 Arthralgia n=5 Headache n=2 Diarrhoea n=2		Nasopharyngitis n=6 Hypertension n=4 Pneumonia n=3 Angina pectoris n=2 Cystitis n=2 Arthralgia n=1 Headache n=1 Diarrhoea n=0	

Nauck MA, Del Prato S, Meier JJ, Duran-Garcia S, Rohwedder K, Elze M, Parikh SJ. **Dapagliflozin versus glipizide as add-on therapy in patients with type 2 diabetes who have inadequate glycaemic control with metformin.** Diabetes Care 2011; 34: 2015-2022[11]		**Funding source:** Astra-Zeneca and Bristol-Myers-Squibb
		SGLT2 inhibitor (up to 10 mg dapagliflozin) + metformin versus metformin + glipizide
Aim: to compare the efficacy, safety and tolerability of dapagliflozin with glipizide in patients with type 2 diabetes inadequately controlled with monotherapy		
Study Quality	High – see quality table for further information	
Study particulars	**Multi-centre:** 95 sites across 10 countries world-wide **Duration of intervention**: 52 weeks **Duration of run in**: 2 weeks **Follow-up:** on completion of 52 weeks, 156 week extension **Design:** 2-arm parallel group RCT, double-blind **Primary outcome:** absolute change from baseline in HbA1c at week 52 **Secondary outcomes:** - Change in total body weight - Proportion with hypoglycaemic episode - Proportion of ≥5% total weight loss	
Participant criteria	**N:** 801 analysed **Inclusion criteria:** participants aged 18 years and older; inadequately controlled type 2 diabetes (HbA1c >6.5 and ≤10%); BMI ≤45kg/m^2; fasting C-peptide ≥0.33 nmol/L, receiving stable dose metformin or metformin and one other OAD at up to half maximal dose for up to 8 weeks prior to enrolling; FPG ≤15 mmol/L **Exclusion criteria:** creatinine clearance <60 mL/min; urine albumin: creatinine ratio >203.4 mg/mmol; AST and/or ALT and/or creatine kinase ≥3 times upper limit of normal; total bilirubin >34 µmol/L; haemoglobin ≤11 g/dL for men and ≤10 g/dL for women; abnormal TSH; systolic blood pressure ≥180 mmHg and/or diastolic blood pressure ≥110 mmHg; significant other disease	
Interventions	**Intervention 1:** dapagliflozin + metformin (dapagliflozin mean dose 9.2 mg/day) **Intervention 2:** glipizide + metformin (glipizide mean dose 16.4 mg/day) **OAD schedule:** metformin 1500 to 2000 mg/day (median dose at enrolment 2000 mg/day); dapagliflozin started at 2.5 mg, up-titrated to maximum tolerable dose (up to 10 mg); glipizide started at 5 mg, up-titrated to maximum tolerable dose (up to 20 mg) **All groups:** diet and lifestyle advice **Lead in period:** before lead in: other OADs discontinued, metformin stabilised to 1500 to 2000 mg/day; 2 weeks single blind placebo lead in prior to randomisation	
Participant baseline data	**Group 1** (start n= 406, analysed n=400): 9.2 mg dapagliflozin + metformin	**Group 2 (**start n= 408, analysed n= 401): 16.4 mg glipizide + metformin
	Age: 58 SD9 years **Sex:** 55.3% male **BMI (kg/m^2):** 31.7 SD5.1 **≥ 25 kg/m^2**: 95% **≥ 30 kg/m^2:** 57% **HbA1c (%):** 7.7% SD0.9 **Duration of diabetes:** 6 SD5 years **FPG (mmol/L):** 9.0 SD2.1	**Age:** 59 SD10 years **Sex:** 54.9% male **BMI (kg/m^2):** 31.2 SD5.1 **≥ 25 kg/m^2**: 90.8% **≥ 30 kg/m^2:** 55.4% **HbA1c (%):** 7.7% SD0.9 **Duration of diabetes:** 7 SD6 years **FPG (mmol/L):** 9.1 SD2.3

Outcome (change from baseline at study end (week 52))				
	Group 1 (n=400): 9.2 mg dapagliflozin + metformin		**Group 2 (n= 401):** 16.4 mg glipizide + metformin	
	Mean	**95% CI**	**Mean**	**95% CI**
ΔHbA1c (%)	-0.52	-0.60 to -0.44	-0.52	-0.60 to -0.44, NS
ΔWeight (kg)	-3.22	-3.56 to -2.87	+1.44	+1.09 to +1.78, p<0.0001
ΔFPG (mmol/L)	-1.24	-1.42 to -1.07	-1.04	-1.22 to -0.98, NS
ΔSBP (mmHg)	-4.3	-5.4 to -3.2 [from graph]	+0.8	-0.3 to 1.9 [from graph], p NR
Adverse events **Safety assessment:** assessed via adverse events from the Medical Dictionary or Regulatory Activities (MedDRA v12.1) via patient questionnaire and active questioning during visits				
	Severe hypoglycaemia (HypoS) = symptomatic episode, needing external assistance with following recovery, capillary glucose <3.0mmol/L **Minor hypoglycaemia** (HypoM) = symptomatic episode, capillary glucose <3.5mmol/L **Other hypoglycaemia** (HypoO) = symptoms, but without measurement confirming		**General events – where frequency is ≥3%** UTI = Urinary Tract Infection GTI = Genital Tract Infection HypoS = Hypoglycaemia (severe) HypoM = Hypoglycaemia (mild) HypoO = Hypoglycaemia other HypoT = Hypotension	**At least one or more adverse event** **Group 1 =** n=318 **Group 2 =** n=318 No deaths in dapagliflozin group 3 deaths in glipizide group
	Group 1 (n=406): 9.2 mg dapagliflozin + metformin		**Group 2 (n= 408):** 16.4 mg glipizide + metformin	
Specific events	UTI n=44, GTI n=50 HypoS n=0, HypoM n=7, HypoO n=7 HypoT n=6 Renal impairment / failure n=24 Events leading to discontinuation n=37 (0 due to hypoglycaemia)		UTI n=26, GTI n=11 HypoS n=3, HypoM n=147, HypoO n=40 HypoT n=3 Renal impairment / failure n=14 Events leading to discontinuation n=24 (6 due to hypoglycaemia)	
	Diarrhoea n=19 Nausea n=14 Vulvovaginal mycotic infection n=14 Back pain n=19 Nasopharyngitis n= 43 Cough n=15 Influenza n=30 Arthralgia n=11 Upper resp. tract Infection n=24 Headache n=21 Hypertension n=30		Diarrhoea n=26 Nausea n=15 Vulvovaginal mycotic infection n=2 Back pain n=20 Nasopharyngitis n=61 Cough n=20 Influenza n=30 Arthralgia n=21 Upper resp. tract Infection n=31 Headache n=17 Hypertension n=35	

