National Institute for Health and Care Excellence

1

Draft for consultation

Type 2 diabetes in adults: management (medicines update)

[F2.2] Evidence reviews for subsequent pharmacological management of type 2 diabetes – Appendix D1

NICE guideline GID-NG10336

Evidence reviews underpinning recommendations 1.8.6-1.8.32, 1.8.34,1.8.38-1.8.60 and recommendations for research in the NICE guideline

August 2025

Draft for Consultation

This evidence review was developed by NICE

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Appendices

Appendix D Effectiveness evidence

Note: In the study characteristics tables, if any baseline characteristic is not mentioned in a table, then this is because the value was either not reported by the study or not reported in a way that could be meaningfully extracted by the analyst assigned to review the study and so was not reported in the data extraction. The exception for this are health-related quality of life, HbA1c, weight and BMI values which are reported in appendix S.

1. Abdul-Ghani, 2020

Bibliographic Reference	Abdul-Ghani, M.; Migahid, O.; Megahed, A.; DeFronzo, R.A.; Al-Ozairi, E.; Jayyousi, A.; Combination Therapy with Pioglitazone/Exenatide Improves Beta Cell Function and Produces Superior Glycemic Control Compared to Basal/Bolus Insulin in Poorly Controlled T2DM: 3-Year Follow-up of the Qatar Study; Diabetes, obesity & metabolism; 2020

1.1. Study details

Secondary publication of another included study- see primary study for details	Abdul-Ghani, Muhammad, Migahid, Osama, Megahed, Ayman et al. (2017) Combination Therapy With Exenatide Plus Pioglitazone Versus Basal/Bolus Insulin in Patients With Poorly Controlled Type 2 Diabetes on Sulfonylurea Plus Metformin: The Qatar Study. Diabetes care 40(3): 325-331

2. Abdul-Ghani, 2017

Bibliographic Reference	Abdul-Ghani, Muhammad; Migahid, Osama; Megahed, Ayman; Adams, John; Triplitt, Curtis; DeFronzo, Ralph A; Zirie, Mahmoud; Jayyousi, Amin; Combination Therapy With Exenatide Plus Pioglitazone Versus Basal/Bolus Insulin in Patients With Poorly Controlled Type 2 Diabetes on Sulfonylurea Plus Metformin: The Qatar Study.; Diabetes care; 2017; vol. 40 (no. 3); 325-331

2.1. Study details

Secondary publication of another included study- see primary study for details	No additional information.
Other publications associated with this study included in review	Abdul-Ghani, M., Migahid, O., Megahed, A. et al. (2020) Combination Therapy with Pioglitazone/Exenatide Improves Beta Cell Function and Produces Superior Glycemic Control Compared to Basal/Bolus Insulin in Poorly Controlled T2DM: 3-Year Follow-up of the Qatar Study. Diabetes, obesity & metabolism
Trial name / registration number	Qatar study. Clinicaltrials registry number = NCT02887625
Study type	Randomised controlled trial (RCT)
Study location	Qatar
Study setting	Outpatient follow-up
Study dates	No additional information.
Sources of funding	Supported by a Qatar Foundation grant NPRP 5-273-3-079. One authors salary is paid in part by the South Texas Veterans Health Care System.
Inclusion criteria	Poorly controlled T2DM (HbA1c >7.5%); age 18-75 years; treated with metformin >1500 mg/day and either glimepiride >4mg or gliclazide >60mg; good general health; normal kidney and liver function, serum chemistry results, electrocardiogram results and urinalysis, stable body weight and a negative pregnancy test.
Exclusion criteria	Haematocrit <34%; medications known to affect glucose metabolism other than sulfonylureas and metformin; diabetic proliferative retinopathy; albumin excretion >300 mg/day; major organ system disease.

Recruitment / selection of participants	No additional information.
Intervention(s)	Pioglitazone + exenatide N=123 Weekly exenatide injection (2 mg/week extended-release) and oral pioglitazone (15 mg/day) was added at week 2 and the dose increased to 30 mg/day at week 4. Mean follow up 32.1 (0.9) months.
Cointervention	Concomitant therapy: People previously received a sulfonylurea plus metformin.
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear "Patients were in good general health as determined by medical history and physician examination. Excluded any major organ system disease." Unclear if this would exclude all people with CHF. No other information relating to this in baseline characteristics.
Strata 2: People with atherosclerotic cardiovascular disease	Not stated/unclear "Patients were in good general health as determined by medical history and physician examination. Excluded any major organ system disease." Unclear if this would exclude all people with CVD. No other information relating to this in baseline characteristics.
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	People without chronic kidney disease Inclusion criteria for normal kidney function. No other information relating to this in baseline characteristics.
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	Not stated/unclear
Subgroup 1: People with moderate or severe frailty	Not stated/unclear
Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear

Subgroup 3: People with non-alcoholic fatty liver disease	Not stated/unclear
Subgroup 4: People with obesity	Not stated/unclear
Subgroup 5: eGFR category at baseline	Not stated/unclear
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Population subgroups	No additional information.
Comparator	Insulin N=108 Insulin glargine before breakfast. Mean follow up 32.4 (1.2) months.
Number of participants	231
Duration of follow-up	Up to 3 years.
Indirectness	No additional information.
Method of analysis	ITT
Additional comments	No additional information.

2.2. Study arms

2.2.1. Pioglitazone + exenatide (N = 123)

Weekly exenatide injection (2 mg/week extended-release) and oral pioglitazone (15 mg/day) was added at week 2 and the dose increased to 30 mg/day at week 4. Mean follow up 32.1 (0.9) months. Concomitant therapy: People previously received a sulfonylurea plus metformin.

2.2.2. Insulin (N = 108)

Insulin glargine before breakfast. Mean follow up 32.4 (1.2) months. Concomitant therapy: People previously received a sulfonylurea plus metformin.

2.3. Characteristics

2.3.1. Arm-level characteristics

Characteristic	Pioglitazone + exenatide (N = 123)	Insulin (N = 108)
% Male Sample size	n = 49 ; % = 40	n = 40 ; % = 37
Mean age (SD) (years) Mean (SD)	52 (1)	52 (1)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA
Qataris Sample size	n = NR ; % = 48	n = NR ; % = 39
Non-Qatari Arabs Sample size	n = NR ; % = 26	n = NR ; % = 29
Asian Indians Sample size	n = NR ; % = 17	n = NR ; % = 25
Others Sample size	n = NR ; % = 9	n = NR ; % = 7
Comorbidities Sample size	n = NR ; % = NR	n = NR ; % = NR
Presence of frailty Sample size	n = NR ; % = NR	n = NR ; % = NR
Time since type 2 diabetes diagnosed (Months) Mean (SD)	10.5 (0.5)	10.9 (0.5)
Cardiovascular risk factors Sample size	n = NR ; % = NR	n = NR ; % = NR

Characteristic	Pioglitazone + exenatide (N = 123)	Insulin (N = 108)
Smoking status Sample size	n = NR ; % = NR	n = NR ; % = NR
Alcohol consumption Sample size	n = NR ; % = NR	n = NR ; % = NR
Presence of severe mental illness Sample size	n = NR ; % = NR	n = NR ; % = NR
People with significant cognitive impairment Sample size	n = NR ; % = NR	n = NR ; % = NR
People with a learning disability Sample size	n = NR ; % = NR	n = NR ; % = NR
Number of people with obesity Sample size	n = NR ; % = NR	n = NR ; % = NR
Other antidiabetic medication used Sample size	n = NA ; % = NA	n = NA ; % = NA
Metformin Sample size	n = NR ; % = 100	n = NR ; % = 100
Glipizide Sample size	n = NR ; % = 61	n = NR ; % = 59
Glimipiride Sample size	n = NR ; % = 39	n = NR ; % = 41
Blood pressure-lowering medication used Sample size	n = NR ; % = NR	n = NR ; % = NR
Statins/lipid-lowering medication used Sample size	n = NR ; % = NR	n = NR ; % = NR
Other treatment being received Sample size	n = NR ; % = NR	n = NR ; % = NR

3. Abreu, 2019

Bibliographic Reference	Abreu, M.; Tumyan, A.; Elhassan, A.; Peicher, K.; Papacostea, O.; Dimachkie, P.; Siddiqui, M. S.; Pop, L. M.; Gunasekaran, U.; Meneghini, L. F.; et, al.; A randomized trial comparing the efficacy and safety of treating patients with type 2 diabetes and highly elevated HbA1c levels with basal-bolus insulin or a glucagon-like peptide-1 receptor agonist plus basal-bolus insulin: the SIMPLE study; Diabetes Obes Metab; 2019; vol. 21 (no. 9); 2133-2141

3.1. Study details

Secondary publication of another included study- see primary study for details	No additional information.
Other publications associated with this study included in review	No additional information.
Trial name / registration number	SIMPLE, Clinicaltrials.gov = NCT01966978
Study type	Randomised controlled trial (RCT)
Study location	United States of America.
Study setting	Outpatient follow up.
Study dates	September 2014 to May 2017.
Sources of funding	Funded by a Novo Nordisk Investigator Initiated Study Grant.
Inclusion criteria	Age no more than 18 years; currently receiving medical care at the hospital; had type 2 diabetes with a confirmed HbA1c at least 10% on any treatment except for current use (within the prior 30 days) of prandial insulin (excluding premix insulin), DPP-4 inhibitors or GLP1RAs.
Exclusion criteria	Type 1 diabetes; history of pancreatitis or pancreatic disease; lipase level more than three times above normal; creatinine clearance <30mL/min; decompensated comorbidities.

Recruitment / selection of participants	No additional information.
Intervention(s)	Liraglutide N=59 Liraglutide 0.6 mg/day subcutaneously titrated as tolerated weekly to 1.2 mg/day and finally 1.8 mg/day.
Cointervention	All people received basal insulin (insulin detemir), initially at 0.3 units/kg once daily at night time, self titrated as required to maintain blood glucose of 71 to 100 mg/dL. Metformin was continued or initiated at 500mg twice daily if not contraindicated, then titrated to 1000mg twice daily or the maximum tolerated dose. All other glucose-lowering agents were discontinued.
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear "Excluded decompensated comorbidities." Unclear if this would exclude all people with HF. No other information relating to this in baseline characteristics.
Strata 2: People with atherosclerotic cardiovascular disease	People without atherosclerotic cardiovascular diseases Excluded "decompensated comorbidities" but this was not defined. Baseline characteristics: only 20% had "macrovascular complications".
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear "Excluded decompensated comorbidities." Unclear if this would exclude all people with CKD. No other information relating to this in baseline characteristics.
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	Not stated/unclear
Subgroup 1: People with moderate or severe frailty	Not stated/unclear
Subgroup 2: Onset of type	Not stated/unclear

2 diabetes mellitus	
Subgroup 3: People with non-alcoholic fatty liver disease	Not stated/unclear
Subgroup 4: People with obesity	Not stated/unclear
Subgroup 5: eGFR category at baseline	Not stated/unclear
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Population subgroups	No additional information.
Comparator	Insulin N=61 Basal-bolus insulin (insulin aspart) initiated at 0.3 units/kg/day divided among the number of meals taken daily. Meal time insulin titrated was driven by the person taking it weekly by a prespecified protocol.
Number of participants	120
Duration of follow-up	6 months
Indirectness	No additional information.
Method of analysis	Modified ITT Randomised people who had at least one study follow-up
Additional comments	No additional information.

3.2. Study arms

3.2.1. Liraglutide (N = 59)

Liraglutide 0.6 mg/day subcutaneously titrated as tolerated weekly to 1.2 mg/day and finally 1.8 mg/day. Concomitant therapy: All people received basal insulin (insulin

detemir), initially at 0.3 units/kg once daily at night time, self titrated as required to maintain blood glucose of 71 to 100 mg/dL. Metformin was continued or initiated at 500mg twice daily if not contraindicated, then titrated to 1000mg twice daily or the maximum tolerated dose. All other glucose-lowering agents were discontinued.

3.2.2. Insulin (N = 61)

Basal-bolus insulin (insulin aspart) initiated at 0.3 units/kg/day divided among the number of meals taken daily. Meal time insulin titrated was driven by the person taking it weekly by a prespecified protocol. Concomitant therapy: All people received basal insulin (insulin detemir), initially at 0.3 units/kg once daily at night time, self titrated as required to maintain blood glucose of 71 to 100 mg/dL. Metformin was continued or initiated at 500mg twice daily if not contraindicated, then titrated to 1000mg twice daily or the maximum tolerated dose. All other glucose-lowering agents were discontinued.

3.3. Characteristics

3.3.1. Arm-level characteristics

Characteristic	Liraglutide (N = 59)	Insulin (N = 61)
% Male Sample size	n = 19 ; % = 32	n = 16 ; % = 26
Mean age (SD) (years) Mean (SD)	46.7 (9)	48.1 (10)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA
Hispanic Sample size	n = 27 ; % = 45.8	n = 21 ; % = 34.4
Non-Hispanic white Sample size	n = 12 ; % = 20.3	n = 10 ; % = 16.4
African American Sample size	n = 20 ; % = 33.9	n = 30 ; % = 49.2
Comorbidities Sample size	n = NA ; % = NA	n = NA ; % = NA
Microvascular complications Sample size	n = 38 ; % = 65.5	n = 42 ; % = 72.4

Characteristic	Liraglutide (N = 59)	Insulin (N = 61)
Macrovascular complications Sample size	n = 14 ; % = 23.7	n = 10 ; % = 16.4
Symptomatic hyperglycaemia Sample size	n = 54 ; % = 92	n = 49 ; % = 80
Presence of frailty Sample size	n = NR ; % = NR	n = NR ; % = NR
Time since type 2 diabetes diagnosed (years) Median (IQR)	10 (6 to 15)	10 (4 to 16)
Cardiovascular risk factors Sample size	n = NA ; % = NA	n = NA ; % = NA
History of hypertension Sample size	n = 44 ; % = 74.6	n = 41 ; % = 67.2
Smoking status (Current smokers) Sample size	n = 6 ; % = 10.2	n = 11 ; % = 18
Alcohol consumption Sample size	n = NR ; % = NR	n = NR ; % = NR
Presence of severe mental illness Sample size	n = NR ; % = NR	n = NR ; % = NR
People with significant cognitive impairment Sample size	n = NR ; % = NR	n = NR ; % = NR
People with a learning disability Sample size	n = NR ; % = NR	n = NR ; % = NR
Number of people with obesity Sample size	n = NR ; % = NR	n = NR ; % = NR
Other antidiabetic medication used Sample size	n = NA ; % = NA	n = NA ; % = NA
Metformin at screening Sample size	n = 40 ; % = 67.8	n = 41 ; % = 67.2
Insulin at screening Sample size	n = 44 ; % = 74.6	n = 47 ; % = 77.1

Characteristic	Liraglutide (N = 59)	Insulin (N = 61)
Blood pressure-lowering medication used Sample size	n = NA ; % = NA	n = NA ; % = NA
Statins/lipid-lowering medication used Sample size	n = NA ; % = NA	n = NA ; % = NA
Other treatment being received Sample size	n = NA ; % = NA	n = NA ; % = NA

4. Adel, 2022

Bibliographic Reference	Adel, S. M. H.; Jorfi, F.; Mombeini, H.; Rashidi, H.; Fazeli, S.; Effect of a low dose of empagliflozin on short-term outcomes in type 2 diabetics with acute coronary syndrome after percutaneous coronary intervention; Saudi Med J; 2022; vol. 43 (no. 5); 458-464

4.1. Study details

Secondary publication of another included study- see primary study for details	No additional information.
Other publications associated with this study included in review	No additional information.
Trial name / registration number	No additional information.
Study type	Randomised controlled trial (RCT)
Study location	2 centres in Iran.
Study setting	Initially inpatients, then outpatient follow-up.
Study dates	2020.
Sources of funding	Medication provided free of charge by Abidi Pharmaceutical Company, Iran. Funded by the Vice Chancellor for Research of Ahvaz Jundishapur University, Iran.
Inclusion criteria	Age over 18 years and previous diagnosis of diabetes mellitus (fasting blood sugar at least 126 mg/dL; oral glucose tolerance test at least 200 mg/dL; HbA1c at least 6.5%; classic symptoms of hyperglycaemia with BS at least 200mg/dL) with acute coronary syndrome (STEMI, NSTEMI, unstable angina) requiring a clinical, biochemical and electrocardiographic criteria associated with signs and symptoms of cardiac ischaemia and common electrocardiographic abnormalities.
Exclusion criteria	People with diabetic ketoacidosis; urinary and genital infections; type 1 diabetes; severe liver failure; any malignancy and cancer; eGFR <30mL/min/1.73m2; non-adherence to treatment procedure.

Recruitment / selection of participants	No additional information.
Intervention(s)	Empagliflozin N=52 Empagliflozin 10mg once daily for 6 months.
Cointervention	Concomitant therapy: People received a PCI and then received standard hypoglycaemic treatments (insulin) in addition to the assigned treatment. Insulin was provided during the first 3 days and then is either continued or changed to an oral hypoglycaemic agent according to an endocrinologist in normal care.
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear
Strata 2: People with atherosclerotic cardiovascular disease	People with atherosclerotic cardiovascular diseases Inclusion criteria was acute coronary syndrome
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	People without chronic kidney disease Baseline characteristics report around 7% had CKD.
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	Not stated/unclear
Subgroup 1: People with moderate or severe frailty	Not stated/unclear
Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear

Subgroup 3: People with non-alcoholic fatty liver disease	Not stated/unclear
Subgroup 4: People with obesity	Not stated/unclear
Subgroup 5: eGFR category at baseline	Not stated/unclear
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Population subgroups	No additional information.
Comparator	Placebo N=54 Matching placebo once daily for 6 months.
Number of participants	106
Duration of follow-up	6 months.
Indirectness	No additional information.
Method of analysis	Per protocol Likely per protocol based on the information available
Additional comments	No additional information.

4.2. Study arms

4.2.1. Empagliflozin (N = 52)

Empagliflozin 10mg once daily for 6 months. Concomitant therapy: People received a PCI and then received standard hypoglycaemic treatments (insulin) in addition to the assigned treatment. Insulin was provided during the first 3 days and then is either continued or changed to an oral hypoglycaemic agent according to an endocrinologist in normal care.

4.2.2. Placebo (N = 54)

Matching placebo once daily for 6 months. Concomitant therapy: People received a PCI and then received standard hypoglycaemic treatments (insulin) in addition to the assigned treatment. Insulin was provided during the first 3 days and then is either continued or changed to an oral hypoglycaemic agent according to an endocrinologist in normal care.