Rosenstock J, Vico M, Wei L, Salsali A, List JF. **Effects of dapagliflozin, an SGLT2 inhibitor, on HbA1c, body weight, and hypoglycaemia risk in patients with type 2 diabetes inadequately controlled in pioglitazone monotherapy.** Diabetes Care 2012; 35: 1473-1478[12]			**Funding source:** Astra-Zeneca and Bristol-Myers-Squibb **SGLT2 inhibitor (5 or 10 mg dapagliflozin) + pioglitazone versus placebo + pioglitazone**
Aim: to examine the safety and efficacy of dapagliflozin added to pioglitazone in type 2 diabetes patients inadequately controlled on pioglitazone			
Study quality	Low – see quality table for further information		
Study particulars	**Multi-centre:** 105 (Argentina, Canada, India, Mexico, Peru, Philippines, Taiwan, USA) **Duration of intervention**: 24 weeks **Duration of run in**: 2 weeks **Follow-up:** 24 week extension period **Design:** 3-arm parallel group RCT, double blind, placebo controlled **Primary outcome:** change from baseline in HbA1c at week 24 **Secondary outcomes:** At week 24, change from baseline in: - Fasting plasma glucose - Postprandial glucose - Total body weight - Blood pressure - Adverse events, laboratory values, vital signs		
Participant criteria	**N:** 420 analysed **Inclusion criteria:** participants with type 2 diabetes; age ≥18 years; fasting C-peptide ≥1.0 ng/mL; BMI ≤45 kg/m^2; Group A: ≥12 weeks of pioglitazone 30 or 45 mg/day and HbA1c ≥7.0 to ≤10.5%; Group B: drug naïve for previous 10 weeks with HbA1c ≥8.0 to ≤11.0% or had received 15 mg/day pioglitazone or any dose of rosiglitazone with hbA1c ≥8.0 and ≤11.0% or had received ≥8 weeks of metformin ≤1700 mg/day or sulphonylurea ≤half maximal dose with HbA1c ≥7.0 to ≤11.0%, not more than one oral antidiabetic medication; Group B underwent 10 week dose optimisation in which initial therapy was discontinued and pioglitazone 30 mg/day was started and increased to 45 mg/day if possible; pre-randomisation HbA1c had to be ≥7.0 and ≤10.5% **Exclusion criteria:** AST or ALT >2.5 times upper limit of normal; total bilirubin >2.0 mg/dL, serum creatinine ≥2.0 mg/dL, urine albumin/creatinine ratio >1800 mg/g, calculated creatinine clearance <50 mL/min, congestive heart failure class III and IV		
Interventions	**Intervention 1:** 5 mg dapagliflozin + pioglitazone **Intervention 2:** 10 mg dapagliflozin + pioglitazone **Intervention 3:** placebo + pioglitazone **OAD schedule:** open-label pioglitazone 30 or 45 mg/day; dapagliflozin once daily; in case of inadequate glycaemic control (FPG >270 mg/dL (week 4 to 8) or >240 mg/dL (week 8 to 12) or >200 mg/dL (week 12 to 24) patients were eligible for open label rescue medication (metformin or sulphonylurea) **All groups:** diet and exercise counselling **Lead in period:** 2 weeks, single blind, placebo lead in		
Participant baseline data	**Group 1 (n=139):** Placebo + pioglitazone	**Group 2 (n=141):** 5 mg dapagliflozin + pioglitazone	**Group 2 (n=140):** 10 mg dapagliflozin + pioglitazone
	Age: 53.5 SD11.4 years **Sex:** 51.1% male **BMI:** 61.2% ≥30 kg/m^2; 87.8% ≥25 kg/m^2 **HbA1c:** 8.34% SD1.00	**Age:** 53.2 SD10.9 years **Sex:** 55.3% male **BMI:** 61.7% ≥30 kg/m^2; 86.5% ≥25 kg/m^2 **HbA1c:** 8.40% SD1.03	**Age:** 53.8 SD10.2 years **Sex:** 42.1% male **BMI:** 51.4% ≥30 kg/m^2; 92.9% ≥25 kg/m^2 **HbA1c:** 8.37% SD0.96

	Duration of diabetes: 5.07 SD5.05 years **FPG (mmol/L):** 8.92 SD2.61		**Duration of diabetes:** 5.64 SD5.36 years **FPG (mmol/L):** 9.36 SD2.89		**Duration of diabetes:** 5.75 SD6.44 years **FPG (mmol/L):** 9.15 SD2.57	
Outcome (change from baseline to study end)						
	Group 1 (n=139): Placebo + pioglitazone		**Group 2 (n=141):** 5 mg dapagliflozin + pioglitazone		**Group 2 (n=140):** 10 mg dapagliflozin + pioglitazone	
	Mean	**SE**	**Mean**		**Mean**	**SE**
ΔHbA1c (%)	*wk 24:* -0.42 *wk 48:* -0.54	0.08 0.08	-0.82 -0.95	0.08, p=0.0007 vs placebo 0.08, p NR	-0.97 -1.21	0.08, p<0.0001 vs placebo 0.07, p NR
ΔWeight (kg)	*wk 24:* +1.64 *wk 48:* +2.99	0.28 0.41	+0.09 +1.35	0.28, p<0.0001 vs placebo 0.38, p NR	-0.14 +0.69	0.28, p<0.0001 vs placebo 0.36, p NR
ΔFPG (mmol/L)	*wk 24:* -0.31 *wk 48:* -0.73	0.16 0.20	-1.38 -1.27	0.16, p<0.0001 vs placebo 0.18, p NR	-1.64 -1.84	0.16, p<0.0001 vs placebo 0.17, p NR
ΔSBP (mmHg)	*wk 24:* +1.3 *wk 48:* +2.0	1.2 1.2	-0.8 -1.0	1.2, p NS 1.1, p NR	-3.4 -2.2	1.2, p NS 0.7, p NR
Adverse events **Safety assessment:** assessed at every visit, questioning, laboratory tests and vital signs						
	Minor hypoglycaemia (HypoM) = symptomatic episode, capillary glucose <3.5mmol/L, asymptomatic episode with glucose <3.5 mmol/L **Severe hypoglycaemia** (HypoS) = symptomatic episode needing external assistance with capillary glucose <3.0mmol/L, recovery following glucose or glucagon administration **Other hypoglycaemia** (HypoO) = symptoms, but without confirmative measurement		**General events – where frequency is >5%** UTI = Urinary Tract Infection GTI = Genital Tract Infection HypoS = Hypoglycaemia (severe) HypoM = Hypoglycaemia (mild) HypoO = Hypoglycaemia other		**At least one or more adverse event** **Group 1 =** 66.9% **Group 2 =** 68.1% **Group 3** = 70.7%	
	Group 1 (n=139): Placebo + pioglitazone		**Group 2 (n=141):** 5 mg dapagliflozin + pioglitazone		**Group 2 (n=140):** 10 mg dapagliflozin + pioglitazone	
Specific events	UTI n=11, GTI n=4 Any hypoglycaemia n=1, HypoS n=0 Decreased renal function n=1 Events leading to discontinuation n=5		UTI n=12, GTI n=13 Any hypoglycaemia n=3, HypoS n=0 Decreased renal function n=2 Events leading to discontinuation n=5		UTI n=7, GTI n=12 Any hypoglycaemia n=0, HypoS n=0 Decreased renal function n=2 Events leading to discontinuation n=3	
	Dyslipidaemia n=9 Nasopharyngitis n=7 Diarrhoea n=6 Back pain n=4 Upper resp. tract infection n=10 Headache n=10 Pain in extremity n=1 Oedema peripheral n=9		Dyslipidaemia n=11 Nasopharyngitis n=7 Diarrhoea n=5 Back pain n=5 Upper resp. tract infection n=10 Headache n=3 Pain in extremity n=10 Oedema peripheral n=6		Dyslipidaemia n=16 Nasopharyngitis n=11 Diarrhoea n=9 Back pain n=8 Upper resp. tract infection n=7 Headache n=4 Pain in extremity n=4 Oedema peripheral n=3	

<table>
<tr><td colspan="4">Strojek K, Yoon KH, Hruba V, Elze M, Langkilde AM, Parikh S. Effect of Dapagliflozin in patients with type 2 diabetes who have inadequate glycaemic control with glimepiride: a randomized, 24-week, double-blind, placebo-controlled trial. Diabetes, Obesity and Metabolism 2011; 13(10): 928-938[13]</td><td>Funding source: Astra-Zeneca and Bristol-Myers-Squibb
SGLT2 Inhibitor (2.5, 5, or 10 mg dapagliflozin)plus glimepiride versus placebo plus glimepiride</td></tr>
<tr><td colspan="5">Aim: to determine the efficacy, safety and tolerability of dapagliflozin treatment, as an add-on therapy to glimepiride, in patients with inadequately controlled type 2 diabetes who had been treated with sulphonylurea monotherapy</td></tr>
<tr><td>Study quality</td><td colspan="4">High – see quality table for further information</td></tr>
<tr><td>Study particulars</td><td colspan="4">Multi-centre: 84 sites across 7 countries world-wide
Duration of intervention: 24 weeks
Duration of run in: 1 week for patients switched to glimepiride
Follow-up: on completion of 24 weeks, 24 week extension
Design: 4-arm parallel group RCT, double blind, placebo controlled
Primary outcome: change in HbA1c from baseline to week 24
Secondary outcomes:
After 24 weeks:
- Change in total body weight
- Change in post challenge plasma glucose (2 hrs) following oral glucose tolerance test
- Proportion of patients with HBA1c <7%
- Change in total body weight from baseline in patients with BMI ≥27kg/m^2
- Change in FPG</td></tr>
<tr><td>Participant criteria</td><td colspan="4">N: 592 analysed
Inclusion criteria: participants aged 18 years and older; inadequately controlled type 2 diabetes (HbA1c ≥7 to ≤10.0%); BMI ≤45kg/m^2; on stable sulphonylurea dose (at least half maximum dose (max 4 mg) for at least 8 weeks prior to enrolment); fasting C-peptide ≥0.33 nmol/ml; FPG ≤15 mmol/L
Exclusion criteria: creatinine clearance <50 mL/minor serum creatinine >177 µmol/L; urine albumin: creatinine ratio >203.4 mg/mmol; AST and/or ALT and/or creatine kinase ≥3 times upper limit of normal; total bilirubin >34 µmol/L; haemoglobin (Hb) ≤10 g/dL for men and ≤9.5 g/dL for women; SBP ≥180 mmHg and/or DBP ≥110 mmHg; any significant other systemic disease; pregnancy or lactation; use of weight loss medication within 30 days</td></tr>
<tr><td>Interventions</td><td colspan="4">Intervention 1: placebo + glimepiride
Intervention 2: 2.5 mg/day dapagliflozin + glimepiride
Intervention 3: 5 mg/day dapagliflozin + glimepiride
Intervention 4: 10 mg/day dapagliflozin + glimepiride
OAD schedule: open-label glimepiride 4 mg/day; glimepiride allowed to be down-titrated to 2 mg/day or discontinued in case of hypoglycaemia, no up-titration allowed; dapagliflozin once daily before the first meal of the day; in case of inadequate glycaemic control, patients could receive open-label rescue therapy of metformin, pioglitazone or rosiglitazone
All groups: all patients received dietary and lifestyle counselling; patients with BMI ≥27 kg/m^2 received advice about reducing caloric intake and increasing physical activity
Lead in period: 1 week for inclusion/exclusion review for those switched to 4 mg/day glimepiride</td></tr>
<tr><td rowspan="2">Participant baseline data</td><td>Group 1 (n= 146)
Placebo + glimepiride</td><td>Group 2 (n= 154)
2.5 mg dapagliflozin + glimepiride</td><td>Group 3 (n= 145)
5 mg dapagliflozin + glimepiride</td><td>Group 4 (n= 151)
10 mg dapagliflozin + glimepiride</td></tr>
<tr><td>Age: 60.3 SD10.16 years
Sex: 49% male</td><td>Age: 59.9 SD10.14 years
Sex: 50% male</td><td>Age: 60.2 SD 9.73 years
Sex: 50% male</td><td>Age: 58.9 SD 8.32 years
Sex: 43.7% male</td></tr>
</table>