4.3. Characteristics

4.3.1. Arm-level characteristics

Characteristic	Empagliflozin (N = 52)	Placebo (N = 54)
% Male Sample size	n = 27 ; % = 60	n = 29 ; % = 60.4
Mean age (SD) (years) Median (IQR)	55 (45.5 to 64)	57 (50 to 66.75)
Ethnicity Sample size	n = NR ; % = NR	n = NR ; % = NR
Comorbidities Sample size	n = NA ; % = NA	n = NA ; % = NA
Chronic kidney disease Sample size	n = 4 ; % = 8.9	n = 3 ; % = 6.3
Hypertension Sample size	n = 26 ; % = 57.8	n = 32 ; % = 66.7
Cerebrovascular accident Sample size	n = 1 ; % = 2.2	n = 2 ; % = 4.2
STEMI Sample size	n = 27 ; % = 60	n = 23 ; % = 50
NSTEMI Sample size	n = 2 ; % = 4.4	n = 4 ; % = 8.3
Unstable angina Sample size	n = 16 ; % = 35.6	n = 21 ; % = 43.8

Characteristic	Empagliflozin (N = 52)	Placebo (N = 54)
Presence of frailty Sample size	n = NR ; % = NR	n = NR ; % = NR
Time since type 2 diabetes diagnosed (years) Median (IQR)	6 (4 to 8)	6 (2 to 9)
Smoking status Sample size	n = 9 ; % = 20	n = 8 ; % = 16.7
Alcohol consumption Sample size	n = NR ; % = NR	n = NR ; % = NR
Presence of severe mental illness Sample size	n = NR ; % = NR	n = NR ; % = NR
People with significant cognitive impairment Sample size	n = NR ; % = NR	n = NR ; % = NR
People with a learning disability Sample size	n = NR ; % = NR	n = NR ; % = NR
Number of people with obesity Sample size	n = NR ; % = NR	n = NR ; % = NR
Other antidiabetic medication used Sample size	n = NR ; % = NR	n = NR ; % = NR
Blood pressure-lowering medication used Sample size	n = NR ; % = NR	n = NR ; % = NR
Statins/lipid-lowering medication used Sample size	n = NR ; % = NR	n = NR ; % = NR
Other treatment being received Sample size	n = NR ; % = NR	n = NR ; % = NR

5. Ahmadi, 2019

Bibliographic Reference	Ahmadi, S S; Filipsson, K; Dimenas, H; Isaksson, S S; Imberg, H; Sjoberg, S; Ahren, B; Dahlqvist, S; Gustafsson, T; Tuomilehto, J; Hirsch, I B; Lind, M; Effect of liraglutide on anthropometric measurements, sagittal abdominal diameter and adiponectin levels in people with type 2 diabetes treated with multiple daily insulin injections: evaluations from a randomized trial (MDI-liraglutide study 5).; Obesity science & practice; 2019; vol. 5 (no. 2); 130-140

5.1. Study details

Secondary publication of another included study- see primary study for details	Parent paper Lind 2015 (population strata details given there)
Other publications associated with this study included in review	The parent study (Lind 2015) associated with this paper: Liraglutide in people treated for type 2 diabetes with multiple daily insulin injections: randomised clinical trial (MDI Liraglutide trial) BMJ; 2015; vol. 351; h5364
Trial name / registration number	MDI-liraglutide/EudraCT 2012-001941-42

5.2. Study arms

5.2.1. Liraglutide 0.6 mg - 1.8 mg daily (N = 64)

Administered subcutaneously at the same time each day

5.2.2. Placebo (N = 60)

Administered subcutaneously at the same time each day

6. Ahmann, 2015

Bibliographic Reference	Ahmann, A.; Rodbard, H. W.; Rosenstock, J.; Lahtela, J. T.; Loredo, L.; Tornoe, K.; Boopalan, A.; Nauck, M. A.; Efficacy and safety of liraglutide versus placebo added to basal insulin analogues (with or without metformin) in patients with type 2 diabetes: A randomized, placebo-controlled trial; Diab Obes Metab; 2015; vol. 17 (no. 11); 1056-64

6.1. Study details

Secondary publication of another included study- see primary study for details	No additional information.
Other publications associated with this study included in review	No additional information.
Trial name / registration number	NCT01617434.
Study type	Randomised controlled trial (RCT)
Study location	Multicentre trial - Argentina, Canada, Finland, Germany, India, Mexico, the Netherlands, Serbia and the United States of America.
Study setting	Outpatient follow-up.
Study dates	10th September 2012-22nd October 2013.
Sources of funding	Funded by Novo Nordisk.
Inclusion criteria	Men and women aged 18-80 years; inadequately controlled type 2 diabetes (HbA1c 7-10%); BMI 20-45 kg/m2; treated with stable doses of basal insulin analogue (glargine or detemir at least 20 units/day) +/- metformin (at least 1500mg/day) for at least 8 weeks before enrolment.
Exclusion criteria	Known or suspected hypersensitivity to trial products; previous participation in the trial; female of child-bearing potential who were pregnant, breast feeding or intending to become pregnant or not using adequate contraception; participation in another trial; episodes of hypoglycaemic unawareness judged by the investigator and/or recurrent severe hypoglycaemic episodes (at least 1 in the last 90 days); impaired

	liver function; impaired renal function; chronic pancreatitis; severe cardiovascular event in the past 6 months; NYHA class IV heart failure; uncontrolled treated or untreated hypertension; any history of cancer in the last 5 years; use of any drug that could interfere with glucose levels; alcohol or narcotic abuse; proliferative retinopathy or maculopathy; surgery scheduled during the trial; mental incapacity, unwillingness or language barrier precluding adequate understanding or cooperation; unwillingness to self monitor; screening calcitonin at least 50 ng/L; any contraindications to the drugs.
Recruitment / selection of participants	No additional information.
Intervention(s)	Liraglutide N=225 Liraglutide 0.6mg/day increased weekly up to 1.8mg/day for a total treatment of 26 weeks (with 1 additional week of follow-up and 2 weeks of screening).
Cointervention	Concomitant therapy: Treatment was added to people's stable pre-study basal insulin analogue regimen with or without metformin (which had to be stable for at least 8 weeks before the study).
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear No information given in inclusion/exclusion or baseline characteristics
Strata 2: People with atherosclerotic cardiovascular disease	Not stated/unclear No information given in inclusion/exclusion or baseline characteristics
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear No information given in inclusion/exclusion or baseline characteristics
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	Not stated/unclear

Subgroup 1: People with moderate or severe frailty	Not stated/unclear
Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear
Subgroup 3: People with non-alcoholic fatty liver disease	Not stated/unclear
Subgroup 4: People with obesity	Mixed population
Subgroup 5: eGFR category at baseline	Not stated/unclear
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Population subgroups	No additional information.
Comparator	Placebo N=225 Equivalent dose of placebo for 26 weeks (with 1 additional week of follow-up and 2 weeks of screening).
Number of participants	450
Duration of follow-up	26 weeks
Indirectness	No additional information.
Method of analysis	ACA Full analysis set - all randomised subjects who received at least 1 dose of the trial product and who provided at least one baseline and one post-baseline efficacy value.
Additional comments	No additional information.

6.2. Study arms

6.2.1. Liraglutide (N = 225)

Liraglutide 0.6mg/day increased weekly up to 1.8mg/day for a total treatment of 26 weeks (with 1 additional week of follow-up and 2 weeks of screening). Concomitant therapy: Treatment was added to people's stable pre-study basal insulin analogue regimen with or without metformin (which had to be stable for at least 8 weeks before the study).

6.2.2. Placebo (N = 225)

Equivalent dose of placebo for 26 weeks (with 1 additional week of follow-up and 2 weeks of screening). Concomitant therapy: Treatment was added to people's stable pre-study basal insulin analogue regimen with or without metformin (which had to be stable for at least 8 weeks before the study).

6.3. Characteristics

6.3.1. Arm-level characteristics

Characteristic	Liraglutide (N = 225)	Placebo (N = 225)
% Male Sample size	n = NA ; % = 53.3	n = NA ; % = 60.4
Mean age (SD) (years) Mean (SD)	59.3 (9.2)	57.5 (11.1)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA
Comorbidities Sample size	n = NA ; % = NA	n = NA ; % = NA
Presence of frailty Sample size	n = NA ; % = NA	n = NA ; % = NA
Time since type 2 diabetes diagnosed (years) Mean (SD)	12.1 (7.1)	12.1 (6.8)
Cardiovascular risk factors Sample size	n = NR ; % = NR	n = NR ; % = NR

Characteristic	Liraglutide (N = 225)	Placebo (N = 225)
Smoking status Sample size	n = NR ; % = NR	n = NR ; % = NR
Alcohol consumption Sample size	n = NR ; % = NR	n = NR ; % = NR
Presence of severe mental illness Sample size	n = NR ; % = NR	n = NR ; % = NR
People with significant cognitive impairment Sample size	n = NR ; % = NR	n = NR ; % = NR
People with a learning disability Sample size	n = NR ; % = NR	n = NR ; % = NR
Number of people with obesity Sample size	n = NR ; % = NR	n = NR ; % = NR
Other antidiabetic medication used Sample size	n = NA ; % = NA	n = NA ; % = NA
Metformin Sample size	n = NR ; % = 92	n = NR ; % = 93.3
Insulin detemir Sample size	n = NR ; % = 33.3	n = NR ; % = 32
Insulin glargine Sample size	n = NR ; % = 66.7	n = NR ; % = 68
Blood pressure-lowering medication used Sample size	n = NR ; % = NR	n = NR ; % = NR
Statins/lipid-lowering medication used Sample size	n = NR ; % = NR	n = NR ; % = NR
Other treatment being received Sample size	n = NR ; % = NR	n = NR ; % = NR

7. Ahmann, 2018

Bibliographic Reference	Ahmann, Andrew J; Capehorn, Matthew; Charpentier, Guillaume; Dotta, Francesco; Henkel, Elena; Lingvay, Ildiko; Holst, Anders G; Annett, Miriam P; Aroda, Vanita R; Efficacy and Safety of Once-Weekly Semaglutide Versus Exenatide ER in Subjects With Type 2 Diabetes (SUSTAIN 3): A 56-Week, Open-Label, Randomized Clinical Trial.; Diabetes care; 2018; vol. 41 (no. 2); 258-266

7.1. Study details

Secondary publication of another included study- see primary study for details	No additional information.
Other publications associated with this study included in review	No additional information.
Trial name / registration number	SUSTAIN 3. Clinicaltrials.gov = NCT01885208.
Study type	Randomised controlled trial (RCT)
Study location	Multicentre - 12 countries in Europe, South America and the United States of America.
Study setting	Outpatient follow up.
Study dates	December 2013 to July 2015.
Sources of funding	Funded by Novo Nordisk A/S.
Inclusion criteria	Age at least 18 years; diagnosed with type 2 diabetes (HbA1c 7.0-10.5%); receiving stable treatment with one or two oral antidiabetic drugs (metformin at least 1500 mg or the maximum tolerated dose, and/or thiazolidinediones and/or sulfonylureas [at least half the maximum dose allowed]) for at least 90 days before screening.
Exclusion criteria	eGFR <60mL/min/1.73 m2; chronic treatment with glucose-lowering agents, other than those specified by the inclusion criteria within 90 days of screening; history of chronic or idiopathic acute pancreatitis; an acute

	coronary or cerebrovascular event within 90 days before randomisation; NYHA class IV heart failure.
Recruitment / selection of participants	No additional information.
Intervention(s)	Semaglutide N=406 Semaglutide 1.0mg subcutaneous once weekly for 56 weeks.
Cointervention	If unacceptable hyperglycaemia, people could receive additional treatment (excluding GLP-1 RAs, DPP-4 inhibitors and pramlintide). Background metformin and/or thiazolidinedione treatments were continued. Sulfonylureas could be titrated down if a person experienced unacceptable hypoglycaemia.
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear Only excluded New York Heart Association class IV heart failure. No other information in baseline characteristics.
Strata 2: People with atherosclerotic cardiovascular disease	Not stated/unclear Only excluded an acute coronary or cerebrovascular event within 90 days before randomization. No other information on CVD in baseline characteristics.
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear Excluded estimated glomerular filtration rate <60 mL/min/1.73 m2 per the MDRD formula, but didn't specify CKD. No other information on CKD diagnosis in baseline characteristics.
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	Not stated/unclear
Subgroup 1: People with moderate or severe frailty	Not stated/unclear
Subgroup 2: Onset of type	Not stated/unclear

2 diabetes mellitus	
Subgroup 3: People with non-alcoholic fatty liver disease	Not stated/unclear
Subgroup 4: People with obesity	Mixed population
Subgroup 5: eGFR category at baseline	eGFR ≥30mL/min/1.73m2
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Population subgroups	No additional information.
Comparator	Exenatide N=407 Exenatide extended release 2.0mg subcutaneous once weekly for 56 weeks.
Number of participants	813
Duration of follow-up	56 weeks
Indirectness	No additional information.
Method of analysis	ACA Full analysis set - people who received at least one dose of the medication and had at least one follow up value
Additional comments	No additional information

7.2. Study arms

7.2.1. Semaglutide (N = 406)

Semaglutide 1.0mg subcutaneous once weekly for 56 weeks. Concomitant therapy: If unacceptable hyperglycaemia, people could receive additional treatment (excluding

GLP-1 RAs, DPP-4 inhibitors and pramlintide). Background metformin and/or thiazolidinedione treatments were continued. Sulfonylureas could be titrated down if a person experienced unacceptable hypoglycaemia.

7.2.2. Exenatide (N = 407)

Exenatide extended release 2.0mg subcutaneous once weekly for 56 weeks. Concomitant therapy: If unacceptable hyperglycaemia, people could receive additional treatment (excluding GLP-1 RAs, DPP-4 inhibitors and pramlintide). Background metformin and/or thiazolidinedione treatments were continued. Sulfonylureas could be titrated down if a person experienced unacceptable hypoglycaemia.

7.3. Characteristics

7.3.1. Arm-level characteristics

Characteristic	Semaglutide (N = 406)	Exenatide (N = 407)
% Male Sample size	n = 219 ; % = 54.2	n = 228 ; % = 56.3
Mean age (SD) (years) Range	20 to 82	21 to 83
Mean age (SD) (years) Mean (SD)	56.4 (NR)	56.7 (NR)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA
White Sample size	n = 341 ; % = 84.4	n = 338 ; % = 83.5
Black or African American Sample size	n = 28 ; % = 6.9	n = 30 ; % = 7.4
Asian Sample size	n = 8 ; % = 2	n = 6 ; % = 1.5
Other Sample size	n = 27 ; % = 6.6	n = 31 ; % = 7.6

Characteristic	Semaglutide (N = 406)	Exenatide (N = 407)
Hispanic or Latino Sample size	n = 91 ; % = 22.5	n = 106 ; % = 26.2
Not hispanic or latino Sample size	n = 313 ; % = 77.5	n = 299 ; % = 73.8
Comorbidities Sample size	n = NR ; % = NR	n = NR ; % = NR
Presence of frailty Sample size	n = NR ; % = NR	n = NR ; % = NR
Time since type 2 diabetes diagnosed (years) Range	0.4 to 37.1	0.3 to 54
Time since type 2 diabetes diagnosed (years) Mean (SD)	9 (NR)	9.4 (NR)
Cardiovascular risk factors Sample size	n = NR ; % = NR	n = NR ; % = NR
Smoking status Sample size	n = NR ; % = NR	n = NR ; % = NR
Alcohol consumption Sample size	n = NR ; % = NR	n = NR ; % = NR
Presence of severe mental illness Sample size	n = NR ; % = NR	n = NR ; % = NR
People with significant cognitive impairment Sample size	n = NR ; % = NR	n = NR ; % = NR
People with a learning disability Sample size	n = NR ; % = NR	n = NR ; % = NR
Number of people with obesity Sample size	n = NR ; % = NR	n = NR ; % = NR
Other antidiabetic medication used Sample size	n = NA ; % = NA	n = NA ; % = NA

Characteristic	Semaglutide (N = 406)	Exenatide (N = 407)
Biguanides at screening Sample size	n = 391 ; % = 96.8	n = 390 ; % = 96.3
Sulfonylureas at screening Sample size	n = 181 ; % = 44.8	n = 208 ; % = 51.4
Thiazolidinediones at screening Sample size	n = 13 ; % = 3.2	n = 6 ; % = 1.5
Other blood glucose-lowering drugs (except insulin) at screening Sample size	n = 1 ; % = 0.2	n = 2 ; % = 0.5
Long-acting insulins and analogs for injection at screening Sample size	n = 0 ; % = 0	n = 1 ; % = 0.2
Blood pressure-lowering medication used Sample size	n = NR ; % = NR	n = NR ; % = NR
Statins/lipid-lowering medication used Sample size	n = NR ; % = NR	n = NR ; % = NR
Other treatment being received Sample size	n = NR ; % = NR	n = NR ; % = NR

8. Ahrén, 2004

Bibliographic Reference	Ahrén, B.; Gomis, R.; Standl, E.; Mills, D.; Schweizer, A.; Twelve- and 52-week efficacy of the dipeptidyl peptidase IV inhibitor LAF237 in metformin-treated patients with type 2 diabetes; Diabetes Care; 2004; vol. 27 (no. 12); 2874-80

8.1. Study details

Secondary publication of another included study- see primary study for details	No additional information.
Other publications associated with this study included in review	Ahren, Bo, Pacini, Giovanni, Foley, James E et al. (2005) Improved meal-related beta-cell function and insulin sensitivity by the dipeptidyl peptidase-IV inhibitor vildagliptin in metformin-treated patients with type 2 diabetes over 1 year. Diabetes care 28(8): 1936-40
Trial name / registration number	No additional information.
Study type	Randomised controlled trial (RCT)
Study location	Multicentre.
Study setting	Outpatient follow-up.
Study dates	No additional information.
Sources of funding	Support from the Swedish Research Council.
Inclusion criteria	Male and infertile female patients aged at least 30 years diagnosed with type 2 diabetes at least 6 months before enrolment and treated with a stable dosage of metformin for at least 3 months.
Exclusion criteria	History of type 1 or secondary forms of diabetes; significant diabetes complications; clinically significant cardiovascular abnormalities; liver disease; acromegaly; asthma; major skin allergies; major gastrointestinal surgery; people with fasting triglyceride levels >5.1 mmol/L or fasting plasma glucose <6.1 or at least 13.3 mmol/L; those treated with any drugs considered possibly able to affect results or their interpretation.

Recruitment / selection of participants	No additional information.
Intervention(s)	Vildagliptin N=56 Vildagliptin (LAF237) 50mg once daily added to metformin 1500-3000 mg/day initially for 12 weeks, then followed for an additional 40 weeks (in 42 people).
Cointervention	No additional information.
Strata 1: People with type 2 diabetes mellitus and heart failure	People without heart failure Excluded "clinically significant cardiovascular abnormalities"
Strata 2: People with atherosclerotic cardiovascular disease	People without atherosclerotic cardiovascular diseases Excluded "clinically significant cardiovascular abnormalities"
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear No information in inclusion/exclusion criteria or baseline characteristics
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	Not stated/unclear
Subgroup 1: People with moderate or severe frailty	Not stated/unclear
Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear

Subgroup 3: People with non-alcoholic fatty liver disease	Not stated/unclear
Subgroup 4: People with obesity	Not stated/unclear
Subgroup 5: eGFR category at baseline	Not stated/unclear
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Population subgroups	No additional information.
Comparator	Placebo N=51 Placebo once daily added to metformin 1500-3000 mg/day initially for 12 weeks, then followed for an additional 40 weeks (in 29 people).
Number of participants	107
Duration of follow-up	52 weeks in total.
Indirectness	No additional information.
Method of analysis	ITT
Additional comments	No additional information.

8.2. Study arms

8.2.1. Vildagliptin (N = 56)

Vildagliptin (LAF237) 50mg once daily added to metformin 1500-3000 mg/day initially for 12 weeks, then followed for an additional 40 weeks (in 42 people). Concomitant therapy: No additional information.

8.2.2. Placebo (N = 51)

Placebo once daily added to metformin 1500-3000 mg/day initially for 12 weeks, then followed for an additional 40 weeks (in 29 people). Concomitant therapy: No additional information.