	BMI: 86.2% ≥25 kg/m^2; 45.5% ≥30 kg/m^2 **HbA1c:** 8.15% SD0.74 **Duration of diabetes:** 7.4 SD5.7 years **FPG (mmol/L):** 9.58 SD2.07 **Systolic BP (mmHg):** 133.3		**BMI:** 84.4% ≥25 kg/m^2; 48.1% ≥30 kg/m^2 **HbA1c:** 8.11% SD0.75 **Duration of diabetes:** 7.7 SD6.0 years **FPG (mmol/L):** 9.56 SD2.13 **Systolic BP (mmHg):** 134.6		**BMI:** 80.3% ≥25 kg/m^2; 51.4% ≥30 kg/m^2 **HbA1c:** 8.12% SD0.78 **Duration of diabetes:** 7.4 SD5.7 years **FPG (mmol/L):** 9.68 SD2.12 **Systolic BP (mmHg):** 130.9		**BMI:** 79.5% ≥25 kg/m^2; 45% ≥30 kg/m^2 **HbA1c:** 8.07% SD0.79 **Duration of diabetes:** 7.2 SD5.5 years **FPG (mmol/L):** 9.55 SD2.04 **Systolic BP (mmHg):** 132.4	
Outcome (change from baseline to study end (week 24))								
	Group 1 (n= 146) Placebo + glimepiride		**Group 2 (n= 154)** 2.5 mg dapagliflozin + glimepiride		**Group 3 (n= 145)** 5 mg dapagliflozin + glimepiride		**Group 4 (n= 151)** 10mg dapagliflozin + glimepiride	
	Mean	**95% CI**	**Mean**	**95% CI**	**Mean**	**95% CI**	**Mean**	**95% CI**
ΔHbA1c (%)	-0.13	-0.26 to 0 [from graph]	-0.58	-0.7 to -0.46 [from graph], p<0.0001 vs placebo	-0.63	-0.76 to -0.5 [from graph], p<0.0001 vs placebo	-0.82	-0.94 to -0.7 [from graph], p<0.0001 vs placebo
ΔWeight (kg)	-0.72	-0.96 to -0.48 [from graph]	-1.18	-1.42 to -0.94 [from graph], NS	-1.56	-1.8 to -1.32 [from graph], p<0.0091 vs placebo	-2.26	-2.5 to -2.02 [from graph], p<0.0001 vs placebo
ΔFPG (mmol/L)	-0.11	-	-0.93	-	-1.18	-	-1.58	-
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
ΔSBP (mmHg)	-1.20	-	-4.7	-	-4.0	-	-5.0	-
Adverse events **Safety assessment:** assessed via adverse events from the Medical Dictionary or Regulatory Activties (MedDRA v12.1) via patient questionnaire and active questioning during visits; hypoglycaemic events, laboratory testing, vital signs								
	Hypoglycaemia not clearly defined				**General events – where frequency is ≥3% in any group** UTI = Urinary Tract Infection GTI = Genital Tract Infection Hypo = Hypoglycaemia		**At least one or more adverse event** **Group 1 =** n=69; **Group 2 =** n=80 **Group 3 =** n=70; **Group 4 =** n=76 1 death in dapagliflozin 2.5 mg 1 death in dapagliflozin 10 mg	
	Group 1 (n= 146) Placebo + glimepiride		**Group 2 (n= 154)** 2.5 mg dapagliflozin + glimepiride		**Group 3 (n= 145)** 5 mg dapagliflozin + glimepiride		**Group 4 (n= 151)** 10 mg dapagliflozin + glimepiride	
Specific events	UTI n=9, GTI n= 1 ≥ 1 Hypo n=7 Renal impairment / failure n=2 Events leading to discontinuation n=3		UTI n=6, GTI n=6 ≥ 1 Hypo n=11 Renal impairment / failure n=1 Events leading to discontinuation n=5		UTI n=10, GTI n=9 ≥ 1 Hypo n=10 Renal impairment / failure n=1 Events leading to discontinuation n=5		UTI n=8, GTI n=10 ≥ 1 Hypo n=12 Renal impairment / failure n=0 Events leading to discontinuation n=4	
	Bronchitis n=1 Diarrhoea n=5 Back pain n= 4 Nasopharyngitis n=4 Arthralgia n=4 Upper resp. tract Infection n=4 Hypertension n=6		Bronchitis n=2 Diarrhoea n=4 Back pain n=3 Nasopharyngitis n=3 Arthralgia n=6 Upper resp. tract Infection n=5 Hypertension n=8		Bronchitis n=3 Diarrhoea n=2 Back pain n=3 Nasopharyngitis n=8 Arthralgia n=0 Upper resp. tract Infection n=6 Hypertension n=2		Bronchitis n=5 Diarrhoea n=0 Back pain n=7 Nasopharyngitis n=5 Arthralgia n=1 Upper resp. tract Infection n=7 Hypertension n=2	

Wilding JPH, Norwood P, T'joen C, Bastien A, List JF, Fiedorek FT. **A study of dapagliflozin in patients with type 2 diabetes receiving high doses of insulin plus insulin sensitizers. Applicability of a novel insulin-independent treatment.** Diabetes Care 2009; 32(9): 1656-1662[14]	**Funding source:** Astra-Zeneca and Bristol-Myers-Squibb **SGLT2 Inhibitor (10 or 20 mg dapagliflozin) + insulin + OAD versus placebo + insulin + OAD**
Aim: to determine if dapagliflozin lowers HbA1c in patients with type 2 diabetes poorly controlled with high insulin doses plus oral antidiabetic agents	
Study quality	Medium – see quality table for further information
Study particulars	**Multi-centre:** 26 (USA and Canada) **Duration of intervention**: 12 weeks **Duration of run in**: 2 weeks **Follow-up:** on completion of 12 weeks, 4 week follow-up **Design:** 3-arm parallel group RCT, double blind, placebo controlled **Primary outcome:** change from baseline in HbA1c at week 12 **Secondary outcomes:** - Change from baseline in FPG - Change in total daily requirement of insulin - Percentage of patients with change in HbA1c ≥0.5% - Percentage of patients with final HbA1c <7% - Change from baseline in total body weight - Change from baseline in post-prandial glucose - Adverse events, vital signs, laboratory measurements
Participant criteria	**N:** 71 analysed **Inclusion criteria:** participants aged between 18 and 75 years; type 2 diabetes; BMI ≤45 kg/m^2; HbA1c 7.5 to 10.0%; taking stable dose metformin (≥1000 mg) and/or pioglitazone (≥30 mg) or rosiglitazone (4 mg) for ≥6 weeks and insulin therapy ≥12 weeks before enrolment (≥50 units of U100, stable for ≥6 weeks); fasting C-peptide ≥0.8 ng/ml, serum creatinine <1.5 mg/dl (men) or <1.4 mg/dl (women), urine microalbumin-to-creatinine ratio <300 mg/g or, if exceeded on spot check, a 24-h urine total protein <3 g/24 h **Exclusion criteria:** type 1 diabetes, AST and/or ALT >2.5 times the upper limit of normal, creatine kinase ≥3 times the upper limit of normal, symptoms of severely uncontrolled diabetes including a history of severe hypoglycaemia; any significant other disease
Interventions	**Intervention 1:** placebo + OAD + insulin **Intervention 2:** 10 mg dapagliflozin + OAD + insulin **Intervention 3:** 20 mg dapagliflozin + OAD + insulin **OAD/insulin schedule:** insulin dose reduced to 50% of pre-study daily insulin (total daily dose mean 51.3 to 55.7 U); dapagliflozin once daily; OAD: insulin sensitiser continued at pre-study dose (metformin ≥1000 mg and/or pioglitazone ≥30 mg or rosiglitazone 4 mg (66.7 to 79.2% metformin only, 8.3 to 25% metformin + TZD, 4.3 to 12.5% TZD only); no dose adjustments to OADs allowed; insulin could be down-titrated in patients at risk of hypoglycaemia **All groups:** diet and exercise programme (American Diabetes Association or similar local guidelines) **Lead in period:** 10-21 days to establish reduced insulin dose

Participant baseline data	**Group 1 (n=23):** Placebo + OAD + insulin		**Group 2 (n= 24):** 10 mg dapagliflozin + OAD + insulin		**Group 3 (n= 24):** 20 mg dapagliflozin + OAD + insulin	
	Age: 58.4 SD6.5 years **Sex:** 69.6% male **BMI (kg/m^2):** 34.8 SD4.6 **HbA1c:** 8.40% SD0.9 **Duration of diabetes:** 13.8 SD 7.3 years **FPG (mmol/L):** 9.22 SD 2.86 **Systolic BP (mmHg):** NR		**Age:** 55.7 SD9.2 years **Sex:** 54.2% male **BMI (kg/m^2):** 35.5 SD3.6 **HbA1c:** 8.4% SD0.7 **Duration of diabetes:** 11.8 SD5.8 years **FPG (mmol/L):** 8.67 SD 2.17 **Systolic BP (mmHg):** NR		**Age:** 56.1 SD10.6 years **Sex:** 54.2% male **BMI (kg/m^2):** 36.2 SD4.6 **HbA1c:** 8.5% SD0.9 **Duration of diabetes:** 11.3 SD5.6 years **FPG (mmol/L):** 8.98 SD 3.06 **Systolic BP (mmHg):** NR	
Outcome (change from baseline at study end (week 12))						
	Group 1 (n=23): Placebo + OAD + insulin		**Group 2 (n= 24):** 10 mg dapagliflozin + OAD + insulin		**Group 3 (n= 24):** 20 mg dapagliflozin + OAD + insulin	
	Mean	**95% CI**	**Mean**	**95% CI**	**Mean**	**95% CI**
ΔHbA1c (%)	+0.09	-0.2 to +0.4	-0.61	-0.9 to -0.4	-0.69	-0.90 to -0.4, p NR
ΔWeight (kg)	-1.9	-2.9 to -0.9	-4.50	-5.5 to -3.5	-4.3	-5.3 to -3.3, p NR
ΔFPG (mmol/L)	+0.99	+0.08 to +1.90	+0.13	-0.75 to +1.02	-0.53	-1.42 to +0.35, p NR
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**
ΔSBP (mmHg)	- (slight increase, NR)	-	-7.2	-	-6.10	-
HbA1c (%)	8.5	0.8	7.80	0.7	7.80	0.60
Adverse events **Safety assessment:** treatment-emergent adverse events, vital signs, laboratory measurements						
	Minor hypoglycaemia = symptomatic episode, capillary glucose <3.5mmol/L **Major hypoglycaemia =** symptomatic episode, needing external assistance with following recovery, capillary glucose <3.0mmol/L		**General events – where frequency is >5%** UTI = Urinary Tract Infection GTI = Genital Tract Infection HypoT = Hypotension, HypoG = Hypoglycaemia HypoS = major hypoglycaemia		**At least one or more adverse event** **Group 1 =** n=15 **Group 2 =** n=18 **Group 3 =** n=16	
	Group 1 (n=23): Placebo + OAD + insulin		**Group 2 (n= 24):** 10 mg dapagliflozin + OAD + insulin		**Group 3 (n= 24):** 20 mg dapagliflozin + OAD + insulin	
Specific events	UTI n=0, GTI n = 1 HypoT n=NR, HypoG n=3, HypoS n=1 Events leading to discontinuation n=1		UTI n= 0, GTI n = 0 HypoT n=NR, HypoG n=7, HypoS n=0 Events leading to discontinuation n=1		UTI n= 1, GTI n = 5 HypoT n=NR, HypoG n=6, HypoS n=0 Events leading to discontinuation n=1	
	Nausea n=1 Pollakiuria n=4 Back pain n=2 Nasopharyngitis n=2 Upper abdominal pain n= 2 Influenza n=2 Pain in extremity n=1 Upper resp. tract Infection n=2 Headache n= 2 Procedural pain n=2		Nausea n=1 Pollakiuria n=2 Back pain n=3 Nasopharyngitis n=2 Fatigue n=2 Influenza n=1 Pain in extremity n=2 Upper resp. tract Infection n=2 Headache n=3 Pharyngolaryngeal pain n=2		Nausea n=3 Pollakiuria n=3 Vomiting n=3 Vulvovaginal mycotic infection n=3 Anxiety n=2 Back pain n=2 Dry Mouth n=2 Nasopharyngitis n=2 Peripheral oedema n=2 Upper abdominal pain n=1 Fatigue n=1 Influenza n=1, Upper resp. tract Infection n=1 Pain in extremity n=1	