8.3. Characteristics

8.3.1. Arm-level characteristics

Characteristic	Vildagliptin (N = 56)	Placebo (N = 51)
% Male Sample size	n = 39 ; % = 69.6	n = 34 ; % = 66.7
Mean age (SD) (years) Mean (SD)	57.9 (10)	55.7 (11)
Ethnicity Sample size	n = NR ; % = NR	n = NR ; % = NR
Comorbidities Sample size	n = NR ; % = NR	n = NR ; % = NR
Presence of frailty Sample size	n = NR ; % = NR	n = NR ; % = NR
Time since type 2 diabetes diagnosed (years) Mean (SD)	5.6 (4.2)	5.5 (3.7)
Cardiovascular risk factors Sample size	n = NR ; % = NR	n = NR ; % = NR
Smoking status Sample size	n = NR ; % = NR	n = NR ; % = NR
Alcohol consumption Sample size	n = NR ; % = NR	n = NR ; % = NR
Presence of severe mental illness Sample size	n = NR ; % = NR	n = NR ; % = NR
People with significant cognitive impairment Sample size	n = NR ; % = NR	n = NR ; % = NR
People with a learning disability	n = NR ; % = NR	n = NR ; % = NR

Characteristic	Vildagliptin (N = 56)	Placebo (N = 51)
Sample size		
Number of people with obesity Sample size	n = NR ; % = NR	n = NR ; % = NR
Other antidiabetic medication used Sample size	n = NR ; % = NR	n = NR ; % = NR
Blood pressure-lowering medication used Sample size	n = NR ; % = NR	n = NR ; % = NR
Statins/lipid-lowering medication used Sample size	n = NR ; % = NR	n = NR ; % = NR
Other treatment being received Sample size	n = NR ; % = NR	n = NR ; % = NR

9. Ahren, 2014

Bibliographic Reference	Ahren, B.; Johnson, S. L.; Stewart, M.; Cirkel, D. T.; Yang, F.; Perry, C.; Feinglos, M. N.; HARMONY 3: 104-week randomized, double-blind, placebo- and active-controlled trial assessing the efficacy and safety of albiglutide compared with placebo, sitagliptin, and glimepiride in patients with type 2 diabetes taking metformin; Diabetes Care; 2014; vol. 37 (no. 8); 2141-8

9.1. Study details

Secondary publication of another included study- see primary study for details	No additional information.
Other publications associated with this study included in review	No additional information.
Trial name / registration number	HARMONY. Clinicaltrial.gov = NCT00838903.
Study type	Randomised controlled trial (RCT)
Study location	Multicentre in 10 countries
Study setting	Outpatient follow-up
Study dates	17 February 2009 to 21 March 2013.
Sources of funding	Funded by GlaxoSmithKline.
Inclusion criteria	At least 18 years of age; type 2 diabetes; experiencing inadequate glycaemic control while taking background metformin (at least 1500 mg or maximum tolerated dose) at least 3 months before screening; baseline HbA1c of 7-10%; BMI 20-45 kg/m2; creatinine clearance >60mL/min; normal TSH or were clinically euthyroid.
Exclusion criteria	Current ongoing symptomatic biliary disease or history of pancreatitis; recent clinically significant cardiovascular and/or cerebrovascular disease (no more than 2 months before screening); treated gastroparesis; history of gastrointestinal surgery thought to significantly affect upper GI function;

	history of most cancers not in remission for at least 3 years; personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia type 2; resting systolic blood pressure >160 mmHg and/or diastolic blood pressure >100 mmHg; lipase above the upper limit of normal; haemoglobinopathy that could affect HbA1c; ALT or AST more than 2.5 times the upper limit of normal.
Recruitment / selection of participants	No additional information.
Intervention(s)	Albiglutide N=302 Albiglutide 30mg injection once a week increased up to 50 mg once a week if they exceeded an HbA1c threshold of 7.5% between week 12 and 143 (there was no titration from week 143 to week 156). Note: Albiglutide is not licensed for use in the United Kingdom so is not included in the analysis. Sitagliptin N=302 Sitagliptin 100mg orally once a day for 156 weeks. Glimepiride N=307 Glimepiride 2mg orally once a day increased up to 4 mg once a week if they exceeded an HbA1c threshold of 7.5% between week 12 and 143 (there was no titration from week 143 to week 156).
Cointervention	All people received background treatment with metformin.
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear Not an inclusion/exclusion criteria and no information in baseline characteristics.
Strata 2: People with atherosclerotic cardiovascular disease	Not stated/unclear Excluded recent clinically significant cardiovascular and/or cerebrovascular disease (≤2 months before screening), but unclear CVD prior to that. Stratification was by history of MI, so this wasn't excluded. No information in baseline characteristics.
Strata 3: People with type 2 diabetes mellitus and	Not stated/unclear Only included people with creatinine clearance >60 mL/min, but CKD diagnosis not specified in inclusion/exclusion. No information in baseline characteristics.

chronic kidney disease	
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	Not stated/unclear
Subgroup 1: People with moderate or severe frailty	Not stated/unclear
Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear
Subgroup 3: People with non-alcoholic fatty liver disease	Not stated/unclear
Subgroup 4: People with obesity	Not stated/unclear
Subgroup 5: eGFR category at baseline	Not stated/unclear
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Population subgroups	No additional information.
Comparator	Placebo N=101 Placebo injection once a week for 156 weeks.
Number of participants	1049
Duration of follow-up	24 months

Indirectness	No additional information.
Method of analysis	ITT
Additional comments	No additional information.

9.2. Study arms

9.2.1. Albiglutide (N = 302)

Albiglutide 30mg injection once a week increased up to 50 mg once a week if they exceeded an HbA1c threshold of 7.5% between week 12 and 143 (there was no titration from week 143 to week 156). Note: Albiglutide is not licensed for use in the United Kingdom so is not included in the analysis. Concomitant therapy: All people received background treatment with metformin.

9.2.2. Sitagliptin (N = 302)

Sitagliptin 100mg orally once a day for 156 weeks. Concomitant therapy: All people received background treatment with metformin.

9.2.3. Glimepiride (N = 307)

Glimepiride 2mg orally once a day increased up to 4 mg once a week if they exceeded an HbA1c threshold of 7.5% between week 12 and 143 (there was no titration from week 143 to week 156). Concomitant therapy: All people received background treatment with metformin.

9.2.4. Placebo (N = 101)

Placebo injection once a week for 156 weeks. Concomitant therapy: All people received background treatment with metformin.

9.3. Characteristics

9.3.1. Arm-level characteristics

Characteristic	Albiglutide (N = 302)	Sitagliptin (N = 302)	Glimepiride (N = 307)	Placebo (N = 101)
% Male Sample size	n = 135 ; % = 44.7	n = 139 ; % = 46	n = 158 ; % = 51.5	n = 50 ; % = 49.5
Mean age (SD) (years) Mean (SD)	54.3 (10.1)	54.3 (9.8)	54.4 (10)	56.1 (10)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
African American/African Sample size	n = 53 ; % = 17.5	n = 35 ; % = 11.6	n = 39 ; % = 12.7	n = 23 ; % = 22.8
White/Caucasian/European heritage Sample size	n = 214 ; % = 70.9	n = 225 ; % = 74.5	n = 220 ; % = 71.7	n = 64 ; % = 63.4
Asian Sample size	n = 18 ; % = 6	n = 20 ; % = 6.6	n = 16 ; % = 5.2	n = 5 ; % = 5
Hispanic/Latino Sample size	n = 99 ; % = 32.8	n = 111 ; % = 36.8	n = 107 ; % = 34.9	n = 32 ; % = 31.7
Comorbidities Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Presence of frailty Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Time since type 2 diabetes diagnosed (years) Mean (SD)	6 (4.3)	5.8 (4.8)	6 (4.8)	6.7 (6.6)
Cardiovascular risk factors Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Smoking status Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Alcohol consumption Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR

Characteristic	Albiglutide (N = 302)	Sitagliptin (N = 302)	Glimepiride (N = 307)	Placebo (N = 101)
Presence of severe mental illness Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
People with significant cognitive impairment Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
People with a learning disability Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Number of people with obesity Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Other antidiabetic medication used Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Blood pressure-lowering medication used Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Statins/lipid-lowering medication used Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Other treatment being received Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR

10. Ahrén, 2013

Bibliographic Reference	Ahrén, B.; Leguizamo Dimas, A.; Miossec, P.; Saubadu, S.; Aronson, R.; Efficacy and safety of lixisenatide once-daily morning or evening injections in type 2 diabetes inadequately controlled on metformin (GetGoal-M); Diabetes Care; 2013; vol. 36 (no. 9); 2543-50

10.1. Study details

Secondary publication of another included study- see primary study for details	No additional information.
Other publications associated with this study included in review	No additional information.
Trial name / registration number	NCT00712673.
Study type	Randomised controlled trial (RCT)
Study location	Multicentre trial - Australia, Canada, Chile, Czech Republic, Germany, Croatia, Mexico, Morocco, the Philippines, Romania, Russian Federation, South Africa, Spain, Ukraine, United States of America and Venezuela.
Study setting	Outpatient follow-up.
Study dates	No additional information.
Sources of funding	Funded by Sanofi.
Inclusion criteria	People with type 2 diabetes inadequately controlled on metformin with a dose of at least 1.5 grams/day for at least 3 months (HbA1c 7-10%).
Exclusion criteria	Use of oral or injectable glucose-lowering agents other than metformin within 3 months prior to the time of screening; fasting plasma glucose at screening >13.9mmol/L; history of unexplained pancreatitis, chronic pancreatitis, pancreatectomy, stomach/gastric surgery, or inflammatory bowel disease; history of metabolic acidosis, including diabetic ketoacidosis, within 1 year prior to screening; previous allergic reaction to

	any GLP-1 agonist; clinically relevant history of gastrointestinal disease, with prolonged nausea and vomiting during the previous 6 months.
Recruitment / selection of participants	No additional information.
Intervention(s)	Lixisenatide AM N=255 Lixisenatide 20 micrograms once daily subcutaneously in the morning for 24 weeks. Lixisenatide PM N=255 Lixisenatide 20 micrograms once daily subcutaneously in the evening for 24 weeks.
Cointervention	Metformin of a dose of at least 1.5 grams/day.
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear Not an inclusion/exclusion criteria and no information in baseline characteristics.
Strata 2: People with atherosclerotic cardiovascular disease	Not stated/unclear Not an inclusion/exclusion criteria and no information in baseline characteristics.
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear Not an inclusion/exclusion criteria and no information in baseline characteristics.
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	Not stated/unclear
Subgroup 1: People with	Not stated/unclear

moderate or severe frailty	
Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear
Subgroup 3: People with non-alcoholic fatty liver disease	Not stated/unclear
Subgroup 4: People with obesity	Not stated/unclear
Subgroup 5: eGFR category at baseline	Not stated/unclear
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Population subgroups	No additional information.
Comparator	Placebo AM N=85 Placebo once daily subcutaneously in the morning for 24 weeks. Placebo PM N=85 Placebo once daily subcutaneously in the evening for 24 weeks.
Number of participants	680
Duration of follow-up	24 weeks
Indirectness	No additional information
Method of analysis	Modified ITT
Additional comments	No additional information

10.2. Study arms

10.2.1. Lixisenatide AM (N = 255)

Lixisenatide 20 micrograms once daily subcutaneously in the morning for 24 weeks. Concomitant therapy: Metformin of a dose of at least 1.5 grams/day.

10.2.2. Lixisenatide PM (N = 255)

Lixisenatide 20 micrograms once daily subcutaneously in the evening for 24 weeks. Concomitant therapy: Metformin of a dose of at least 1.5 grams/day.

10.2.3. Placebo AM and PM (N = 170)

Placebo once daily subcutaneously in the morning (n=85) and the evening (n=85) for 24 weeks. Concomitant therapy: Metformin of a dose of at least 1.5 grams/day.

10.3. Characteristics

10.3.1. Arm-level characteristics

Characteristic	Lixisenatide AM (N = 255)	Lixisenatide PM (N = 255)	Placebo AM and PM (N = 170)
% Male Sample size	n = NR ; % = 38.4	n = NR ; % = 44.7	n = NR ; % = 47.6
Mean age (SD) (years) Mean (SD)	54.5 (9.2)	54.8 (10.4)	55 (9.4)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
Caucasian Sample size	n = NR ; % = 86.7	n = NR ; % = 89.4	n = NR ; % = 91.2
Black Sample size	n = NR ; % = 2.7	n = NR ; % = 2.4	n = NR ; % = 2.4
Asian Sample size	n = NR ; % = 8.6	n = NR ; % = 7.8	n = NR ; % = 6.5

Characteristic	Lixisenatide AM (N = 255)	Lixisenatide PM (N = 255)	Placebo AM and PM (N = 170)
Other Sample size	n = NR ; % = 2	n = NR ; % = 0.4	n = NR ; % = 0
Comorbidities Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Presence of frailty Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Time since type 2 diabetes diagnosed (years) Mean (SD)	6.2 (5.3)	6.2 (5.4)	5.9 (4.7)
Cardiovascular risk factors Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Smoking status Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Alcohol consumption Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Presence of severe mental illness Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
People with significant cognitive impairment Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
People with a learning disability Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Number of people with obesity Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Other antidiabetic medication used Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Blood pressure-lowering medication used	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR

Characteristic	Lixisenatide AM (N = 255)	Lixisenatide PM (N = 255)	Placebo AM and PM (N = 170)
Sample size			
Statins/lipid-lowering medication used Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Other treatment being received Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR

11. Ahrén, 2017

Bibliographic Reference	Ahrén, B.; Masmiquel, L.; Kumar, H.; Sargin, M.; Karsbol, J. D.; Jacobsen, S. H.; Chow, F.; Efficacy and safety of once-weekly semaglutide versus once-daily sitagliptin as an add-on to metformin, thiazolidinediones, or both, in patients with type 2 diabetes (SUSTAIN 2): A 56-week, double-blind, phase 3a, randomised trial; Lancet Diabetes Endocrinol; 2017; vol. 5 (no. 5); 341-354

11.1. Study details

Secondary publication of another included study- see primary study for details	No additional information.
Other publications associated with this study included in review	No additional information.
Trial name / registration number	SUSTAIN 2. Clinicaltrials.gov = NCT01930188.
Study type	Randomised controlled trial (RCT)
Study location	Multicentre trial - Bulgaria, Czech Republic, Hungary, Norway, Portugal, Romania, Spain, Sweden, Turkey, Ukraine, Argentina, Hong Kong, India, Japan, Mexico, Russia, South Africa and Thailand.
Study setting	Outpatient follow up.
Study dates	December 2nd 2013 to August 5th 2014.
Sources of funding	Novo Nordisk A/S.
Inclusion criteria	Aged 18 years or older (or aged 20 years or older in Japan) and diagnosed with type 2 diabetes, with insufficient glycaemic control (HbA1c 7.0-10.5%) for a period of 90 days before screening while on a stable treatment with either metformin, pioglitazone, rosiglitazone or a combination of metformin and pioglitazone or metformin and rosiglitazone. For people unable to tolerate these doses, a maximum tolerated dose was used.

Exclusion criteria	Treatment with glucose-lowering drugs other than those defined in the eligibility criteria in the 90 days before screening (except insulin treatment for up to 7 days); history of chronic or idiopathic acute pancreatitis; screening calcitonin value of 50 ng/L or greater; personal or family history of medullar thyroid carcinoma or multiple endocrine neoplasia syndrome type 2; impaired renal function (eGFR <60mL/min/1.73 m2); an acute coronary or cerebrovascular event within 90 days before randomisation or heart failure at any time (NYHA class IV); a BMI of less than 18 mg/kg2.
Recruitment / selection of participants	No additional information.
Intervention(s)	Semaglutide 0.5 mg N=410 Semaglutide 0.5 mg weekly (n=410) plus oral sitagliptin placebo once daily for 56 weeks. Semaglutide 1.0 mg N=410 Semaglutide 1.0 mg weekly (n=410) plus oral sitagliptin placebo once daily for 56 weeks.
Cointervention	Concomitant therapy: People could be receiving metformin (at least 1500 mg), pioglitazone (at least 30 mg), rosiglitazone (at least 4 mg) or a combination of metformin and pioglitazone or metformin and rosiglitazone.
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear Excluded "heart failure at any time (New York Heart Association class IV)", unclear if this excludes all heart failure. No information in baseline characteristics.
Strata 2: People with atherosclerotic cardiovascular disease	Not stated/unclear Excluded an acute coronary or cerebrovascular event within 90 days before randomisation. No information in baseline characteristics.
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear Excluded impaired renal function (estimated glomerular filtration [eGFR] <60 mL/min/1·73 m²) but does not specify excluding CKD diagnosis. No information in baseline characteristics.
Strata 4: People with type 2 diabetes	Not stated/unclear

mellitus and high cardiovascular risk	
Subgroup 1: People with moderate or severe frailty	Not stated/unclear
Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear
Subgroup 3: People with non-alcoholic fatty liver disease	Not stated/unclear
Subgroup 4: People with obesity	Not stated/unclear
Subgroup 5: eGFR category at baseline	Not stated/unclear
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Population subgroups	No additional information.
Comparator	Sitagliptin N=411 Sitagliptin 100mg once daily and subcutaneous semaglutide placebo once weekly for 56 weeks.
Number of participants	1231
Duration of follow-up	56 weeks.
Indirectness	No additional information.
Method of analysis	Modified ITT

Additional comments	No additional information.

11.2. Study arms

11.2.1. Semaglutide 0.5 mg (N = 410)

Semaglutide 0.5 mg weekly (n=410) plus oral sitagliptin placebo once daily for 56 weeks. Concomitant therapy: People could be receiving metformin (at least 1500 mg), pioglitazone (at least 30 mg), rosiglitazone (at least 4 mg) or a combination of metformin and pioglitazone or metformin and rosiglitazone.

11.2.2. Semaglutide 1.0 mg (N = 410)

Semaglutide 1.0 mg weekly (n=410) plus oral sitagliptin placebo once daily for 56 weeks. Concomitant therapy: People could be receiving metformin (at least 1500 mg), pioglitazone (at least 30 mg), rosiglitazone (at least 4 mg) or a combination of metformin and pioglitazone or metformin and rosiglitazone.

11.2.3. Sitagliptin (N = 411)

Sitagliptin 100mg once daily and subcutaneous semaglutide placebo once weekly for 56 weeks. Concomitant therapy: People could be receiving metformin (at least 1500 mg), pioglitazone (at least 30 mg), rosiglitazone (at least 4 mg) or a combination of metformin and pioglitazone or metformin and rosiglitazone.

11.3. Characteristics

11.3.1. Arm-level characteristics

Characteristic	Semaglutide 0.5 mg (N = 410)	Semaglutide 1.0 mg (N = 410)	Sitagliptin (N = 411)
% Male Sample size	n = 207 ; % = 51	n = 205 ; % = 50	n = 208 ; % = 51
Mean age (SD) (years) Mean (SD)	54.8 (10.2)	56 (9.4)	54.6 (10.4)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA

Characteristic	Semaglutide 0.5 mg (N = 410)	Semaglutide 1.0 mg (N = 410)	Sitagliptin (N = 411)
White Sample size	n = 279 ; % = 68	n = 279 ; % = 68	n = 281 ; % = 69
Black or African American Sample size	n = 18 ; % = 4	n = 24 ; % = 6	n = 17 ; % = 4
Asian Sample size	n = 106 ; % = 26	n = 99 ; % = 24	n = 102 ; % = 25
Hispanic or Latino Sample size	n = 69 ; % = 17	n = 67 ; % = 16	n = 73 ; % = 18
Not hispanic or latino Sample size	n = 340 ; % = 83	n = 342 ; % = 84	n = 334 ; % = 82
Comorbidities Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Presence of frailty Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Time since type 2 diabetes diagnosed (years) Mean (SD)	6.4 (4.7)	6.7 (5.6)	6.6 (5.1)
Cardiovascular risk factors Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Smoking status Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Alcohol consumption Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Presence of severe mental illness Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
People with significant cognitive impairment Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR

Characteristic	Semaglutide 0.5 mg (N = 410)	Semaglutide 1.0 mg (N = 410)	Sitagliptin (N = 411)
People with a learning disability Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Number of people with obesity Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Other antidiabetic medication used Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
Metformin Sample size	n = 404 ; % = 99	n = 407 ; % = 100	n = 405 ; % = 100
Sulfonylureas Sample size	n = 1 ; % = 1	n = 0 ; % = 0	n = 1 ; % = 1
Thiazolidinediones Sample size	n = 23 ; % = 6	n = 20 ; % = 5	n = 23 ; % = 6
Metformin plus Thiazolidiones Sample size	n = 20 ; % = 5	n = 18 ; % = 4	n = 22 ; % = 5
Combinations Sample size	n = 0 ; % = 0	n = 0 ; % = 0	n = 1 ; % = 1
Blood pressure-lowering medication used Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
ACE inhibitors Sample size	n = 95 ; % = 23	n = 107 ; % = 26	n = 109 ; % = 27
ACE inhibitors and diuretics Sample size	n = 15 ; % = 4	n = 25 ; % = 6	n = 15 ; % = 4
Angiotensin II receptor antagonists Sample size	n = 82 ; % = 20	n = 69 ; % = 17	n = 69 ; % = 17
Angiotensin II receptor antagonists and diuretics Sample size	n = 27 ; % = 7	n = 21 ; % = 5	n = 20 ; % = 5

Characteristic	Semaglutide 0.5 mg (N = 410)	Semaglutide 1.0 mg (N = 410)	Sitagliptin (N = 411)
Beta-blocking drugs, selective Sample size	n = 68 ; % = 17	n = 71 ; % = 17	n = 79 ; % = 19
Thiazides Sample size	n = 40 ; % = 10	n = 28 ; % = 7	n = 28 ; % = 7
Statins/lipid-lowering medication used Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
Statins Sample size	n = 154 ; % = 38	n = 158 ; % = 39	n = 155 ; % = 38
Fibrates Sample size	n = 26 ; % = 6	n = 23 ; % = 6	n = 17 ; % = 4
Other treatment being received Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA

12. Ahren, 2005

Bibliographic Reference	Ahren, Bo; Pacini, Giovanni; Foley, James E; Schweizer, Anja; Improved meal-related beta-cell function and insulin sensitivity by the dipeptidyl peptidase-IV inhibitor vildagliptin in metformin-treated patients with type 2 diabetes over 1 year.; Diabetes care; 2005; vol. 28 (no. 8); 1936-40

12.1. Study details

Secondary publication of another included study- see primary study for details	Ahrén, B., Gomis, R., Standl, E. et al. (2004) Twelve- and 52-week efficacy of the dipeptidyl peptidase IV inhibitor LAF237 in metformin-treated patients with type 2 diabetes. Diabetes Care 27(12): 2874-80

13. Ando, 2021

Bibliographic Reference Ando, Y.; Shigiyama, F.; Hirose, T.; Kumashiro, N.; Simplification of complex insulin regimens using canagliflozin or liraglutide in patients with well-controlled type 2 diabetes: A 24-week randomized controlled trial; Journal of Diabetes Investigation; 2021; vol. 12 (no. 10); 1816-1826

13.1. Study details

Secondary publication of another included study- see primary study for details	No additional information.
Other publications associated with this study included in review	No additional information.
Trial name / registration number	UMIN000019382.
Study type	Randomised controlled trial (RCT)
Study location	Japan.
Study setting	Outpatient follow-up.
Study dates	October 2015 to February 2018.
Sources of funding	Supported by the Initiative for Realizing Diversity in the Research Environment 2016.
Inclusion criteria	People with type 2 diabetes mellitus who received MDI of ultra-rapid insulin and insulin glargine or degludec for at least 24 weeks before screening; aged at least 20 years; glycated haemoglobin <7.5%; diabetes duration of 1-25 years; BMI >22kg/m2.
Exclusion criteria	Use of GLP-1RAs; DPP-4 inhibitors or SGLT2 inhibitors; severe or acute complications; chronic bowel disease; malignancy and heavy alcohol consumption.
Recruitment / selection of participants	No additional information.