Wilding JPH, Woo V, Soler NG, Pahor A, Sugg J, Rohwedder K, Parikh S. **Long-term efficacy of dapagliflozin in patients with type 2 diabetes mellitus receiving high doses of insulin. A randomized trial.** Annals of Internal Medicine 2012; 156(6): 405-415[15]				**Funding source:** Astra-Zeneca and Bristol-Myers-Squibb
				SGLT2 Inhibitor (2.5, 5 or 10 mg dapagliflozin) + insulin ± OAD versus placebo + insulin ± OAD
Aim: to evaluate the efficacy and safety of adding dapagliflozin to patients whose type 2 diabetes is inadequately controlled with insulin with or without oral antidiabetic drugs				
Study quality	High – see quality table for further information			
Study particulars	**Multi-centre:** 126 worldwide **Duration of intervention**: 24 weeks **Duration of run in**: 2 week enrolment **Follow-up:** on completion of 24 weeks, 24 week extension plus further 56 week extension in progress **Design:** 4-arm parallel group RCT, double blind, placebo controlled **Primary outcome:** change from baseline in HbA1c to week 24 **Secondary outcomes:** - Change in total body weight - Change in calculated mean daily insulin dose - Proportion with mean daily insulin reductions of ≥10% from baseline - Change in FPG - Laboratory tests, adverse events, vital signs			
Participant criteria	**N:** 800 analysed **Inclusion criteria:** participants aged between 18 and 80 years; type 2 diabetes; BMI ≤45 kg/m^2; inadequate glycaemic control (HbA1c ≥7.5 to ≤10.5%); stable insulin regimen with mean daily dose of ≥30 U for ≥8 weeks; additional treatment with up to two OADs allowed (≥1500 mg metformin or maximum tolerated dose or at least half maximum dose of other OADS for ≥8 weeks) **Exclusion criteria:** type 1 diabetes; signs of poorly controlled diabetes; calculated creatinine clearance <50 ml/min per 1.73 m^2 or serum creatinine ≥177 µmol/L, or if receiving metformin >133 µmol/L for men or ≥124 µmol/L for women			
Interventions	**Intervention 1:** placebo + insulin ± OAD **Intervention 2:** 2.5 mg dapagliflozin + insulin ± OAD **Intervention 3:** 5 mg dapagliflozin + insulin ± OAD **Intervention 4:** 10 mg dapagliflozin + insulin ± OAD **OAD/insulin schedule:** dapagliflozin once daily; open label treatment with usual daily dose of insulin (mean daily dose 77.1 U) and existing OADs (none in ~50%, metformin only in ~40%, metformin in combination in ~5 to 8%, other OAD / combination in ~1.5 to 6%); OAD doses could be decreased when hypoglycaemia was a concern; insulin could be up-or down-titrated if needed **All groups:** instructed to follow stable diet and exercise regimen; **Lead in period:** unclear			
Participant baseline data	**Group 1 (n analysed=193):** Placebo + insulin ± OAD	**Group 2 (n=202):** 2.5 mg dapagliflozin + insulin ± OAD	**Group 3 (n=211):** 5 mg dapagliflozin + insulin ± OAD	**Group 4 (n=194):** 10 mg dapagliflozin + insulin ± OAD
	Age: 58.8 SD8.6 years **Sex:** 49.2% male **BMI (kg/m^2):** 33.1 SD5.9 **HbA1c (%):** 8.47% SD0.77 **Duration of diabetes:** 13.5 SD7.3 years **FPG (mmol/L):** 9.5 SD3.2	**Age:** 59.8 SD7.6 years **Sex:** 49.5% male **BMI (kg/m^2):** 33.0 SD5.0 **HbA1c (%):** 8.46% SD0.78 **Duration of diabetes:** 13.6 SD6.6 years **FPG (mmol/L):** 10.0 SD3.3	**Age:** 59.3 SD7.9 years **Sex:** 47.4% male **BMI (kg/m^2):** 33.0 SD5.3 **HbA1c (%):** 8.62% SD0.89 **Duration of diabetes:** 13.1 SD7.8 years **FPG (mmol/L):** 10.3 SD3.3	**Age:** 59.3 SD8.8 years **Sex:** 44.8% male **BMI (kg/m^2):** 33.4 SD5.1 **HbA1c (%):** 8.57% SD0.82 **Duration of diabetes:** 14.2 SD7.3 years **FPG (mmol/L):** 9.6 SD3.0

	Systolic BP (mmHg): 136.1 SD17.2		**Systolic BP (mmHg):** 139.6 SD17.7		**Systolic BP (mmHg):** 137.8 SD16.2		**Systolic BP (mmHg):** 140.6 SD16.7	
Outcome (change from baseline to study end)								
	Group 1 (n analysed=193): Placebo + insulin ± OAD		**Group 2 (n=202):** 2.5 mg dapagliflozin + insulin ± OAD		**Group 3 (n=211):** 5 mg dapagliflozin + insulin ± OAD		**Group 4 (n=194):** 10 mg dapagliflozin + insulin ± OAD	
	Mean	**95% CI**	**Mean**	**95% CI**	**Mean**	**95% CI**	**Mean**	**95% CI**
ΔHbA1c (%)	*wk 24:* -0.39 *wk 48:* -0.47	-0.5 to -0.28 [graph] -0.59 to -0.35 [graph]	-0.79 -0.79	-0.89 to -0.69 [graph] -0.9 to -0.68 [graph] P<0.0001 vs placebo	-0.89 -0.96	-0.99 to -0.79 -1.07 to -0.85 p<0.0001 vs placebo	-0.96 -1.01	-1.06 to -0.86 -1.12 to -0.9 p<0.0001 vs placebo
ΔWeight (kg)	*wk 24:* 0.43 *wk 48:* 0.82	0.05 to 0.81 [graph] 0.29 to 1.35 [graph]	-0.92 -0.96	-1.29 to -0.55 -1.48 to -0.44 p<0.0001 vs placebo	-1.0 -1.0	-1.37 to -0.63 -1.52 to -0.48 p<0.0001 vs placebo	-1.61 -1.61	-1.98 to -1.24 -2.14 to -1.08 p<0.0001 vs placebo
ΔFPG (mmol/L)	*wk 24:* NR *wk 48:* NR	-	-0.65 -0.69	-1.19 to -0.11, p NR -1.28 to -0.11, p NR p<0.0001 vs placebo	-1.12 -0.90	-1.66 to -0.59, p NR -1.48 to -0.33, p NR p<0.0001 vs placebo	-1.10 -0.94	-1.64 to -0.56. p NR -1.53 to -0.36, p NR p<0.0001 vs placebo
ΔSBP (mmHg)	*wk 24:* -3.56 *wk 48:* -1.49	-5.47 to -1.64 -3.55 to 0.57	-4.21 -5.70	-6.05 to -2.38, p NR -7.25 to -3.34, p NR	-5.93 -4.33	-7.74 to -4.12, p NR -6.28 to -2.38, p NR	-6.66 -4.09	-8.53 to -4.80, p NR -6.09 to -2.09, p NR
Adverse events **Safety assessment**: adverse events, laboratory values, vital signs								
	Minor hypoglycaemia = symptomatic episode, capillary glucose <3.5mmol/L **Major hypoglycaemia =** symptomatic episode, needing external assistance with following recovery, capillary glucose <3.0mmol/L **Other hypoglycaemia** = suggestive criteria not meeting criteria for major or minor hypoglycaemia				**General events – where frequency is ≥5%** UTI = Urinary Tract Infection GTI = Genital Tract Infection HypoT = Hypotension HypoS = Hypoglycaemia (severe) HypoM = Hypoglycaemia (mild) HypoO = Hypoglycaemia (other)		**At least one or more adverse event** **Group 1 =** n=144 **Group 2 =** n=153 **Group 3 =** n=153 **Group 4 =** n=145 2 deaths in the 5 mg dapagliflozin group	
	Group 1 (n analysed=193): Placebo + insulin ± OAD		**Group 2 (n=202):** 2.5 mg dapagliflozin + insulin ± OAD		**Group 3 (n=211):** 5 mg dapagliflozin + insulin ± OAD		**Group 4 (n=194):** 10 mg dapagliflozin + insulin ± OAD	
Specific events	UTI n=10, GTI n=5 HypoT n=2 HypoS n=2, HypoM n=99, HypoO n=11 Renal impairment / failure n=3 Events leading to discontinuation n=3		UTI n=16, GTI n=13 HypoT n=5 HypoS n=3, HypoM n=118, HypoO n=19 Renal impairment / failure n=2 Events leading to discontinuation n=2		UTI n=23, GTI n=21 HypoT n=5 HypoS n=2, HypoM n=113, HypoO n=24 Renal impairment / failure n=6 Events leading to discontinuation n=5		UTI n=20, GTI n=21 HypoT n=3 HypoS n=3, HypoM n=99, HypoO n=21 Renal impairment / failure n=4 Events leading to discontinuation n=5	
	Nasopharyngitis n=23 Headache n=15 Back pain n=11 Hypertension n=20 Diarrhoea n=8 Constipation n=3Peripheral oedema n=15 Upper resp. tract Infection n=12 Arthralgia n=11		Nasopharyngitis n=32 Headache n=11 Back pain n=11 Hypertension n=18 Diarrhoea n=7 Constipation n=12 Peripheral oedema n=8 Upper resp. tract Infection n=6 Arthralgia n=4		Nasopharyngitis n=35 Headache n=14 Back pain n=8 Hypertension n=16 Diarrhoea n=11 Constipation n=7 Peripheral oedema n=5 Upper resp. tract Infection n=8 Arthralgia n=3		Nasopharyngitis n=25 Headache n=5 Back pain n=11 Hypertension n=11 Diarrhoea n=10 Constipation n=6 Peripheral oedema n=9 Upper resp. tract Infection n=9 Arthralgia n=7	

Canagliflozin

Rosenstock J, Aggarwal N, Polidori D, Zhao Y, Sha S, Arbit D, Usiskin K et al. **Dose-ranging effects of canagliflozin, a sodium-glucose cotransporter 2 inhibitor, as add-on to metformin in subjects with type 2 diabetes.** Diabetes Care 2012; 35(6): 1232-1238[16]	**Funding source:** Janssen Global Services
	SGLT2 Inhibitor (50, 100, 200, or 300 mg OD or 300 mg BD canagliflozin) + metformin versus sitaglipitin + metformin versus placebo + metformin

Aim: to assess the safety, tolerability and efficacy of canagliflozin in patients with type 2 diabetes who have inadequate glycaemic control on metformin monotherapy

Study quality: Medium – see quality table for further information

Study particulars

Multi-centre: 85 (12 countries)
Duration of intervention: 12 weeks
Duration of run in: 4 weeks
Follow-up: 2 weeks post-treatment
Design: 7-arm parallel group RCT, double blind, placebo controlled
Primary outcome: change from baseline in HbA1c to week 12
Secondary outcomes:
- Change in FPG
- Change in weight
- Overnight glucose-to-creatinine ratio
- Change in proportion of participants with HbAc <7.0% and <6.5%
- Loss of beta cell function measured using HOMA2-%B
- Serum lipids
- Adverse events, laboratory assessments, vital signs

Participant criteria

N: 451 analysed
Inclusion criteria: participants with type 2 diabetes for ≥3 months; 18 to 65 years old; HbA1c level ≥7% and ≤10.5%; metformin monotherapy at a stable (≥3 months) dose of ≥1500 mg/day; stable body weight; BMI 25 (24 for Asians) to 45 kg/m^2; serum creatinine <1.5mg/dl for men and <1.4mg/dl for women
Exclusion criteria: not specifically reported

Interventions

Intervention 1: placebo (pla) + metformin
Intervention 2: canagliflozin (cana) 50 mg OD + metformin (met)
Intervention 3: canagliflozin 100 mg OD + metformin
Intervention 4: canagliflozin 200 mg OD + metformin
Intervention 5: canagliflozin 300 mg OD + metformin
Intervention 6: canagliflozin 300 mg BD + metformin
Intervention 7: sitagliptin (sita) 100 mg OD + metformin
OAD schedule: metformin mean dose 1890 SD479 mg/day
Lead in period: pre-treatment screening phase