Intervention(s)	Canagliflozin N=20 Canagliflozin 100mg per day for 24 weeks. People were switched from bolus insulin to canagliflozin.
Cointervention	All people received basal insulin (either dose <15 or at least 15 units/day).
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear Not an inclusion/exclusion criteria and no information in baseline characteristics.
Strata 2: People with atherosclerotic cardiovascular disease	Not stated/unclear Excluded MI in the past 3 months but unclear prior to that. No information in baseline characteristics.
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	People without chronic kidney disease Excluded "severe renal dysfunction". No information in baseline characteristics.
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	Not stated/unclear
Subgroup 1: People with moderate or severe frailty	Not stated/unclear
Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear
Subgroup 3: People with non-alcoholic fatty liver disease	Not stated/unclear

Subgroup 4: People with obesity	Not stated/unclear
Subgroup 5: eGFR category at baseline	Not stated/unclear
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Population subgroups	No additional information.
Comparator	Liraglutide N=20 Liraglutide 0.3 mg per day increased every 2 weeks until it reached 0.9 mg per day for 24 weeks. People were switched from bolus insulin to liraglutide.
Number of participants	40
Duration of follow-up	24 weeks.
Indirectness	No additional information.
Method of analysis	Per protocol Full analysis set - people enrolled in the study and completed the 24 week treatment period.

13.2. Study arms

13.2.1. Canagliflozin (N = 20)

Canagliflozin 100mg per day for 24 weeks. People were switched from bolus insulin to canagliflozin. Concomitant therapy: All people received basal insulin (either dose <15 or at least 15 units/day).

13.2.2. Liraglutide (N = 20)

Liraglutide 0.3 mg per day increased every 2 weeks until it reached 0.9 mg per day for 24 weeks. People were switched from bolus insulin to liraglutide. Concomitant therapy: All people received basal insulin (either dose <15 or at least 15 units/day).

13.3. Characteristics

13.3.1. Arm-level characteristics

Characteristic	Canagliflozin (N = 20)	Liraglutide (N = 20)
% Male Sample size	n = 13 ; % = 76.5	n = 13 ; % = 76.5
Mean age (SD) (years) Mean (SD)	55.9 (13)	58.2 (11.5)
Ethnicity Sample size	n = NR ; % = NR	n = NR ; % = NR
Comorbidities Sample size	n = NR ; % = NR	n = NR ; % = NR
Presence of frailty Sample size	n = NR ; % = NR	n = NR ; % = NR
Time since type 2 diabetes diagnosed (years) Mean (SD)	10.4 (6.9)	7.8 (7)
Cardiovascular risk factors Sample size	n = NR ; % = NR	n = NR ; % = NR
Smoking status Sample size	n = NR ; % = NR	n = NR ; % = NR
Alcohol consumption Sample size	n = NR ; % = NR	n = NR ; % = NR
Presence of severe mental illness Sample size	n = NR ; % = NR	n = NR ; % = NR
People with significant cognitive impairment Sample size	n = NR ; % = NR	n = NR ; % = NR
People with a learning disability Sample size	n = NR ; % = NR	n = NR ; % = NR
Number of people with obesity Sample size	n = NR ; % = NR	n = NR ; % = NR

Characteristic	Canagliflozin (N = 20)	Liraglutide (N = 20)
Other antidiabetic medication used Sample size	n = NA ; % = NA	n = NA ; % = NA
None Sample size	n = 10 ; % = 58.8	n = 13 ; % = 76.5
Biguanides Sample size	n = 6 ; % = 35.3	n = 4 ; % = 23.5
Alpha-glucosidase inhibitors Sample size	n = 1 ; % = 5.9	n = 0 ; % = 0
Glinides Sample size	n = 1 ; % = 5.9	n = 0 ; % = 0
Blood pressure-lowering medication used Sample size	n = NR ; % = NR	n = NR ; % = NR
Statins/lipid-lowering medication used Sample size	n = NR ; % = NR	n = NR ; % = NR
Other treatment being received Sample size	n = NR ; % = NR	n = NR ; % = NR

14. Araki, 2015

Bibliographic Reference	Araki, E.; Inagaki, N.; Tanizawa, Y.; Oura, T.; Takeuchi, M.; Imaoka, T.; Efficacy and safety of once-weekly dulaglutide in combination with sulphonylurea and/or biguanide compared with once-daily insulin glargine in Japanese patients with type 2 diabetes: a randomized, open-label, phase III, non-inferiority study; Diabetes Obes Metab; 2015; vol. 17 (no. 10); 994-1002

14.1. Study details

Secondary publication of another included study- see primary study for details	
Other publications associated with this study included in review	Inagaki N, Araki E, Oura T, Matsui A, Takeuchi M, Tanizawa Y. The combination of dulaglutide and biguanide reduced bodyweight in Japanese patients with type 2 diabetes. Diabetes Obes Metab. 2016 Dec;18(12):1279-1282. doi: 10.1111/dom.12758 Suzuki S, Oura T, Takeuchi M, Boye KS. Evaluation of the impact of once weekly dulaglutide on patient-reported outcomes in Japanese patients with type 2 diabetes: comparisons with liraglutide, insulin glargine, and placebo in two randomized studies. Health Qual Life Outcomes. 2017 Jun 12;15(1):123. doi: 10.1186/s12955-017-0696-7. PMID: 28606095; PMCID: PMC5468988.
Trial name / registration number	NCT01584232
Study type	Randomised controlled trial (RCT)
Study location	35 sites in Japan
Study setting	No additional information
Study dates	June 2012 to July 2013
Sources of funding	Sponsored by Eli Lilly K. K. Japan. Multiple authors declare funding and honoraria from numerous pharmaceutical companies

Inclusion criteria	Japanese men and women with T2D, aged ≥20 years, with a BMI ≥18.5 and <35.0 kg/m2 and HbA1c at screening ≥7.0 and ≤10.0%, who were taking stable doses of sulphonylureas (2.5–5 mg of glibenclamide, 60–80 mg of gliclazide, or 2–3 mg of glimepiride) and/or biguanides (750–1500 mg of metformin or 100–150 mg of buformin).
Exclusion criteria	patients with type 1 diabetes; patients previously treated with any GLP-1 receptor agonist; patients who had received therapy with an α-glucosidase inhibitor, thiazolidinedione, glinide or dipeptidyl peptidase-4 inhibitor, or insulin within 3 months before screening; patients undergoing chronic systemic glucocorticoid therapy; and patients who had a clinically significant gastric emptying abnormality, cardiovascular disease, liver disease, renal disease, active or untreated malignancy, poorly controlled hypertension, a history of chronic or acute pancreatitis, obvious clinical signs or symptoms of pancreatitis, or a self or family history of medullary C-cell hyperplasia, focal hyperplasia or medullary thyroid carcinoma.
Recruitment / selection of participants	No additional information
Intervention(s)	Dulaglutide (n= 181) Patients received subcutaneous injections of once-weekly dulaglutide 0.75 mg for 26 weeks.
Cointervention	Sulphonylurea / biguanide Patients continued their sulphonylureas and/or biguanides at the baseline dose throughout the study; the dose of sulphonylurea may have been reduced if daytime hypoglycaemia was observed
Strata 1: People with type 2 diabetes mellitus and heart failure	People without heart failure Excluded "cardiovascular disease"
Strata 2: People with atherosclerotic cardiovascular disease	People without atherosclerotic cardiovascular diseases Excluded cardiovascular disease
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	People without chronic kidney disease Excluded renal disease
Strata 4: People with	Not stated/unclear

type 2 diabetes mellitus and high cardiovascular risk	
Subgroup 1: People with moderate or severe frailty	Not stated/unclear
Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear
Subgroup 3: People with non-alcoholic fatty liver disease	Not stated/unclear
Subgroup 4: People with obesity	Not stated/unclear
Subgroup 5: eGFR category at baseline	Not stated/unclear
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Comparator	Insulin glargine (n= 180) Insulin glargine was administered once daily at bedtime by subcutaneous injection. with an initial dose of glargine between 4.0 and 8.0 IU and a fasting serum glucose (FSG) target of ≤6.1 mmol/l for investigator-driven adjustments. Glargine doses were to be adjusted once a week based on the average of self-monitored fasting blood glucose values over the previous 3 days. Dose adjustments were to be made as needed once weekly for up to 8 weeks; adjustments at later times were allowed if needed for further optimization of glycaemic control, based on the investigators' discretion. Patients continued their sulphonylureas and/or biguanides at the baseline dose throughout the study; the dose of sulphonylurea may have been reduced if daytime hypoglycaemia was observed.
Number of participants	361

Duration of follow-up	26 weeks
Indirectness	NA
Method of analysis	Modified ITT
Additional comments	0.05. Efficacy analyses were conducted on the full analysis set (all randomized patients who received at least one dose of study drug). Safety analyses were conducted on the as-treated population, according to the patients' actual treatments (safety analysis set). For the assessment of efficacy and hypoglycaemia events, only data obtained before the initiation of other antihyperglycaemic medication were used. For the assessment of safety, only data obtained while the patient was on study treatment were used

14.2. Study arms

14.2.1. Dulaglutide (0.75 mg) (N = 181)

Patients received subcutaneous injections of once-weekly dulaglutide 0.75 mg for 26 weeks. Patients continued their sulphonylureas and/or biguanides at the baseline dose throughout the study.

14.2.2. Insulin glargine (N = 180)

Patients received subcutaneous injections of once-daily Insulin glargine with an initial dose of between 4.0 and 8.0 IU and a fasting serum glucose (FSG) target of ≤6.1 mmol/l for investigator-driven adjustments. Patients continued their sulphonylureas and/or biguanides at the baseline dose throughout the study.

14.3. Characteristics

14.3.1. Arm-level characteristics

Characteristic	Dulaglutide (0.75 mg) (N = 181)	Insulin glargine (N = 180)
% Male Sample size	n = 125 ; % = 69	n = 133 ; % = 74
Mean age (SD) (Years (mean, SD)) Mean (SD)	57.5 (10.5)	56.1 (11.3)

Characteristic	Dulaglutide (0.75 mg) (N = 181)	Insulin glargine (N = 180)
Ethnicity Sample size	n = NR ; % = NR	n = NR ; % = NR
Time since type 2 diabetes diagnosed (Years (mean, SD)) Mean (SD)	8.9 (6.7)	8.8 (6.1)
Smoking status Sample size	n = NR ; % = NR	n = NR ; % = NR
Alcohol consumption Sample size	n = NR ; % = NR	n = NR ; % = NR
Presence of severe mental illness Sample size	n = NR ; % = NR	n = NR ; % = NR
People with significant cognitive impairment Sample size	n = NR ; % = NR	n = NR ; % = NR
People with a learning disability Sample size	n = NR ; % = NR	n = NR ; % = NR
Number of people with obesity Sample size	n = NR ; % = NR	n = NR ; % = NR
Other antidiabetic medication used Sample size	n = NA ; % = NA	n = NA ; % = NA
Sulphonylurea only Sample size	n = 34 ; % = 19	n = 33 ; % = 18
Biguanide only Sample size	n = 64 ; % = 35	n = 66 ; % = 37
Sulfonlyurea + biguanides Sample size	n = 83 ; % = 46	n = 81 ; % = 45
Blood pressure-lowering medication used Sample size	n = NR ; % = NR	n = NR ; % = NR
Statins/lipid-lowering medication used	n = NR ; % = NR	n = NR ; % = NR

Characteristic	Dulaglutide (0.75 mg) (N = 181)	Insulin glargine (N = 180)
Sample size		
Other treatment being received Sample size	n = NR ; % = NR	n = NR ; % = NR

15. Araki, 2015

Bibliographic Reference	Araki, E.; Tanizawa, Y.; Tanaka, Y.; Taniguchi, A.; Koiwai, K.; Kim, G.; Salsali, A.; Woerle, H. J.; Broedl, U. C.; Long-term treatment with empagliflozin as add-on to oral antidiabetes therapy in Japanese patients with type 2 diabetes mellitus; Diabetes Obes Metab; 2015; vol. 17 (no. 7); 665-674

15.1. Study details

Secondary publication of another included study- see primary study for details	No additional information.
Other publications associated with this study included in review	No additional information.
Trial name / registration number	NCT01368081.
Study type	Randomised controlled trial (RCT)
Study location	Japan (86 centres).
Study setting	Outpatient follow-up.
Study dates	No additional information.
Sources of funding	Funded by Boehringer Ingelheim and Eli Lilly and Company.
Inclusion criteria	People with type 2 diabetes aged at least 20 years; BMI no more than 45.0 kg/m2; HbA1c 7.0-10.0% at screening, despite diet and exercise regimens and monotherapy with a sulfonylurea, biguanide, thiazolidinedione, alpha-glucosidase inhibitor, DPP-4 inhibitor or glinide; type, dose and timing of background therapy were to have been unchanged for at least 10 weeks (18 weeks for thiazolidinedione); people receiving antihypertensive therapy were required to have been on a stable dose for at least 4 weeks before randomisation.

Exclusion criteria	Uncontrolled hyperglycaemia (glucose >13.3 mmol/L) after an overnight fast, confirmed by a second measurement; eGFR during screening or run-in of <60mL/min/1.73m2 for people on background biguanide or <30mL/min/1.73m2 for people on other background therapies; any uncontrolled endocrine disorder except T2DM; treatment with anti-obesity drugs <12 weeks before consent; treatment with systemic steroids or change in dosage of thyroid hormones <6 weeks before consent; contraindications to the background therapy according to the package insert; and for the background sulfonylurea group, contraindications to metformin.
Recruitment / selection of participants	Everyone underwent a 2 week placebo run-in to study compliance with treatment, those who were not compliant (where the percentage of tablets taken were not between 80 and 120% of those that should have been taken) were not randomised for the study.
Intervention(s)	Empagliflozin 10mg N=136 Empagliflozin 10mg orally once a daily (people with an eGFR at least 60mL/min/1.73m2). Empagliflozin 25mg N=137 Empagliflozin 25mg orally once a daily (people with an eGFR at least 60mL/min/1.73m2). Note: The study includes other arms that receive empagliflozin on a background of other concomitant therapy. However, these arms do not have a relevant comparator arm so are not included in this data extraction.
Cointervention	All people received a sulfonylurea before and during the study.
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear Not an inclusion/exclusion criteria and no information in baseline characteristics.
Strata 2: People with atherosclerotic cardiovascular disease	Not stated/unclear Not an inclusion/exclusion criteria and no information in baseline characteristics.
Strata 3: People with type 2	Not stated/unclear Exclusion criteria based on eGFR but not diagnosis of CKD. Baseline characteristics give eGFR breakdowns but not diagnosis of CKD.

diabetes mellitus and chronic kidney disease	
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	Not stated/unclear
Subgroup 1: People with moderate or severe frailty	Not stated/unclear
Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear
Subgroup 3: People with non-alcoholic fatty liver disease	Not stated/unclear
Subgroup 4: People with obesity	Not stated/unclear
Subgroup 5: eGFR category at baseline	Not stated/unclear
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Population subgroups	No additional information.
Comparator	Metformin N=63 Open label metformin immediate release (people with an eGFR at least 60mL/min/1.73m2). Metformin immediate release was given twice or three times daily at an initial dose of 500 mg/day increasing to at least 1000 mg/day at week 12 and up to a maximum dose of 2250 mg/day. The dose was not to be changed after week 12 if there were no safety concerns.

Number of participants	336
Duration of follow-up	52 weeks.
Indirectness	No additional information.
Method of analysis	ACA Full analysis set - all people who received at least 1 dose of the study drug and had a baseline HbA1c measurement Modified ITT Safety analysis - all people who received at least 1 dose of the study drug
Additional comments	No additional information.

15.2. Study arms

15.2.1. Empagliflozin 10mg (N = 136)

Empagliflozin 10mg orally once a daily (people with an eGFR at least 60mL/min/1.73m2). Concomitant therapy: All people received a sulfonylurea before and during the study.

15.2.2. Empagliflozin 25mg (N = 137)

Empagliflozin 25mg orally once a daily (people with an eGFR at least 60mL/min/1.73m2). Concomitant therapy: All people received a sulfonylurea before and during the study.

15.2.3. Metformin (N = 63)

Open label metformin immediate release (people with an eGFR at least 60mL/min/1.73m2). Metformin immediate release was given twice or three times daily at an initial dose of 500 mg/day increasing to at least 1000 mg/day at week 12 and up to a maximum dose of 2250 mg/day. The dose was not to be changed after week 12 if there were no safety concerns. Concomitant therapy: All people received a sulfonylurea before and during the study.

15.3. Characteristics

15.3.1. Arm-level characteristics

Characteristic	Empagliflozin 10mg (N = 136)	Empagliflozin 25mg (N = 137)	Metformin (N = 63)
% Male Sample size	n = 99 ; % = 73	n = 96 ; % = 70	n = 47 ; % = 75
Mean age (SD) (years) Mean (SD)	61.3 (9.9)	61.8 (9.6)	60 (10.2)
Ethnicity Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Comorbidities Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Presence of frailty Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Time since type 2 diabetes diagnosed Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
At least 1 year Sample size	n = 7 ; % = 5	n = 2 ; % = 2	n = 1 ; % = 2
>1 to 5 years Sample size	n = 33 ; % = 24	n = 38 ; % = 28	n = 16 ; % = 25
>5 to 10 years Sample size	n = 48 ; % = 35	n = 49 ; % = 36	n = 22 ; % = 35
>10 years Sample size	n = 48 ; % = 35	n = 48 ; % = 35	n = 24 ; % = 38
Cardiovascular risk factors Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Smoking status Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Alcohol consumption Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR

Characteristic	Empagliflozin 10mg (N = 136)	Empagliflozin 25mg (N = 137)	Metformin (N = 63)
Presence of severe mental illness Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
People with significant cognitive impairment Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
People with a learning disability Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Number of people with obesity Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Other antidiabetic medication used Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Blood pressure-lowering medication used Sample size	n = NR	n = NR ; % = NR	n = NR ; % = NR
Statins/lipid-lowering medication used Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Other treatment being received Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR

16. Arechavaleta, 2011

Bibliographic Reference	Arechavaleta, R.; Seck, T.; Chen, Y.; Krobot, K. J.; O'Neill, E. A.; Duran, L.; Kaufman, K. D.; Williams-Herman, D.; Goldstein, B. J.; Efficacy and safety of treatment with sitagliptin or glimepiride in patients with type 2 diabetes inadequately controlled on metformin monotherapy: a randomized, double-blind, non-inferiority trial; Diabetes Obes Metab; 2011; vol. 13 (no. 2); 160-8

16.1. Study details

Secondary publication of another included study- see primary study for details	No additional information.
Other publications associated with this study included in review	No additional information.
Trial name / registration number	NCT00701090. Sitagliptin Protocol 803.
Study type	Randomised controlled trial (RCT)
Study location	Multicentre trial.
Study setting	Outpatient follow-up.
Study dates	No additional information.
Sources of funding	Funded by Merck Sharp & Dohme Corp.
Inclusion criteria	At least 18 years of age; type 2 diabetes with inadequate glycaemic control (HbA1c 6.5-9.0%) while on a stable dose of metformin (at least 1500 mg/day) as well as diet and exercise for at least 12 weeks prior to the screening visit.
Exclusion criteria	History of type 1 diabetes; used any antihyperglycaemic agent besides metformin within 12 weeks of the screening visit; had renal function impairment prohibiting the use of metformin or had a fasting fingerstick glucose of <6.1 or >13.3 mmol/L at randomisation.

Recruitment / selection of participants	No additional information.
Intervention(s)	Sitagliptin N=516 Sitagliptin 100mg daily and matching glimepiride placebo for 30 weeks.
Cointervention	All people received metformin (at least 1500 mg/day) combined with diet and exercise for at least 12 weeks prior to the trial.
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear Not an inclusion/exclusion criteria and no information in baseline characteristics.
Strata 2: People with atherosclerotic cardiovascular disease	Not stated/unclear Not an inclusion/exclusion criteria and no information in baseline characteristics.
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear Excludes renal function impairment prohibiting the use of metformin, but unclear if this would exclude all CKD. No information in baseline characteristics.
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	Not stated/unclear
Subgroup 1: People with moderate or severe frailty	Not stated/unclear
Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear
Subgroup 3: People with non-alcoholic	Not stated/unclear

fatty liver disease	
Subgroup 4: People with obesity	Not stated/unclear
Subgroup 5: eGFR category at baseline	Not stated/unclear
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Population subgroups	No additional information.
Comparator	Glimepiride N=519 Glimepiride 1mg/day up-titrated during the first 18 weeks up to a maximum of 6mg/day with matching sitagliptin placebo. Total treatment of 30 weeks.
Number of participants	1035
Duration of follow-up	30 weeks
Indirectness	No additional information.
Method of analysis	ACA Full analysis set (all randomised people who took at least one dose of the study medication and had both a baseline measurement and at least one postbaseline measurement of the respective efficacy outcome) Per protocol
Additional comments	No additional information.

16.2. Study arms

16.2.1. Sitagliptin (N = 516)

Sitagliptin 100mg daily and matching glimepiride placebo for 30 weeks. Concomitant therapy: All people received metformin (at least 1500 mg/day) combined with diet and exercise for at least 12 weeks prior to the trial.

16.2.2. Glimepiride (N = 519)

Glimepiride 1mg/day up-titrated during the first 18 weeks up to a maximum of 6mg/day with matching sitagliptin placebo. Total treatment of 30 weeks. Concomitant therapy: All people received metformin (at least 1500 mg/day) combined with diet and exercise for at least 12 weeks prior to the trial.

16.3. Characteristics

16.3.1. Arm-level characteristics

Characteristic	Sitagliptin (N = 516)	Glimepiride (N = 519)
% Male Sample size	n = 284 ; % = 55	n = 279 ; % = 53.8
Mean age (SD) (years) Mean (SD)	56.3 (9.7)	56.2 (10.1)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA
White Sample size	n = 297 ; % = 57.6	n = 298 ; % = 57.4
Asian Sample size	n = 109 ; % = 21.1	n = 111 ; % = 21.4
Multiracial Sample size	n = 78 ; % = 15.1	n = 76 ; % = 14.6
Other Sample size	n = 26 ; % = 5	n = 28 ; % = 5.4
Black or African American Sample size	n = 6 ; % = 1.2	n = 6 ; % = 1.2
Hispanic or Latino Sample size	n = 196 ; % = 38	n = 196 ; % = 37.8
Comorbidities Sample size	n = NR ; % = NR	n = NR ; % = NR
Presence of frailty Sample size	n = NR ; % = NR	n = NR ; % = NR

Characteristic	Sitagliptin (N = 516)	Glimepiride (N = 519)
Time since type 2 diabetes diagnosed (years) Mean (SD)	6.8 (4.6)	6.7 (4.8)
Cardiovascular risk factors Sample size	n = NR ; % = NR	n = NR ; % = NR
Smoking status Sample size	n = NR ; % = NR	n = NR ; % = NR
Alcohol consumption Sample size	n = NR ; % = NR	n = NR ; % = NR
Presence of severe mental illness Sample size	n = NR ; % = NR	n = NR ; % = NR
People with significant cognitive impairment Sample size	n = NR ; % = NR	n = NR ; % = NR
People with a learning disability Sample size	n = NR ; % = NR	n = NR ; % = NR
Number of people with obesity Sample size	n = NR ; % = NR	n = NR ; % = NR
Other antidiabetic medication used Sample size	n = NR ; % = NR	n = NR ; % = NR
Blood pressure-lowering medication used Sample size	n = NR ; % = NR	n = NR ; % = NR
Statins/lipid-lowering medication used Sample size	n = NR ; % = NR	n = NR ; % = NR
Other treatment being received Sample size	n = NR ; % = NR	n = NR ; % = NR

17. Aroda, 2017

Bibliographic Reference	Aroda, V. R.; Bain, S. C.; Cariou, B.; Piletic, M.; Rose, L.; Axelsen, M.; Rowe, E.; DeVries, J. H.; Efficacy and safety of once-weekly semaglutide versus once-daily insulin glargine as add-on to metformin (with or without sulfonylureas) in insulin-naive patients with type 2 diabetes (SUSTAIN 4): A randomised, open-label, parallel-group, multicentre, multinational, phase 3a trial; Lancet Diabetes Endocrinol; 2017; vol. 5 (no. 5); 355-366

17.1. Study details

Secondary publication of another included study- see primary study for details	No additional information.
Other publications associated with this study included in review	No additional information.
Trial name / registration number	SUSTAIN 4. NCT02128932.
Study type	Randomised controlled trial (RCT)
Study location	Multicentre trial.
Study setting	Outpatient follow-up.
Study dates	4 August 2014 to 3 September 2015.
Sources of funding	Funded by Novo Nordisk A/S.
Inclusion criteria	HbA1c value of 7.0-10.0%; insulin naive subjects; at least 18 years old; diagnosed with type 2 diabetes and on stable treatment with metformin alone or in combination with sulphonylureas 90 days prior to screening.
Exclusion criteria	History of chronic or idiopathic acute pancreatitis; screening calcitonin value of at least 50 ng/L; any personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia syndrome type 2; severely impaired renal function (eGFR <30mL/min/1.73m2); heart failure (NYHA class IV) or any acute coronary or cerebrovascular events within

	the last 90 days; known proliferative retinopathy or maculopathy requiring acute treatment.
Recruitment / selection of participants	No additional information.
Intervention(s)	Semaglutide 0.5mg N=362 Semaglutide 0.5mg once weekly subcutaneously for 30 weeks. Semaglutide 1.0mg N=362 Semaglutide 1.0mg once weekly subcutaneously for 30 weeks.
Cointervention	People could receive metformin (49%) or metformin and sulfonylurea (51%).
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear Excluded heart failure (New York Heart Association class IV) but unclear if all HF. No information in baseline characteristics
Strata 2: People with atherosclerotic cardiovascular disease	Not stated/unclear Excluded any acute coronary or cerebrovascular events within the last 90 days, unclear prior to that. No information in baseline characteristics.
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear Excluded severely impaired renal function (estimated glomerular filtration rate [eGFR] <30 ml/min/1·73 m2) but CKD not specified. No information in baseline characteristics.
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	Not stated/unclear
Subgroup 1: People with moderate or severe frailty	Not stated/unclear

Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear
Subgroup 3: People with non-alcoholic fatty liver disease	Not stated/unclear
Subgroup 4: People with obesity	Not stated/unclear
Subgroup 5: eGFR category at baseline	Not stated/unclear
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Population subgroups	No additional information.
Comparator	Insulin glargine N=365 Insulin glargine once daily started at a dose of 10 IU, titrated up to achieve a pre-breakfast self-measured plasma glucose target of 4.0-5.5 mmol/L.
Number of participants	1089
Duration of follow-up	30 weeks.
Indirectness	No additional information.
Method of analysis	Modified ITT
Additional comments	No additional information.

17.2. Study arms

17.2.1. Semaglutide 0.5mg (N = 362)

Semaglutide 0.5mg once weekly subcutaneously for 30 weeks. Concomitant therapy: People could receive metformin (49%) or metformin and sulfonylurea (51%).

17.2.2. Semaglutide 1.0mg (N = 362)

Semaglutide 1.0mg once weekly subcutaneously for 30 weeks. Concomitant therapy: People could receive metformin (49%) or metformin and sulfonylurea (51%).

17.2.3. Insulin glargine (N = 365)

Insulin glargine once daily started at a dose of 10 IU, titrated up to achieve a pre-breakfast self-measured plasma glucose target of 4.0-5.5 mmol/L. Concomitant therapy: People could receive metformin (49%) or metformin and sulfonylurea (51%).

17.3. Characteristics

17.3.1. Arm-level characteristics

Characteristic	Semaglutide 0.5mg (N = 362)	Semaglutide 1.0mg (N = 362)	Insulin glargine (N = 365)
% Male Sample size	n = 197 ; % = 54.4	n = 182 ; % = 50.6	n = 195 ; % = 54.2
Mean age (SD) (years) Mean (SD)	56.5 (10.3)	56.7 (10.4)	56.2 (10.6)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
American Indian or Alaska Native Sample size	n = 1 ; % = 0.3	n = 0 ; % = 0	n = 1 ; % = 0.3
Asian Sample size	n = 42 ; % = 11.6	n = 39 ; % = 10.8	n = 38 ; % = 10.6
Black or African American Sample size	n = 32 ; % = 8.8	n = 34 ; % = 9.4	n = 33 ; % = 9.2
White Sample size	n = 279 ; % = 77.1	n = 279 ; % = 77.5	n = 276 ; % = 76.7
Other	n = 3 ; % = 0.8	n = 3 ; % = 0.8	n = 5 ; % = 1.4

Characteristic	Semaglutide 0.5mg (N = 362)	Semaglutide 1.0mg (N = 362)	Insulin glargine (N = 365)
Sample size			
N/A Sample size	n = 5 ; % = 1.4	n = 5 ; % = 1.4	n = 7 ; % = 1.9
Hispanic or Latino Sample size	n = 61 ; % = 16.9	n = 74 ; % = 20.6	n = 78 ; % = 21.7
Comorbidities Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Presence of frailty Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Time since type 2 diabetes diagnosed (years) Mean (SD)	7.8 (5.14)	9.3 (7.17)	8.6 (6.29)
Cardiovascular risk factors Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Smoking status Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Alcohol consumption Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Presence of severe mental illness Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
People with significant cognitive impairment Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
People with a learning disability Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Number of people with obesity Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR

Characteristic	Semaglutide 0.5mg (N = 362)	Semaglutide 1.0mg (N = 362)	Insulin glargine (N = 365)
Other antidiabetic medication used Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
Metformin Sample size	n = 176 ; % = 48.6	n = 175 ; % = 48.6	n = 172 ; % = 47.8
Metformin and sulfonylurea Sample size	n = 186 ; % = 51.4	n = 185 ; % = 51.4	n = 188 ; % = 52.2
Blood pressure-lowering medication used Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Statins/lipid-lowering medication used Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Other treatment being received Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR

18. Aroda, 2019

Bibliographic Reference	Aroda, V. R.; Gonzalez-Galvez, G.; Gron, R.; Halladin, N.; Haluzik, M.; Jermendy, G.; Kok, A.; Orsy, P.; Sabbah, M.; Sesti, G.; Silver, R.; Durability of insulin degludec plus liraglutide versus insulin glargine U100 as initial injectable therapy in type 2 diabetes (DUAL VIII): a multicentre, open-label, phase 3b, randomised controlled trial; The Lancet Diabetes & Endocrinology; 2019; vol. 7 (no. 8); 596-605

18.1. Study details

Secondary publication of another included study- see primary study for details	No additional information.
Other publications associated with this study included in review	Sesti, G., Bardtrum, L., Dagdelen, S. et al. (2020) A greater proportion of participants with type 2 diabetes achieve treatment targets with IDegLira (insulin degludec/liraglutide) versus insulin glargine U100 at 26weeks: DUAL VIII a randomized trial designed to resemble clinical practice. Diabetes, obesity & metabolism
Trial name / registration number	NCT02501161. DUAL VIII.
Study type	Randomised controlled trial (RCT)
Study location	Multicentre trial.
Study setting	Outpatient follow-up.
Study dates	January 8th 2016 to October 3rd 2018.
Sources of funding	Funded by Novo Nordisk.
Inclusion criteria	People aged 18 years and older; diagnosed with type 2 diabetes before the day of screening; had an HbA1c of 7.0-11.0%; a BMI of 20 kg/m2 or higher; on stable doses of biguanides (metformin at least 1500 mg or maximum tolerated dose), sulfonylureas, glinides, pioglitazone or DPP-4 inhibitors (greater than or equal to half of the maximum approved dose according to local label or maximum tolerated dose).
Exclusion criteria	Treatment with any medication for diabetes or obesity other than that stated in the inclusion criteria during the 90 calendar days before screening; anticipated initiation or change in concomitant medications

	known to affect weight or glucose metabolism; renal impairment (eGFR <60mL/min/1.73m2).
Recruitment / selection of participants	No additional information.
Intervention(s)	Insulin degludec/liraglutide N=506 Insulin degludec/liraglutide 10 U (1 U = 1 U degludec + 0.036 mg liraglutide) increased up to a maximum of 50 U (50 U degludec + 1.8 mg liraglutide) (titrated twice weekly to a fasting plasma glucose target of 4.0-5.0 mmol/L with adjustments made in increments of 2 U).
Cointervention	People were on oral hyperglycaemic therapy before the trial (biguanides - metformin at least 1500 mg or maximum tolerated dose, sulphonylureas, glinides, pioglitazone or DPP-4 inhibitors). DPP-4 inhibitors and glinides were not allowed as monotherapies or in combination with each other. Other therapies were continued during the trial (though a reduction in dose of sulfonylurea was considered based on safety reasons).
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear Excluded Patients presently classified as being in NYHA Class IV", otherwise unclear. No information in baseline characteristics.
Strata 2: People with atherosclerotic cardiovascular disease	Not stated/unclear Excluded "myocardial infarction, stroke or hospitalisation for unstable angina and/or transient ischaemic attack within the past 180 days prior to the day of screening", prior unclear. No information in baseline characteristics.
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear Excluded renal impairment (estimated glomerular filtration rate <60 mL/min/1·73 m²) but not specified by CKD. No information in baseline characteristics.
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	Not stated/unclear
Subgroup 1: People with	Not stated/unclear

moderate or severe frailty	
Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear
Subgroup 3: People with non-alcoholic fatty liver disease	Not stated/unclear
Subgroup 4: People with obesity	Not stated/unclear
Subgroup 5: eGFR category at baseline	Not stated/unclear
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Population subgroups	No additional information.
Comparator	Insulin glargine N=506 Insulin glargine 10 U increased as required (there was no maximum dose) (titrated twice weekly to a fasting plasma glucose target of 4.0-5.0 mmol/L with adjustments made in increments of 2 U).
Number of participants	1012
Duration of follow-up	104 weeks.
Indirectness	No additional information.
Method of analysis	ACA Full analysis set - all randomly assigned people. Safety set - All people receiving at least one dose of the trial product.
Additional comments	No additional information.

18.2. Study arms

18.2.1. Insulin degludec/liraglutide (N = 506)

Insulin degludec/liraglutide 10 U (1 U = 1 U degludec + 0.036 mg liraglutide) increased up to a maximum of 50 U (50 U degludec + 1.8 mg liraglutide) (titrated twice weekly to a fasting plasma glucose target of 4.0-5.0 mmol/L with adjustments made in increments of 2 U). Concomitant therapy: People were on oral hyperglycaemic therapy before the trial (biguanides - metformin at least 1500 mg or maximum tolerated dose, sulphonylureas, glinides, pioglitazone or DPP-4 inhibitors). DPP-4 inhibitors and glinides were not allowed as monotherapies or in combination with each other. Other therapies were continued during the trial (though a reduction in dose of sulfonylurea was considered based on safety reasons).

18.2.2. Insulin glargine (N = 506)

Insulin glargine 10 U increased as required (there was no maximum dose) (titrated twice weekly to a fasting plasma glucose target of 4.0-5.0 mmol/L with adjustments made in increments of 2 U). Concomitant therapy: People were on oral hyperglycaemic therapy before the trial (biguanides - metformin at least 1500 mg or maximum tolerated dose, sulphonylureas, glinides, pioglitazone or DPP-4 inhibitors). DPP-4 inhibitors and glinides were not allowed as monotherapies or in combination with each other. Other therapies were continued during the trial (though a reduction in dose of sulfonylurea was considered based on safety reasons).

18.3. Characteristics

18.3.1. Arm-level characteristics

Characteristic	Insulin degludec/liraglutide (N = 506)	Insulin glargine (N = 506)
% Male Sample size	n = 280 ; % = 55	n = 275 ; % = 54
Mean age (SD) (years) Mean (SD)	56.8 (10)	56.4 (10.1)
Ethnicity Sample size	n = NR ; % = NR	n = NR ; % = NR
Comorbidities Sample size	n = NR ; % = NR	n = NR ; % = NR
Presence of frailty Sample size	n = NR ; % = NR	n = NR ; % = NR

Characteristic	Insulin degludec/liraglutide (N = 506)	Insulin glargine (N = 506)
Time since type 2 diabetes diagnosed (years) Mean (SD)	10 (6.2)	10.2 (6.1)
Cardiovascular risk factors Sample size	n = NR ; % = NR	n = NR ; % = NR
Smoking status Sample size	n = NR ; % = NR	n = NR ; % = NR
Alcohol consumption Sample size	n = NR ; % = NR	n = NR ; % = NR
Presence of severe mental illness Sample size	n = NR ; % = NR	n = NR ; % = NR
People with significant cognitive impairment Sample size	n = NR ; % = NR	n = NR ; % = NR
People with a learning disability Sample size	n = NR ; % = NR	n = NR ; % = NR
Number of people with obesity Sample size	n = NR ; % = NR	n = NR ; % = NR
Other antidiabetic medication used Sample size	n = NA ; % = NA	n = NA ; % = NA
Metformin Sample size	n = 495 ; % = 98	n = 494 ; % = 98
Sulphonylurea Sample size	n = 320 ; % = 63	n = 334 ; % = 66
DPP-4 inhibitor Sample size	n = 171 ; % = 34	n = 145 ; % = 29
Pioglitazone Sample size	n = 38 ; % = 8	n = 42 ; % = 8
Glinide	n = 7 ; % = 1	n = 7 ; % = 1

Characteristic	Insulin degludec/liraglutide (N = 506)	Insulin glargine (N = 506)
Sample size		
Alpha-glucosidase inhibitor Sample size	n = 1 ; % = 1	n = 0 ; % = 0
Blood pressure-lowering medication used Sample size	n = NA ; % = NA	n = NA ; % = NA
Statins/lipid-lowering medication used Sample size	n = NA ; % = NA	n = NA ; % = NA
Other treatment being received Sample size	n = NA ; % = NA	n = NA ; % = NA

19. Aroda, 2016

Bibliographic Reference	Aroda, Vanita R; Rosenstock, Julio; Wysham, Carol; Unger, Jeffrey; Bellido, Diego; Gonzalez-Galvez, Guillermo; Takami, Akane; Guo, Hailing; Niemoeller, Elisabeth; Souhami, Elisabeth; Bergenstal, Richard M; Efficacy and Safety of LixiLan, a Titratable Fixed-Ratio Combination of Insulin Glargine Plus Lixisenatide in Type 2 Diabetes Inadequately Controlled on Basal Insulin and Metformin: The LixiLan-L Randomized Trial.; Diabetes care; 2016; vol. 39 (no. 11); 1972-1980

19.1. Study details

Secondary publication of another included study- see primary study for details	No additional information.
Other publications associated with this study included in review	Achievement of glycaemic control is associated with improvements in lipid profile with iGlarLixi versus iGlar: A post hoc analysis of the LixiLan-L trial. Diabetes, obesity & metabolism; 2019; vol. 21 (no. 12); 2712-2717
Trial name / registration number	LixiLan-L/NCT02058160
Study type	Randomised controlled trial (RCT)
Study location	Australia Canada Chile Czech Republic Denmark Estonia Hungary Lithuania