Participant baseline data

	Group 1 pla + met (n=65)	**Group 2** cana 50 mg OD + met (n=64)	**Group 3** cana 100 mg OD + met (n=64)	**Group 4** cana 200 mg OD + met (n=65)	**Group 5** cana 300 mg OD + met (n=64)	**Group 6** cana 300 mg BD + met (n=64)	**Group 7** sita 100 mg OD + met (n=65)
Age (years)	53.3 SD7.8	53.3 SD8.5	51.7 SD8.0	52.9 SD9.6	52.3 SD6.9	55.2 SD7.1	51.7 SD8.1
Sex (% male)	48%	53%	56%	51%	56%	44%	58%

	BMI (kg/m^2)	30.6 SD4.6	31.7 SD4.6	31.7 SD5.0	31.4 SD5.2	31.6 SD4.9	31.8 SD5.2	31.6 SD5.0
	HbA1c (%)	7.75 SD0.83	8.00 SD0.99	7.83 SD0.96	7.61 SD0.80	7.69 SD1.02	7.73 SD0.89	7.64 SD0.95
	Diab. duration (years)	6.4 SD5.0	5.6 SD5.0	6.1 SD4.7	6.4 SD5.7	5.9 SD5.2	5.8 SD4.6	5.6 SD4.7
	FPG (mmol/L)	9.1 SD2.1	9.4 SD2.5	9.3 SD2.3	8.9 SD2.1	8.8 SD2.4	8.7 SD1.9	8.8 SD2.3
	SBP (mmHg)	125 SD10	127 SD11	127 SD13	124 SD11	126 SD12	128 SD13	129 SD13
Outcome (change from baseline at study end (12 weeks))								
	Group 1 pla + met (n=65)	**Group 2** cana 50 mg OD + met (n=64)	**Group 3** cana 100 mg OD + met (n=64)	**Group 4** cana 200 mg OD + met (n=65)	**Group 5** cana 300 mg OD + met (n=64)	**Group 6** cana 300 mg BD + met (n=64)	**Group 7** sita 100 mg OD + met (n=65)	
ΔHbA1c (%) [SE from graph]	-0.22 SE0.08	-0.79 SE0.1 p<0.001 vs placebo	-0.76 SE0.12 p<0.001 vs placebo	-0.70 SE0.08 p<0.001 vs placebo	-0.92 SE0.08 p<0.001 vs placebo	-0.95 SE0.08 p<0.001 vs placebo	-0.74 SE0.08 p<0.001 vs placebo	
ΔWeight (kg) [SE from graph]	-1.1 SE0.29	-2.3 SE0.39 p<0.001 vs placebo	-2.6 SE0.29 p<0.001 vs placebo	-2.7 SE0.39 p<0.001 vs placebo	-3.4 SE0.39 p<0.001 vs placebo	-3.4 SE0.29 p<0.001 vs placebo	-0.6 SE0.39 NS vs placebo	
ΔFPG (mmol/L) [SE from graph]	+0.2 SE0.20	-0.9 SE0.22 p<0.001 vs placebo	-1.4 SE0.22 p<0.001 vs placebo	-1.5 SE0.20 p<0.001 vs placebo	-1.4 SE0.22 p<0.001 vs placebo	-1.3 SE0.20 p<0.001 vs placebo	-0.7 SE0.20 p NR	
ΔSBP (mmHg)	-1.3 SE1.5	-0.9 SE1.7, p NR	+1.0 SE1.3, p NR	-2.1 SE1.8, p NR	-4.9 SE1.5, p NR	-3.6 SE1.4, p NR	-0.8 SE1.4, p NR	
Adverse events								
Safety assessment: adverse event reports (Medical Dictionary for Regulatory Activities), vital signs, physical examinations, laboratory assessments, self-administered vaginal swabs								
	Minor hypoglycaemia (HypoM) = symptomatic episode, capillary glucose <3.5mmol/l) **Severe hypoglycaemia** (HypoS) = symptomatic episode, needing external assistance with following recovery, capillary glucose <3.0mmol/l) **Other hypoglycaemia** (HypoO) = symptoms, but without measurement confirming		**General events – where frequency is ≥10 participants** UTI = Urinary Tract Infection GTI = Genital Tract Infection Hypo = Hypoglycaemia HypoT = AEs suggestive of hypotension		**At least one or more adverse event** **Group 1 =** n=26 **Group 2 =** n=32 **Group 3 =** n=30 **Group 4 =** n=26 **Group 5 =** n=26 **Group 6 =** n=36 **Group 7 =** n=23			
		Group 1 pla (n=65)	**Group 2** cana 50 mg OD (n=64)	**Group 3** cana 100 mg OD (n=64)	**Group 4** cana 200 mg OD (n=65)	**Group 5** cana 300 mg OD (n=64)	**Group 6** cana 300 mg BD (n=64)	**Group 7** sita 100 mg OD (n=65)
Specific Events	UTI	n=4	n=3	n=2	n=6	n=2	n=3	n=1
	GTI	n=1	n=5	n=4	n=2	n=2	n=4	n=1
	Symptomatic Hypo	n=1	n=0	n=1	n=4	n=0	n=2	n=3
	HyopoT	n=1	n=0	n=4	n=3	n=1	n=1	n=1
	AEs leading to discontinuation	n=2	n=1	n=3	n=1	n=2	n=2	n=0
	Headache	n=2	n=1	n=5	n=2	n=3	n=1	n=1
	Nausea	n=0	n=3	n=1	n=1	n=3	n=5	n=1
	Nasopharyngitis	n=2	n=5	n=0	n=0	n=1	n=1	n=3
	Diarrhoea	n=2	n=1	n=1	n=0	n=2	n=3	n=2
	Pollakiuria	n=1	n=2	n=3	n=1	n=2	n=0	n=2
	Vulvovaginal mycotic infect.	n=0	n=4	n=2	n=4	n=1	n=3	n=1

Abbreviations: AE – adverse event; ALT – alanine transaminase; AST – aspartate transaminase; OD – once daily; BD – twice daily; BMD – bone mineral density; BMI – body mass index; BP – blood pressure; CI – confidence interval; DBP – diastolic blood pressure; FPG – fasting plasma glucose; NR – not reported; GTI – genital tract infection; NS – not significant; OAD – oral antidiabetic drug; SBP – systolic blood pressure; SD – standard deviation, SE – standard error; TZD – thiazolidinedione (pioglitazone or rosiglitazone); UTI – urinary tract infection; vs – versus; WMD – weighted mean difference