	Mexico Netherlands Poland Romania Russia Slovakia Spain Sweden Ukraine
Study setting	Diabetes medical centre
Study dates	01/2014 - 07/2015
Sources of funding	Sanofi
Inclusion criteria	Patients aged ≥18 years with type 2 diabetes diagnosed at least 1 year before screening were eligible to enrol. Patients had to have been treated with a basal insulin for at least 6 months before screening, with a stable regimen for at least 3 months. The total daily basal insulin dose was required to have been stable (± 20%) between 15 and 40 units/day for at least 2 months before the screening visit. The dose(s) of any oral glucose-lowering therapies must have been stable during the 3 months before the screening visit.
Exclusion criteria	Use of an oral or injectable glucose-lowering agent other than those stated above; history of hypoglycemia unawareness or metabolic acidosis, including diabetic ketoacidosis within 1 year before screening; patients who previously discontinued GLP-1 RAs because of poor safety, tolerability, or lack of efficacy; and previous use of non-basal insulin (e.g., prandial or premixed insulin) in the year before screening, with the exception of treatment with non-basal insulin for ≤10 days because of intercurrent illness. Also exclusionary were amylase and/or lipase levels >3 times the upper limit of the normal laboratory range or calcitonin ≥20 pg/mL (5.9 pmol/L).
Recruitment / selection of participants	Eligible patients entered a 6-week run-in phase during which any oral antidiabetic drugs other than metformin was stopped, patients were switched to iGlar (if they had previously been receiving another basal insulin), and the daily dose of iGlar was titrated and/or stabilized for all patients. At the end of the run-in phase, patients who had an HbA1c level of 7–10% (53–86 mmol/mol), a mean fasting self-measured plasma glucose (SMPG) of ≤140 mg/dL (7.8 mmol/L), iGlar daily dose of 20–50 units (inclusive), calcitonin of ≤20 pg/mL (5.9 pmol/L), and amylase and/or lipase levels ,3 times the upper limit of normal were randomized in a 1:1 ratio stratified by HbA1c value (<8%, ≥8% [<64, ≥64 mmol/mol]) at week –

	1 and metformin use at screening (yes/no) to receive once-daily open-label treatment with iGlarLixi or iGlar for 30 weeks.
Intervention(s)	Insulin glargine + lixisenatide (iGlarLixi) administered subcutaneously once daily
Cointervention	Metformin Patients were on insulin +/- at least two other oral antidiabetic drugs at screening but entered a 6-week run-in period where all oral antidiabetic drugs were stopped other than metformin.
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear Not an inclusion/exclusion criteria and no information in baseline characteristics.
Strata 2: People with atherosclerotic cardiovascular disease	Not stated/unclear Not an inclusion/exclusion criteria and no information in baseline characteristics.
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear Not an inclusion/exclusion criteria and no information in baseline characteristics.
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	Not stated/unclear
Subgroup 1: People with moderate or severe frailty	Not stated/unclear
Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear

Subgroup 3: People with non-alcoholic fatty liver disease	Not stated/unclear
Subgroup 4: People with obesity	Mixed population
Subgroup 5: eGFR category at baseline	Not stated/unclear
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Comparator	Insulin glargine administered subcutaneously once daily
Number of participants	N=736
Duration of follow-up	30 weeks
Method of analysis	Modified ITT

19.2. Study arms

19.2.1. Insulin glargine + lixisenatide (iGlarLix) once daily (N = 367)

Administered subcutaneously

19.2.2. Insulin glargine once daily (N = 369)

Administered subcutaneously

19.3. Characteristics

19.3.1. Arm-level characteristics

Characteristic	Insulin glargine + lixisenatide (iGlarLix) once daily (N = 367)	Insulin glargine once daily (N = 369)
% Male No of events	n = 165 ; % = 45	n = 179 ; % = 48.5
Mean age (SD) Mean (SD)	59.6 (9.4)	60.3 (8.7)
White No of events	n = 338 ; % = 92	n = 340 ; % = 92
Black No of events	n = 18 ; % = 5	n = 22 ; % = 6
Other No of events	n = 11 ; % = 3	n = 7 ; % = 2
Total hispanic No of events	n = 66 ; % = 18	n = 66 ; % = 18
Total non-hispanic No of events	n = 301 ; % = 82	n = 303 ; % = 82
Presence of frailty Nominal	NR	NR
Time since type 2 diabetes diagnosed (years) Mean (SD)	12 (6.6)	12.1 (6.9)
People with significant cognitive impairment Nominal	NR	NR
People with a learning disability Nominal	NR	NR
Metformin No of events	n = 169 ; % = 46	n = 192 ; % = 52
Sulfonylurea	n = 15 ; % = 4	n = 15 ; % = 4

Characteristic	Insulin glargine + lixisenatide (iGlarLix) once daily (N = 367)	Insulin glargine once daily (N = 369)
No of events		
DPP4-inhibitors No of events	n = 4 ; % = 1	n = 4 ; % = 1
Metformin + Sulfonylurea No of events	n = 136 ; % = 37	n = 118 ; % = 32
Metformin + DPP4 inhibitor No of events	n = 18 ; % = 5	n = 20 ; % = 5
Metformin + glinide No of events	n = 4 ; % = 1	n = 4 ; % = 1
None No of events	n = 18 ; % = 5	n = 20 ; % = 5

20. Arturi, 2017

Bibliographic Reference	Arturi, F.; Succurro, E.; Miceli, S.; Cloro, C.; Ruffo, M.; Maio, R.; Perticone, M.; Sesti, G.; Perticone, F.; Liraglutide improves cardiac function in patients with type 2 diabetes and chronic heart failure; Endocrine; 2017; vol. 57 (no. 3); 464-473

20.1. Study details

Secondary publication of another included study- see primary study for details	Not applicable
Other publications associated with this study included in review	Not applicable
Trial name / registration number	Not reported
Study type	Randomised controlled trial (RCT)
Study location	Italy
Study setting	Single-centre trial. No further details about setting reported
Study dates	Not reported
Sources of funding	No funding from any specific grant from any funding agency in the public, commercial, or not-for profit sector.
Inclusion criteria	• Patients aged 45 to 75 years with type 2 diabetes • BMI ≤ kg/m2 • HbA1c 7.0 to 10% • treated with metformin and/or sulfonylurea • history of previous acute myocardial infarction • New York Heart Association (NYHA) class II/ III and/or LVEF ≤ 45 %
Exclusion criteria	Patients who • had CHF due to or associated with uncorrected thyroid disease

	• had clinically significant active cardiovascular disease, • had conventional myocardial revascularization procedure within 30 days prior to enrolment • had hospitalization for acute heart failure in the last 60 days • had previous treatment with agonists of the GLP-1 (including liraglutide, exenatide, and lixisenatide) or DPP-4 inhibitors in the last 3 months • had uncontrolled hypertension treated/untreated (defined as systolic blood pressure greater than or equal to 160 mmHg and/or diastolic blood pressure greater than or equal to 100 mmHg) • had history of chronic pancreatitis • had history of any malignant disease • had history of alcohol or drug abuse • had liver or kidney failure • used any drug which could interfere with glucose metabolism, including systemic corticosteroids • had known or suspected hypersensitivity to trial products or related products.
Recruitment / selection of participants	No details reported
Intervention(s)	**Group 1 - 1.8 mg liraglutide (Novo Nordisk)** Starting dose was 0.6 mg and was increased every week to 1.2 mg and then to 1.8 mg. **Group 2 - 100 mg sitagliptin (Merck & Co)** Underwent standard therapy before beginning dose of 100 mg sitagliptin at week 2. **Group 3 - glargine insulin (SanofAventis)** Starting dose was 10 IU, and dosage was titrated weekly according to treat to target protocol with a target fasting plasma glucose of less than or equal to 100 mg/dl (less than or equal to 5.6 mmol/l).
Cointervention	• Metformin and/or sulfonylurea • Standard therapy for CHF was continued at pre-study dosages
Strata 1: People with type 2 diabetes	People with heart failure Inclusion criteria history of post-ischemic chronic heart failure (New York Heart Association (NYHA) class II/ III and/or LVEF ≤45 %)

mellitus and heart failure	
Strata 2: People with atherosclerotic cardiovascular disease	People with atherosclerotic cardiovascular diseases Inclusion criteria history of previous acute myocardial infarction
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear Excluded history of kidney failure. Otherwise, CKD not an inclusion or exclusion. No information in baseline characteristics.
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	Not stated/unclear Excluded patients with clinically significant active cardiovascular disease, however, report did not report a QRISK2 score or explicitly mention cardiovascular risk.
Subgroup 1: People with moderate or severe frailty	Not stated/unclear
Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear
Subgroup 3: People with non-alcoholic fatty liver disease	Not stated/unclear
Subgroup 4: People with obesity	Not stated/unclear
Subgroup 5: eGFR category at baseline	Not stated/unclear
Subgroup 6: Albuminuria	Not stated/unclear

category at baseline	
Population subgroups	Patients with type 2 diabetes and chronic heart failure
Comparator	Multi-arm trial
Number of participants	32 participants
Duration of follow-up	6, 12, 26 and 52 weeks after randomization
Indirectness	Directly applicable
Method of analysis	Not stated/unclear
Additional comments	• ANOVA with post hoc Bonferroni correction for multiple comparisons was used to compare differences of continuous variables between groups. • Within each group, a paired Student's t-test was used to compare mean values at baseline and at 52-week follow-up.

20.2. Study arms

20.2.1. Liraglutide (N = 10)

20.2.2. Sitagliptin (N = 10)

20.2.3. Glargine (N = 12)

20.3. Characteristics

20.3.1. Arm-level characteristics

Characteristic	Liraglutide (N = 10)	Sitagliptin (N = 10)	Glargine (N = 12)
% Male Sample size	n = 7 ; % = 70	n = 6 ; % = 60	n = 9 ; % = 75

Characteristic	Liraglutide (N = 10)	Sitagliptin (N = 10)	Glargine (N = 12)
Mean age (SD) Mean (SD)	59.5 (9)	60.5 (10)	60 (8)
Caucasian Sample size	n = 10 ; % = 100	n = 10 ; % = 100	n = 12 ; % = 100
HbA1c (%) Mean (SD)	8.2 (1)	8.3 (0.9)	7.9 (0.8)
Blood pressure (mmHg) Systolic blood pressure Mean (SD)	132.5 (9)	135 (7)	130 (11)
Heart rate (Beat/min) Mean (SD)	66 (8)	62 (11)	71 (10)
BMI (kg/m²) Mean (SD)	33.2 (2)	30.9 (2.8)	30.8 (6)
Cholesterol and lipid levels (mg/dL) Total cholesterol Mean (SD)	237 (17)	228 (9)	222 (12)
Blood pressure (mmHg) Diastolic blood pressure Mean (SD)	72 (6)	70 (10)	74 (8)
Cholesterol and lipid levels (mg/dL) HDL-cholesterol Mean (SD)	43.7 (15)	40.5 (12)	40 (6)
Cholesterol and lipid levels (mg/dL) LDL-cholesterol Mean (SD)	84 (22)	73 (18)	83 (31)

21. Aschner, 2012

Bibliographic Reference	Aschner, P.; Chan, J.; Owens, D. R.; Picard, S.; Wang, E.; Dain, M. P.; Pilorget, V.; Echtay, A.; Fonseca, V.; Insulin glargine versus sitagliptin in insulin-naive patients with type 2 diabetes mellitus uncontrolled on metformin (EASIE): a multicentre, randomised open-label trial; Lancet; 2012; vol. 379 (no. 9833); 2262-9

21.1. Study details

Trial name / registration number	EASIE trial. NCT00751114
Study type	Randomised controlled trial (RCT)
Study location	Multicentre, 17 countries
Study setting	NR
Study dates	Nov 12, 2008, to July 28, 2011
Sources of funding	Sanofi
Inclusion criteria	Aged 35–70 years (inclusive); diagnosed with type 2 diabetes for at least 6 months; metformin-treated; HbA1c of 7% or greater and less than 11%; body mass index (BMI) between 25 kg/m² and 45 kg/m² (inclusive); willing to take structured self-monitored blood glucose measurements and complete a monitoring diary.
Exclusion criteria	Had been treated with oral glucose-lowering drugs other than metformin within the past 3 months; had received combination treatment with metformin plus a sulphonylurea in the past year; had previous treatment with glucagon-like peptide-1 agonists or DPP-4 inhibitors; fasting plasma glucose of 15·4 mmol/L or more; impaired renal function (serum creatinine ≥133 μmol/L in men or ≥124 μmol/L in women) or hepatic function (greater than three times the upper limit of the normal range for alanine aminotransferase or aspartate aminotransferase); any disorder (present or expected) that the investigator felt would compromise the patient's safety or restrict the patient's successful participation in the study.
Recruitment / selection of participants	NR
Intervention(s)	Sitagliptin
Cointervention	All on metformin at recruitment and throughout

Strata 1: People with type 2 diabetes mellitus and heart failure	People without heart failure Not an exclusion criteria. Baseline characteristics show that only 1% had heart failure.
Strata 2: People with atherosclerotic cardiovascular disease	Not stated/unclear Excluded any disorder (present or expected) that the investigator felt would compromise the patient's safety or restrict the patient's successful participation in the study, CVD not exclusion criteria. Baseline characteristics give breakdown of specific CVD but overlap unclear.
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear Excluded impaired renal function (serum creatinine ≥133 µmol/L in men or ≥124 µmol/L in women). Also excluded any disorder (present or expected) that the investigator felt would compromise the patient's safety or restrict the patient's successful participation in the study. Otherwise CKD not specified. No information in baseline characteristics on CKD diagnosis.
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	Not stated/unclear
Subgroup 1: People with moderate or severe frailty	Not stated/unclear
Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear
Subgroup 3: People with non-alcoholic fatty liver disease	Not stated/unclear
Subgroup 4: People with obesity	Not stated/unclear

Subgroup 5: eGFR category at baseline	Not stated/unclear
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Population subgroups	
Comparator	Insulin glargine
Number of participants	515
Duration of follow-up	24 weeks treatment period
Indirectness	None
Method of analysis	ACA
Additional comments	Efficacy analysis included all randomly assigned participants who had received at least one dose of study drug and had at least one on-treatment assessment of any primary or secondary efficacy variable. All participants who were randomly assigned to treatment groups and who were treated were included in the safety population for analysis. For the primary endpoint, we undertook ANCOVA with the change from baseline in HbA1c as the dependent variable, treatment group as fi xed eff ect, and baseline HbA1c value as covariate.

21.2. Study arms

21.2.1. Sitagliptin (N = 265)

100mg daily, oral dose, taken in the morning either with or without food and no changes in dose were allowed during the trial

21.2.2. Insulin glargine (N = 250)

Titrated from an initial subcutaneous dose of 0·2 units per kg bodyweight to attain fasting plasma glucose of 4·0–5·5 mmol/L. Injected at dinner or bedtime using a prefilled SoloSTAR pen (sanofi -aventis, Frankfurt, Germany). The dose was either decreased by two units if fasting plasma glucose concentration was less than 4·0 mmol/L with or without symptomatic hypoglycaemia, increased by two units if the concentration was 5·6–7·7 mmol/L, and increased by four units if the concentration

was greater than 7·7 mmol/L. Participants monitored fasting plasma glucose daily and generally used the middle of the past three values to undertake the titration twice a week.

21.3. Characteristics

21.3.1. Arm-level characteristics

Characteristic	Sitagliptin (N = 265)	Insulin glargine (N = 250)
% Male Sample size	n = 132 ; % = 52	n = 114 ; % = 50
Mean age (SD) Mean (SD)	53.3 (8.7)	53.9 (8.9)
Ethnicity Sample size	n = NR ; % = NR	n = NR ; % = NR
Comorbidities Sample size	n = NA ; % = NA	n = NA ; % = NA
Any late diabetes complication Sample size	n = 67 ; % = 26	n = 65 ; % = 29
Myocardial infarction Sample size	n = 16 ; % = 6	n = 11 ; % = 5
Angina Pectoris Sample size	n = 11 ; % = 4	n = 10 ; % = 4
Coronary artery disease Sample size	n = 20 ; % = 8	n = 26 ; % = 11
Heart failure Sample size	n = 0 ; % = 0	n = 4 ; % = 2
Stroke Sample size	n = 3 ; % = 1	n = 5 ; % = 2
Transient ischaemic attack Sample size	n = 2 ; % = 1	n = 2 ; % = 1
Peripheral vascular disease	n = 8 ; % = 3	n = 4 ; % = 2

Characteristic	Sitagliptin (N = 265)	Insulin glargine (N = 250)
Sample size		
Diabetic neuropathy Sample size	n = 28 ; % = 11	n = 24 ; % = 11
Diabetic nephropathy Sample size	n = 7 ; % = 3	n = 11 ; % = 5
Diabetic retinopathy Sample size	n = 9 ; % = 4	n = 12 ; % = 5
Presence of frailty Sample size	n = NR ; % = NR	n = NR ; % = NR
Time since type 2 diabetes diagnosed (years) Median (IQR)	4.8 (1.9 to 8.2)	3.9 (1.9 to 8.2)
Cardiovascular risk factors Sample size	n = NR ; % = NR	n = NR ; % = NR
Smoking status Sample size	n = NR ; % = NR	n = NR ; % = NR
Alcohol consumption Mean (SD)	NR (NR)	NR (NR)
Presence of severe mental illness Sample size	n = NR ; % = NR	n = NR ; % = NR
People with significant cognitive impairment Sample size	n = NR ; % = NR	n = NR ; % = NR
People with a learning disability Sample size	n = NR ; % = NR	n = NR ; % = NR
Number of people with obesity Sample size	n = NR ; % = NR	n = NR ; % = NR
Other antidiabetic medication used Sample size	n = NA ; % = NA	n = NA ; % = NA
Metformin	n = 253 ; % = 100	n = 227 ; % = 100

Characteristic	Sitagliptin (N = 265)	Insulin glargine (N = 250)
Sample size		
Alpha glucosidase inhibitors Sample size	n = 0 ; % = 0	n = 1 ; % = 0.4
Fast-acting insulin or insulin analogues Sample size	n = 0 ; % = 0	n = 1 ; % = 0.4
Blood pressure-lowering medication used Sample size	n = NA ; % = NA	n = NA ; % = NA
Beta blocker Sample size	n = 47 ; % = 19	n = 52 ; % = 23
Calcium channel blocker Sample size	n = 39 ; % = 15	n = 33 ; % = 15
Statins/lipid-lowering medication used Sample size	n = 114 ; % = 45	n = 111 ; % = 49
Other treatment being received Sample size	n = NA ; % = NA	n = NA ; % = NA
Any concomitant treatment (other than OADs) Sample size	n = 217 ; % = 86	n = 198 ; % = 87
Diuretic agents Sample size	n = 35 ; % = 14	n = 41 ; % = 18
Agents acting on renin-angiotensin system Sample size	n = 134 ; % = 53	n = 131 ; % = 58
Anti-thrombotic agents Sample size	n = 90 ; % = 36	n = 75 ; % = 33

Baseline characteristics given for patients included in the efficacy analysis: Sitagliptin n=253; Insulin n=227

22. Attaran, 2023

Bibliographic Reference	Attaran, Fereshte; Emami, Sepideh; Sohrabi, Masoudreza; Malek, Mojtaba; Ajdarkosh, Hossein; Khoonsari, Mahmoodreza; Ismail-Beigi, Faramarz; Khamseh, Mohammad E; Effect of Empagliflozin and Pioglitazone on left ventricular function in patients with type two diabetes and nonalcoholic fatty liver disease without established cardiovascular disease: a randomized single-blind clinical trial.; BMC gastroenterology; 2023; vol. 23 (no. 1); 327

22.1. Study details

Secondary publication of another included study- see primary study for details	None
Other publications associated with this study included in review	No
Trial name / registration number	IRCT20190122042450N3 (Iranian Registry of Clinical Trials)
Study type	Randomised controlled trial (RCT) Single-blind, active-controlled, parallel-group RCT
Study location	Iran
Study setting	Outpatient
Study dates	Not reported
Sources of funding	Supported by the Iran University of Medical Sciences No. IR.IUMS.REC.1398.1408. Medication provided by Abidi Pharmaceutical company
Inclusion criteria	• Aged 20-80 years • Type 2 diabetes diagnosis • HbA1c >7% and <10.5% • Controlled attenuation parameter ≥302 dB/m • On established anti-diabetic therapy for at least 6 months before enrolment

	• Without established atherosclerotic cardiovascular disease (documented history of, at screening, at least one of: acute myocardial infarction, ischemic stroke, peripheral artery disease, coronary revascularization, and hospitalisation for heart failure.
Exclusion criteria	• EF<50% • Current use of SGLT2 inhibitors, GLP-1 RAs, thiazolidinediones, tamoxifen, amiodarone, non-steroidal anti-inflammatory drugs (NSAIDs), vitamin C, vitamin E, selenium, and antioxidants • Pregnancy or breastfeeding • Uncontrolled hypothyroidism or hyperthyroidism • Acute viral hepatitis or autoimmune hepatitis • eGFR<45 ml/min/1.73 m2 • Active cancer • Clinical signs of cirrhosis • Alcohol consumption >20 g daily (females) or >30 g daily (males) for at least 2 consecutive months over past 5 years
Recruitment / selection of participants	Eligible participants entered 3-wk run-in period and were screened using standard medical history, biochemical tests, liver elastography and echocardiography. All participants asked to follow standard ADA lifestyle modification recs. Participants block randomised 1:1 using computer. Intervention medications sealed sequentially and numbered according to allocation sequence (generated and kept by independent staff). Care provided blinded to intervention. Anti-hyperglycaemic treatment changed during trial in line with ADA 2019 recommendations.
Intervention(s)	• Pioglitazone 30 mg daily Oral pioglitazone 30 mg daily for 24 weeks in addition to metformin. No changes to dose were allowed.
Cointervention	• Metformin • Statin All participants continued to receive metformin for duration of trial. All participants not receiving statins at enrolment started moderate-intensity statin according to ADA diabetes recs.
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear
Strata 2: People with atherosclerotic cardiovascular disease	People without atherosclerotic cardiovascular diseases Exclusion criteria: documented previous history (at least 6-mo before enrolment) of at least one of: acute myocardial infarction, ischemic stroke, peripheral artery disease, coronary revascularization, and hospitalization for heart failure.

Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	Not stated/unclear
Subgroup 1: People with moderate or severe frailty	Not stated/unclear
Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear
Subgroup 3: People with non-alcoholic fatty liver disease	People with non-alcoholic fatty liver disease
Subgroup 4: People with obesity	Not stated/unclear
Subgroup 5: eGFR category at baseline	eGFR ≥30mL/min/1.73m2 Exclusion criteria: eGR<45 mL/min/1.73 m2
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Comparator	• Empagliflozin 10 mg daily Oral empagliflozin 10 mg daily for 24 weeks, in addition to metformin. No dose changes were permitted.
Number of participants	N=73 randomised (N=70 completers)

Duration of follow-up	24 weeks
Indirectness	None
Method of analysis	ITT ITT analysis for all outcomes, missing data strategy not reported

22.2. Study arms

22.2.1. Pioglitazone 30 mg daily (N = 36)

Oral pioglitazone 30 mg daily for 24 weeks, in addition to background metformin.

22.2.2. Empagliflozin 10 mg daily (N = 37)

Oral empagliflozin 30 mg for 24 weeks, in addition to background metformin.

22.3. Characteristics

22.3.1. Arm-level characteristics

Characteristic	Pioglitazone 30 mg daily (N = 36)	Empagliflozin 10 mg daily (N = 37)
% Male Sample size	n = 21 ; % = 41.7	n = 20 ; % = 46
Mean age (SD) (years) Mean (SD)	52 (7)	52 (7)
Ethnicity Nominal	NR	NR
Comorbidities Nominal	NR	NR
Presence of frailty Nominal	NR	NR
Time since type 2 diabetes diagnosed (years) Mean (SD)	7.9 (5.3)	8 (6.1)

Characteristic	Pioglitazone 30 mg daily (N = 36)	Empagliflozin 10 mg daily (N = 37)
Cardiovascular risk factors Nominal	NR	NR
Smoking status Nominal	NR	NR
Alcohol consumption Nominal	NR	NR
Presence of severe mental illness Nominal	NR	NR
People with significant cognitive impairment Nominal	NR	NR
People with a learning disability Nominal	NR	NR
Number of people with obesity Nominal	NR	NR
Other antidiabetic medication used Concurrent treatment at baseline; Data for this characteristic is for N=35 in both arms. Sample size	n = NA ; % = NA	n = NA ; % = NA
Metformin Sample size	n = 35 ; % = 100	n = 35 ; % = 100
DPP-4 inhibitor Sample size	n = 19 ; % = 54.3	n = 17 ; % = 48.6
Sulphonylurea Sample size	n = 19 ; % = 54.3	n = 17 ; % = 48.6
Insulin Sample size	n = 5 ; % = 14.3	n = 5 ; % = 14.3
Blood pressure-lowering medication used Sample size	n = NA ; % = NA	n = NA ; % = NA
ACE inhibitors	n = 1 ; % = 2.9	n = 1 ; % = 2.9

Characteristic	Pioglitazone 30 mg daily (N = 36)	Empagliflozin 10 mg daily (N = 37)
Sample size		
Angiotensin II receptor antagonists Sample size	n = 12 ; % = 35.3	n = 12 ; % = 35.3
Beta-blockers Sample size	n = 6 ; % = 17.7	n = 3 ; % = 8.8
Calcium channel blockers Sample size	n = 1 ; % = 2.9	n = 3 ; % = 8.6
Statins/lipid-lowering medication used Concurrent statin treatment at baseline; Data for this characteristic is for N=35 in both arms. Sample size	n = 35 ; % = 100	n = 35 ; % = 100
Other treatment being received Diuretic use at baseline Sample size	n = 1 ; % = 2.9	n = 1 ; % = 2.9

23. Avilés-Santa, 1999

Bibliographic Reference	Avilés-Santa, L.; Sinding, J.; Raskin, P.; Effects of metformin in patients with poorly controlled, insulin-treated type 2 diabetes mellitus. A randomized, double-blind, placebo-controlled trial; Ann Intern Med; 1999; vol. 131 (no. 3); 182-8

23.1. Study details

Study location	Texas, US
Study setting	Outpatient diabetes clinic at a university medical centre
Study dates	NR
Sources of funding	Partly by Bristol-Myers Squibb
Inclusion criteria	Type 2 diabetes diagnosed after 30 years of age and treated for at least 2 years with at least 50 units of insulin per day; age at enrolment younger than 70 years; hemoglobin A1c level greater than or equal to 8.0%.
Exclusion criteria	Pregnant women; women trying to become pregnant; patients with a serum creatinine concentration greater than 132.6 mmol/L (1.5 mg/dL) or hepatic enzyme levels greater than twice the upper limit of normal; and patients with medical conditions that could promote lactic acidosis, such as renal or hepatic disease, congestive heart failure, or chronic obstructive pulmonary disease.
Intervention(s)	Metformin titrated up to maximum 2500mg/d. The mean metformin dosage was 4.2 tablets (2100 mg) per day, and the mean placebo dosage was 3.8 tablets per day.
Cointervention	Current insulin therapy continued. The insulin dose was decreased if the fasting plasma glucose concentrations were consistently equal to or less than 5.55 mmol/L (100 mg/dL) or if the patient reported symptomatic or asymptomatic hypoglycemia (blood glucose concentrations less than or equal to 2.78 mmol/L [50 mg/dL]). All changes in insulin dose were made by study personnel. Dietary counselling was offered to every patient at screening and at subsequent visits as needed. General guidelines regarding portion sizes from all food groups were given without calculated caloric plans. Changes in daily caloric intake were assessed through review of a 3-day food record at baseline and at the end of the study. Patients were encouraged to maintain baseline levels of physical activity throughout the study.
Strata 1: People with type 2 diabetes	People without heart failure Excluded people with congestive heart failure

mellitus and heart failure	
Strata 2: People with atherosclerotic cardiovascular disease	Not stated/unclear Not an inclusion/exclusion criteria. No information in baseline characteristics.
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	People without chronic kidney disease Excluded people with renal disease
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	Not stated/unclear
Subgroup 1: People with moderate or severe frailty	Not stated/unclear
Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear
Subgroup 3: People with non-alcoholic fatty liver disease	Not stated/unclear
Subgroup 4: People with obesity	Not stated/unclear
Subgroup 5: eGFR category at baseline	Not stated/unclear
Subgroup 6: Albuminuria	Not stated/unclear

category at baseline	
Comparator	Placebo
Number of participants	54 randomised but of these 43 met the entrance criteria and completed the study
Duration of follow-up	24 weeks
Additional comments	The efficacy analysis included all patients who had a baseline hemoglobin A1c measurement and at least one postbaseline hemoglobin A1c measurement.

23.2. Study arms

23.2.1. Metformin (N = 21)

Metformin (2500mg/d) administered as 500-mg tablets. During first 2 weeks patients ingested one tablet of the study drug with breakfast and one tablet with supper. At week 2, dosage increased to 1500 mg/d (one tablet three times daily with meals). At week 4, dosage increased to 2000mg/d, and the insulin dose was adjusted accordingly. At week 8, dosage increased to the maximum dose of 2500 mg/d (five tablets per day). Dose was adjusted when necessary to prevent adverse effects. People continued to receive the maximum tolerated dosage from weeks 8 to 24. Patients were on insulin at recruitment to the study and study interventions were taken in addition to current insulin therapy.

23.2.2. Placebo (N = 22)

Matched placebo tablets. During first 2 weeks patients ingested one tablet with breakfast and one tablet with supper. At week 2, increased to one tablet three times daily with meals. At week 4, one tablet four times daily, and the insulin dose was adjusted accordingly. At week 8, increased to five tablets per day. Dose was adjusted when necessary to prevent adverse effects. People continued to receive the maximum tolerated dosage from weeks 8 to 24. Patients were on insulin at recruitment to the study and study interventions were taken in addition to current insulin therapy.

23.3. Characteristics

23.3.1. Arm-level characteristics

Characteristic	Metformin (N = 21)	Placebo (N = 22)
% Male Sample size	n = 6 ; % = 28.6	n = 10 ; % = 45.5
Mean age (SD) Mean (SD)	53.1 (9.4)	54.6 (7.8)
Non-hispanic white Sample size	n = 10 ; % = 47.6	n = 15 ; % = 68.2
African-American Sample size	n = 5 ; % = 23.8	n = 4 ; % = 18.2
Hispanics Sample size	n = 5 ; % = 23.8	n = 3 ; % = 13.6
Other Sample size	n = 1 ; % = 4.8	n = 0 ; % = 0
Comorbidities Sample size	n = NR ; % = NR	n = NR ; % = NR
Presence of frailty Sample size	n = NR ; % = NR	n = NR ; % = NR
Time since type 2 diabetes diagnosed Mean (SD)	9.2 (6.4)	10.1 (4.7)
HbA1c (%) Mean (SD)	9 (1.4)	9.1 (1.5)
Cardiovascular risk factors Sample size	n = NR ; % = NR	n = NR ; % = NR
Blood pressure Mean (SD)	NR (NR)	NR (NR)
Heart rate Mean (SD)	NR (NR)	NR (NR)
Smoking status	n = NR ; % = NR	n = NR ; % = NR

Characteristic	Metformin (N = 21)	Placebo (N = 22)
Sample size		
Alcohol consumption Mean (SD)	NR (NR)	NR (NR)
Presence of severe mental illness Sample size	n = NR ; % = NR	n = NR ; % = NR
People with significant cognitive impairment Sample size	n = NR ; % = NR	n = NR ; % = NR
People with a learning disability Sample size	n = NR ; % = NR	n = NR ; % = NR
Weight Mean (SD)	103.9 (25.2)	106.6 (23.2)
BMI Mean (SD)	NR (NR)	NR (NR)
Number of people with obesity Sample size	n = NR ; % = NR	n = NR ; % = NR
Cholesterol and lipid levels (mg/dL) Mean (SD)	NR (NR)	NR (NR)
Total cholesterol (mg/dL) Mean (SD)	215.1 (40.5)	218.6 (58.4)
HDL (mg/dL) Mean (SD)	35.8 (10.1)	33.7 (10.1)
LDL (mg/dL) Mean (SD)	121.8 (31.7)	136.4 (41.2)
Triglycerides (mg/dL) Mean (SD)	202.3 (114.2)	222.5 (191.3)
Albumin creatinine ratio Mean (SD)	NR (NR)	NR (NR)
eGFR mL/min/1.73m2 Mean (SD)	NR (NR)	NR (NR)

Characteristic	Metformin (N = 21)	Placebo (N = 22)
Other antidiabetic medication used Mean (SD)	NR (NR)	NR (NR)
Duration of insulin therapy (years) Mean (SD)	5.4 (5)	3.5 (4.2)
Blood pressure-lowering medication used Sample size	n = NR ; % = NR	n = NR ; % = NR
Statins/lipid-lowering medication used Sample size	n = NR ; % = NR	n = NR ; % = NR

24. Ba, 2017

Bibliographic Reference	Ba, J.; Han, P.; Yuan, G.; Mo, Z.; Pan, C.; Wu, F.; Xu, L.; Hanson, M. E.; Engel, S. S.; Shankar, R. R.; Randomized trial assessing the safety and efficacy of sitagliptin in Chinese patients with type 2 diabetes mellitus inadequately controlled on sulfonylurea alone or combined with metformin; J Diabetes; 2017; vol. 9; 667-676

24.1. Study details

Trial name / registration number	NCT01590771; Merck Protocol PN253
Study type	Randomised controlled trial (RCT)
Study location	Multicentre; 32 centres in China
Study setting	NR
Study dates	From July 2012 to June 2014
Sources of funding	Merck & Co. Inc. FW, LX, MEH, SSE, and RRS are all current or former employees of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co. Inc. (Kenilworth, NJ, USA) and may own stock or stock options in the company. FW also reports employment at Novartis Pharmaceuticals.
Inclusion criteria	Men and women aged ≥18 to ≤79 years, with T2DM, on stable doses of gliclazide (modified release ≥60 mg/day or immediate release ≥160 mg/day) or glimepiride (≥3 mg/day), with or without metformin (≥1500 mg/day) for at least 10 weeks, and HbA1c ≥7.5 % and ≤11.0 %
Exclusion criteria	Had a history of type 1 diabetes or intolerance, hypersensitivity or contraindication to sitagliptin, gliclazide or glimepiride, or metformin. Patients with active liver disease (including chronic active hepatitis B or C, primary biliary cirrhosis, or symptomatic gallbladder disease), new or worsening signs of coronary heart disease within 3 months (including acute coronary syndrome, coronary artery intervention, stroke or transient ischemic neurological disorder), severe peripheral vascular disease, or exclusionary laboratory values. Women with a positive pregnancy test; those with reproductive potential were required to remain abstinent or use an acceptable method of birth control throughout the study period.
Recruitment / selection of participants	NR
Intervention(s)	Sitagliptin
Cointervention	All on sulphonylureas at recruitment and throughout (some also on metformin). Open-label gliclazide, glimepiride, and metformin were administered as recommended in the China drug label through the end of

	the double-blind treatment period and doses were kept constant unless down-titration was required for hypoglycemia.
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear Not an inclusion/exclusion criteria. No information in baseline characteristics.
Strata 2: People with atherosclerotic cardiovascular disease	Not stated/unclear Excluded "new or worsening signs of coronary heart disease within 3 months (including acute coronary syndrome, coronary artery intervention, stroke or transient ischemic neurological disorder)", unclear prior to this. No information in baseline characteristics.
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear Not an inclusion/exclusion criteria. No information in baseline characteristics.
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	Not stated/unclear
Subgroup 1: People with moderate or severe frailty	Not stated/unclear
Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear
Subgroup 3: People with non-alcoholic fatty liver disease	Not stated/unclear
Subgroup 4: People with obesity	Not stated/unclear

Subgroup 5: eGFR category at baseline	Not stated/unclear
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Population subgroups	Paper reports subgroup of background metformin / no metformin
Comparator	Placebo
Number of participants	498
Duration of follow-up	24 weeks
Indirectness	None
Method of analysis	Other
Additional comments	The change from baseline in HbA1c at Week 24 was analysed using an ANCOVA model controlled for treatment, metformin stratum (on or not on metformin), and baseline HbA1c value,. Analysis included all patients who received one or more doses of study therapy, except for the following: 1. For analyses that used the analysis of covariance (ANCOVA) method, the FAS excluded patients who did not have one or more observations for the analysis endpoint subsequent to the first dose of study treatment, or who did not have baseline data for the analysis endpoint.

24.2. Study arms

24.2.1. Sitagliptin (N = 249)

Sitagliptin 100 mg supplied as an oral tablet once daily. In addition to ongoing open-label therapy with stable doses of gliclazide or glimepiride with or without metformin. 2-week single-blind placebo run-in period.

24.2.2. Placebo (N = 249)

Matching placebo was supplied as an oral tablet; once daily. In addition to ongoing open-label therapy with stable doses of gliclazide or glimepiride with or without metformin. 2-week single-blind placebo run-in period.

24.3. Characteristics

24.3.1. Study-level characteristics

Characteristic	Study (N = 498)
Comorbidities Sample size	n = NR ; % = NR
Presence of frailty Sample size	n = NR ; % = NR
Cardiovascular risk factors Sample size	n = NR ; % = NR
Blood pressure Sample size	n = NR ; % = NR
Heart rate Sample size	n = NR ; % = NR
Smoking status Sample size	n = NR ; % = NR
Alcohol consumption Sample size	n = NR ; % = NR
Presence of severe mental illness Sample size	n = NR ; % = NR
People with significant cognitive impairment Sample size	n = NR ; % = NR
People with a learning disability Sample size	n = NR ; % = NR
Number of people with obesity Sample size	n = NR ; % = NR
Cholesterol and lipid levels Sample size	n = NR ; % = NR

Characteristic	Study (N = 498)
Albumin creatinine ratio Mean (SD)	NR (NR)
eGFR mL/min/1.73m2 Mean (SD)	NR (NR)
Blood pressure-lowering medication used Sample size	n = NR ; % = NR
Statins/lipid-lowering medication used Sample size	n = NR ; % = NR
Other treatment being received Sample size	n = NR ; % = NR

24.3.2. Arm-level characteristics

Characteristic	Sitagliptin (N = 249)	Placebo (N = 249)
% Male Sample size	n = 117 ; % = 47	n = 132 ; % = 53
Mean age (SD) Mean (SD)	57.5 (9.5)	56.5 (9.3)
Chinese Sample size	n = 249 ; % = 100	n = 249 ; % = 100
Time since type 2 diabetes diagnosed Mean (SD)	7.1 (5.4)	6.9 (4.9)
Sulphonylurea alone Sample size	n = 134 ; % = 53.8	n = 134 ; % = 53.8
Sulphonylurea + metformin Sample size	n = 115 ; % = 46.2	n = 115 ; % = 46.2

25. Babar, 2021

Bibliographic Reference	Babar, M.; Hussain, M.; Ahmad, M.; Akhtar, L.; Comparison Of Efficacy And Safety Profile Of Empagliflozin As A Combination Therapy In Obese Type 2 Diabetic Patients; Journal of Ayub Medical College, Abbottabad: JAMC; 2021; vol. 33 (no. 2); 188-191

25.1. Study details

Trial name / registration number	NR
Study location	Pakistan
Study setting	Medical college/hospital
Study dates	Jan 2018 - Feb 2019
Sources of funding	NR
Inclusion criteria	Obese type 2 diabetic patients with inadequate glycaemic control (i.e, HbA1c≥7%) with metformin and sitagliptin. Age ≥18 years; T2D; BMI ≥35 Kg/m2; taking a stable dose of metformin (1500mg/d) and sitagliptin (100mg/d) for ≥12 weeks with inadequate glycaemic control (i.e, HbA1c≥7%).
Exclusion criteria	Serum creatinine ≥1.3 mg/dl, having symptoms of poor diabetes control such as polydipsia or polyuria; coronary heart disease.
Recruitment / selection of participants	NR
Intervention(s)	Empagliflozin
Cointervention	On metformin (1500mg/d) and Sitagliptin (100mg/d) at recruitment and continued throughout study. Rescue medications were advised if patients fasting blood sugar (FBS) were >140 mg/dL. In case of hypoglycaemia the dose of rescue medications reduced or totally discontinued.
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear Not an inclusion/exclusion criteria. No information in baseline characteristics.

Strata 2: People with atherosclerotic cardiovascular disease	Not stated/unclear Excluded "coronary heart disease", unclear if only current or history, and other types of atherosclerotic CV disease unclear. No information in baseline characteristics.
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear Not an inclusion/exclusion criteria. No information in baseline characteristics.
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	People at higher risk of developing cardiovascular disease Only recruited people with obesity so likely to all be at higher risk due to the presence of at least 1 risk factor.
Subgroup 1: People with moderate or severe frailty	Not stated/unclear
Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear
Subgroup 3: People with non-alcoholic fatty liver disease	Not stated/unclear
Subgroup 4: People with obesity	People with obesity Only recruited people with obesity (BMI ≥35 Kg/m2)
Subgroup 5: eGFR category at baseline	Not stated/unclear
Subgroup 6: Albuminuria category at baseline	Not stated/unclear

Comparator	Placebo
Number of participants	240
Duration of follow-up	24 weeks
Indirectness	None
Additional comments	

25.2. Study arms

25.2.1. Empagliflozin (N = 120)

20mg (empagliflozin 10mg twice a day). On Metformin 1500mg/d (750mg twice a day) and Sitagliptin 100mg/d (50mg twice a day) at recruitment and continued throughout study.

25.2.2. Placebo (N = 120)

Placebo. On Metformin 1500mg/d (750mg twice a day) and Sitagliptin 100mg/d (50mg twice a day) at recruitment and continued throughout study.

25.3. Characteristics

25.3.1. Study-level characteristics

Characteristic	**Study (N = 240)**
Asian Sample size	n = 240 ; % = 100
Presence of frailty Sample size	n = NR ; % = NR
Blood pressure Mean (SD)	NR (NR)
Heart rate Mean (SD)	NR (NR)

Characteristic	Study (N = 240)
Smoking status Sample size	n = NR ; % = NR
Alcohol consumption Mean (SD)	NR (NR)
Presence of severe mental illness Sample size	n = NR ; % = NR
People with significant cognitive impairment Sample size	n = NR ; % = NR
People with a learning disability Sample size	n = NR ; % = NR
BMI Mean (SD)	NR (NR)
Number of people with obesity Sample size	n = 240 ; % = 100
Cholesterol and lipid levels Mean (SD)	NR (NR)
Albumin creatinine ratio Mean (SD)	NR (NR)
eGFR mL/min/1.73m2 Mean (SD)	NR (NR)
Metformin + Sitagliptin Sample size	n = 240 ; % = 100
Blood pressure-lowering medication used Sample size	n = NR ; % = NR
Statins/lipid-lowering medication used Sample size	n = NR ; % = NR
Other treatment being received Sample size	n = NR ; % = NR

25.3.2. Arm-level characteristics

Characteristic	Empagliflozin (N = 120)	Placebo (N = 120)
% Male Sample size	n = 110 ; % = 91.7	n = 106 ; % = 88.3
Mean age (SD) Mean (SD)	53.4 (9.1)	52.53 (8.6)
≤1 years Sample size	n = 8 ; % = 6.6	n = 12 ; % = 10
>1 to 5 years Sample size	n = 48 ; % = 40	n = 38 ; % = 31.6
>5 to 10 years Sample size	n = 44 ; % = 36.7	n = 46 ; % = 38.3
More than 10 years Sample size	n = 20 ; % = 16.7	n = 24 ; % = 20

26. Bae, 2021

Bibliographic Reference	Bae, J.; Huh, J. H.; Lee, M.; Lee, Y. H.; Lee, B. W.; Glycaemic control with add-on thiazolidinedione or a sodium-glucose co-transporter-2 inhibitor in patients with type 2 diabetes after the failure of an oral triple antidiabetic regimen: A 24-week, randomized controlled trial; Diabetes, Obesity & Metabolism; 2021; vol. 23 (no. 2); 609-618

26.1. Study details

Secondary publication of another included study- see primary study for details	NA
Other publications associated with this study included in review	NA
Trial name / registration number	NCT04013581
Study type	Randomised controlled trial (RCT)
Study location	Multicentre, South Korea
Study setting	NR
Study dates	NR
Sources of funding	Supported by research grants from Yuhan Corporation (Pharmaceutical company)
Inclusion criteria	1. 19 ≤ age ≤ 80, male or female 2. Type 2 diabetes patients who have taken triple combination therapy of oral antidiabetic agents as followed : Metformin (≥1000 mg/day), Sulfonylurea (Glimepiride ≥ 4 mg/day or Gliclazide ≥ 60 mg/day), DPP-4 inhibitor (Full dose) for over 12 weeks 3. At screening, 7% < HbA1c ≤ 10%

	4. Patients who refused insulin therapy. 5. Subjects who understood the contents of the clinical trial and are cooperative in the trial progress, and are considered to be able to participate until the end of the trial.
Exclusion criteria	1. Type 1 diabetes, gestational diabetes, and other types of diabetes than type 2 diabetes. 2. Patients who have the history of allergy of hypersensitivity for the medication of the clinical trial. 3. Patients who have the history of taking TZD or SGLT-2i within a year prior to screening visit or have the history of discontinuation of them due to severe side effects. 4. Patients who have the history of acute or chronic metabolic acidosis including diabetic ketoacidosis (with or without coma), or any kinds of ketosis within 12 weeks prior to screening visit. 5. Patients who have genetic metabolic diseases, such as galactose intolerance, Lapp lactase deficiency, or glucose-galactose malabsorption 6. Patients who have the history of taking steroids for more than 2 weeks, within 8 weeks prior to screening visit. 7. Patients who have the history of malignancy within 5 years prior to screening visit (In case of bladder cancer, subjects will be excluded regardless of the time of diagnosis) 8. Patients who have the history of coronary artery bypass surgery or percutaneous coronary intervention, or suffered from heart failure (New York Heart Association (NYHA) functional classification III, IV) 9. Patients who have the history of uncontrolled arrhythmia, unstable angina, myocardial infarction, stroke, transient ischemic attacks, and cerebral vascular disease within 24 weeks prior to the screening date. 10. Patients of chronic renal failure, chronic kidney disease stage 3~5 (estimated glomerular filtration rate calculated via CKD-EPI <60 mL/min/1.73m2) or on dialysis therapy. 11. Elevated liver enzymes (AST, ALT, ALP ≥ 2.5*ULN or Total bilirubin ≥ 2.5*ULN) or Child-Pugh class B or C (for the patients of liver cirrhosis) 12. Subjects who are pregnant or lactating 13. Perioperative patients, patients with severe infections or severe trauma 14. Patients with unexamined gross hematuria 15. Any other subjects who is determined to be ineligible for the clinical trials by researchers."

Recruitment / selection of participants	T2D patients with inadequate glycaemic control (7% < HbA1c ≤ 10%) despite sufficient triple combination therapy including metformin (≥1000 mg/day), sulphonylurea (glimepiride ≥4 mg/day or gliclazide ≥60 mg/day) and DPP-4 inhibitor (standard doses of DPP-4 inhibitor tablets) for more than 12 weeks. Because these patients were candidates for injection therapy in a general clinical setting, clinicians initially advised them to start insulin therapy. Only patients who declined insulin therapy were included in this study.
Intervention(s)	Empagliflozin
Cointervention	Triple combination therapy including metformin (≥1000 mg/day), sulphonylurea (glimepiride ≥4 mg/day or gliclazide ≥60 mg/day) and DPP-4 inhibitor (standard doses of DPP-4 inhibitor tablets) for more than 12 weeks
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear Excluded New York Heart Association (NYHA) functional classification III, IV, otherwise unclear. No information in baseline characteristics.
Strata 2: People with atherosclerotic cardiovascular disease	Not stated/unclear Excluded "history of uncontrolled arrhythmia, unstable angina, myocardial infarction, stroke, transient ischemic attacks, and cerebral vascular disease within 24 weeks prior to the screening date", prior to this unclear. No information in baseline characteristics.
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear Excluded "chronic renal failure, chronic kidney disease stage 3~5 (estimated glomerular filtration rate calculated via CKD-EPI <60 mL/min/1.73m2) or on dialysis therapy", other stages of CKD unclear. No information in baseline characteristics.
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	Not stated/unclear
Subgroup 1: People with moderate or severe frailty	Not stated/unclear

Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear
Subgroup 3: People with non-alcoholic fatty liver disease	Not stated/unclear
Subgroup 4: People with obesity	Mixed population Around 63% had obesity at baseline
Subgroup 5: eGFR category at baseline	eGFR ≥30mL/min/1.73m2 Excluded eGFR <60mL/min/1.73m2, so all must have had eGFR more than 30
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Population subgroups	NA
Comparator	Pioglitazone
Number of participants	119
Duration of follow-up	24 weeks
Indirectness	None
Method of analysis	ACA
Additional comments	Overall analysis was performed on the full analysis set, which included all randomized patients treated with quadruple therapy who had baseline measurements. Data obtained after discontinuation of the clinical trial or loss to follow-up were set as missing.

26.2. Study arms

26.2.1. Empagliflozin (N = 60)

Empagliflozin 10 mg once daily as an add-on therapy to their pre-existing triple therapy for the first 12 weeks. Patients with adequate glycaemic control (HbA1c ≤7.0%) at 12 weeks maintained the quadruple therapy for an additional 12 weeks, for a total of 24 weeks. If patients did not reach the target HbA1c level (>7.0%) at 12 weeks then the dose of empagliflozin was increased from 10 to 25 mg once daily.

26.2.2. Pioglitazone (N = 59)

Pioglitazone 15 mg once daily as an add-on therapy to their pre-existing triple therapy for the first 12 weeks. Patients with adequate glycaemic control (HbA1c ≤7.0%) at 12 weeks maintained the quadruple therapy for an additional 12 weeks, for a total of 24 weeks. If patients did not reach the target HbA1c level (>7.0%) at 12 weeks then the dose of pioglitazone was increased from 15 to 30 mg once daily.

26.3. Characteristics

26.3.1. Arm-level characteristics

Characteristic	Empagliflozin (N = 60)	Pioglitazone (N = 59)
% Male Sample size	n = 36 ; % = 60	n = 33 ; % = 55.9
Mean age (SD) Mean (SD)	61.83 (10.15)	61.88 (9.7)
Ethnicity Nominal	NR	NR
Comorbidities Sample size	n = NR ; % = NR	n = NR ; % = NR
Presence of frailty Sample size	n = NR ; % = NR	n = NR ; % = NR
Time since type 2 diabetes diagnosed Mean (SD)	13.86 (7.29)	13.92 (8.42)
Cardiovascular risk factors Sample size	n = NA ; % = NA	n = NA ; % = NA
History of hypertension Sample size	n = 40 ; % = 66.7	n = 42 ; % = 71.2

Characteristic	Empagliflozin (N = 60)	Pioglitazone (N = 59)
History of dyslipidaemia Sample size	n = 47 ; % = 78.3	n = 52 ; % = 88.1
Smoking status Sample size	n = NR ; % = NR	n = NR ; % = NR
Alcohol consumption Sample size	n = NR ; % = NR	n = NR ; % = NR
Presence of severe mental illness Sample size	n = NR ; % = NR	n = NR ; % = NR
People with significant cognitive impairment Sample size	n = NR ; % = NR	n = NR ; % = NR
People with a learning disability Sample size	n = NR ; % = NR	n = NR ; % = NR
Number of people with obesity Sample size	n = 38 ; % = 63.3	n = 37 ; % = 62.7
eGFR mL/min/1.73m2 Mean (SD)	86.88 (13.46)	86.32 (12.28)
Other antidiabetic medication used Sample size	n = 60 ; % = 100	n = 59 ; % = 100
Metformin + sulphonylurea + Linagliptin Sample size	n = 29 ; % = 48.3	n = 29 ; % = 49.2
Metformin + sulphonylurea + Vildagliptin Sample size	n = 10 ; % = 16.7	n = 10 ; % = 16.9
Metformin + sulphonylurea + Sitagliptin Sample size	n = 4 ; % = 6.7	n = 2 ; % = 3.4
Metformin + sulphonylurea + Other DPP4-I Sample size	n = 17 ; % = 28.3	n = 18 ; % = 30.5
Blood pressure-lowering medication used Sample size	n = 37 ; % = 61.7	n = 38 ; % = 64.4

Characteristic	Empagliflozin (N = 60)	Pioglitazone (N = 59)
Statins/lipid-lowering medication used Sample size	n = 36 ; % = 60	n = 41 ; % = 71.2
Other treatment being received Sample size	n = NR ; % = NR	n = NR ; % = NR

27. Bailey, 2010

Bibliographic Reference	Bailey, C. J.; Gross, J. L.; Pieters, A.; Bastien, A.; List, J. F.; 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; vol. 375 (no. 9733); 2223-33

27.1. Study details

Other publications associated with this study included in review	Bailey CJ, Gross JL, Hennicken D, Iqbal N, Mansfield TA, List JF. Dapagliflozin add-on to metformin in type 2 diabetes inadequately controlled with metformin: a randomized, double-blind, placebo-controlled 102-week trial. BMC Med. 2013 Feb 20;11:43. doi: 10.1186/1741-7015-11-43.
Trial name / registration number	NCT00528879
Study type	Randomised controlled trial (RCT)
Study location	80 sites across USA, Canada, Argentina, Mexico and Brazil
Study setting	No additional information
Study dates	Patients were accrued from 18 September 2007 to 10 April 2008, the 24 week data cutoff date was 4th November 2008 and the extension period continued for 78 weeks
Sources of funding	Bristol-Myers Squibb and AstraZeneca. The authors also declare numerous grants and honoraria from multiple pharmaceutical companies
Inclusion criteria	Patients were eligible for inclusion if they were aged 18–77 years, had type 2 diabetes, HbA1c 7–10%, C-peptide concentration ≥0·34 nmol/L, BMI ≤45 kg/m², and were taking a stable dose of metformin (≥1500 mg per day) for at least 8 weeks before enrolment.
Exclusion criteria	Exclusion criteria included serum creatinine ≥133 µmol/L for men or ≥124 µmol/L for women; urine albumin/creatinine ratio >203·4 mg/mmol; aspartate aminotransferase or alanine aminotransferase >3X the upper limit of normal; creatine kinase >3X 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); clinically significant renal, hepatic, haematological, oncological, endocrine, psychiatric, or rheumatic disease; recent cardiovascular event (within 6 months) or New York Heart Association class III or IV congestive heart failure; and systolic blood pressure ≥180 mm Hg or diastolic blood pressure ≥110 mm Hg.

Recruitment / selection of participants	No additional information
Intervention(s)	Patients received once-daily dapagliflozin 2·5 mg, 5 mg, or 10 mg given orally before the morning meal for 102 weeks
Cointervention	Concomitant therapy: Participants continued on metformin (≥1,500 mg) throughout study period. Glycaemic measurements were assessed from week 4 to week 24 to determine the need for open-label pioglitazone or acarbose as a rescue medication for fasting plasma glucose concentrations more than 15·0 mmol/L (week 4–8), 13·3 mmol/L (week 8–12), or 11·1 mmol/L (week 12–24).
Strata 1: People with type 2 diabetes mellitus and heart failure	People without heart failure
Strata 2: People with atherosclerotic cardiovascular disease	Not stated/unclear Excluded recent cardiovascular event (within 6 months), unclear prior to this. No information in baseline characteristics.
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear Excluded clinically significant renal disease; unclear if all CKD. No information in baseline characteristics.
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	Not stated/unclear
Subgroup 1: People with moderate or severe frailty	Not stated/unclear
Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear

Subgroup 3: People with non-alcoholic fatty liver disease	Not stated/unclear
Subgroup 4: People with obesity	Not stated/unclear
Subgroup 5: eGFR category at baseline	Not stated/unclear
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Comparator	Placebo, received once-daily given orally before the morning meal for 102 weeks
Number of participants	546
Duration of follow-up	102 weeks
Indirectness	No additional information
Method of analysis	ITT
Additional comments	The primary efficacy dataset consisted of all randomised patients who received at least one dose of double-blind study medication and who had both a baseline and at least one post-baseline measurement. For rescued patients, measurements obtained after initiation of rescue medication were not included in the efficacy analysis, but were included in the safety analysis. Analyses of continuous outcomes were based on separate ANCOVA models with treatment group as an effect and the baseline value as a covariate, last observation carried forward. As part of the secondary analyses, the comparison of proportions of patients achieving a therapeutic glycaemic response was done with logistic regression based on established methodology, with adjustment for baseline. For the primary analysis (change from baseline in HbA1c percentage at week 24), comparisons between each dapagliflozin group and placebo group were done at α=0·019 applying Dunnett's adjustment. Only summary statistics were reported for safety.

	At week 102, longitudinal repeated measures analyses using observed data without any data imputation were used to determine the change in HbA1c, FPG, and total body weight from baseline over time; the model included the categorical fixed effects of treatment, week, and treatment-by-week interaction as well as the continuous fixed covariates of baseline measurement and baseline measurement-by-week interaction. Rescue was added as an additional categorical fixed effect in this mixed model when the analysis was performed on data regardless of rescue.

27.2. Study arms

27.2.1. Dapagliflozin 2.5mg (N = 137)

Patients received once-daily dapagliflozin 2·5 mg given orally before the morning meal for 24 weeks. Patients who completed 24 weeks of study were eligible for continuation into a long-term study for a total of 102 weeks. Prior to the randomisation process, participants underwent a 2-week, single-blind, lead-in period in which individuals received placebo for two weeks. Participants were also assigned open-label 500 mg metformin tablets throughout the study so that pre-study metformin dosing could continue. Glycaemic measurements were assessed from week 4 to week 24 to determine the need for open-label pioglitazone or acarbose as a rescue medication for fasting plasma glucose concentrations more than 15·0 mmol/L (week 4–8), 13·3 mmol/L (week 8–12), or 11·1 mmol/L (week 12–24). During lead-in and throughout the duration of the study, patients received diet and exercise counselling consistent with American Diabetes Association recommendations or similar local guidelines.

27.2.2. Dapagliflozin 5 mg (N = 137)

Patients received once-daily dapagliflozin 5 mg given orally before the morning meal for 24 weeks. Patients who completed 24 weeks of study were eligible for continuation into a long-term study for a total of 102 weeks. Prior to the randomisation process, participants underwent a 2-week, single-blind, lead-in period in which individuals received placebo for two weeks. Participants were also assigned open-label 500 mg metformin tablets throughout the study so that pre-study metformin dosing could continue. During lead-in and throughout the duration of the study, patients received diet and exercise counselling consistent with American Diabetes Association recommendations or similar local guidelines.

27.2.3. Dapagliflozin 10 mg (N = 135)

Patients received once-daily dapagliflozin 10 mg given orally before the morning meal for 24 weeks. Patients who completed 24 weeks of study were eligible for continuation into a long-term study for a total of 102 weeks. Prior to the randomisation process, participants underwent a 2-week, single-blind, lead-in period

in which individuals received placebo for two weeks. Participants were also assigned open-label 500 mg metformin tablets throughout the study so that pre-study metformin dosing could continue. During lead-in and throughout the duration of the study, patients received diet and exercise counselling consistent with American Diabetes Association recommendations or similar local guidelines.

27.2.4. Placebo (N = 137)

Patients received once-daily placebo given orally before the morning meal for 24 weeks. Patients who completed 24 weeks of study were eligible for continuation into a long-term study for a total of 102 weeks. Prior to the randomisation process, participants underwent a 2-week, single-blind, lead-in period in which individuals received placebo for two weeks. Participants were also assigned open-label 500 mg metformin tablets throughout the study so that pre-study metformin dosing could continue. During lead-in and throughout the duration of the study, patients received diet and exercise counselling consistent with American Diabetes Association recommendations or similar local guidelines.

27.3. Characteristics

27.3.1. Arm-level characteristics

Characteristic	Dapagliflozin 2.5mg (N = 137)	Dapagliflozin 5 mg (N = 137)	Dapagliflozin 10 mg (N = 135)	Placebo (N = 137)
% Male Sample size	n = 70 ; % = 51	n = 69 ; % = 50	n = 77 ; % = 57	n = 76 ; % = 55
Mean age (SD) (Years (mean, SD)) Mean (SD)	55 (9.3)	54.3 (9.4)	52.7 (9.9)	53.7 (10.3)
Ethnicity Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Time since type 2 diabetes diagnosed (Years (mean, SD)) Mean (SD)	6 (6.2)	6.4 (5.8)	61.1 (5.4)	5.8 (5.1)
Smoking status Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Alcohol consumption Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR

Characteristic	Dapagliflozin 2.5mg (N = 137)	Dapagliflozin 5 mg (N = 137)	Dapagliflozin 10 mg (N = 135)	Placebo (N = 137)
Presence of severe mental illness Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
People with significant cognitive impairment Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
People with a learning disability Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Number of people with obesity Mean (SD)	NR (NR)	NR (NR)	NR (NR)	NR (NR)
Other antidiabetic medication used Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
Metformin use Sample size	n = 137 ; % = 100	n = 137 ; % = 100	n = 135 ; % = 100	n = 137 ; % = 100
Blood pressure-lowering medication used Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Statins/lipid-lowering medication used Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR

28. Bailey, 2013

Bibliographic Reference	Bailey, Clifford J; Gross, Jorge L; Hennicken, Delphine; Iqbal, Nayyar; Mansfield, Traci A; List, James F; Dapagliflozin add-on to metformin in type 2 diabetes inadequately controlled with metformin: a randomized, double-blind, placebo-controlled 102-week trial.; BMC medicine; 2013; vol. 11; 43

28.1. Study details

Secondary publication of another included study- see primary study for details	Parent study 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 Jun 26;375(9733):2223-33. doi: 10.1016/S0140-6736(10)60407-2.

29. Bailey, 2016

Bibliographic Reference	Bailey, T. S.; Takacs, R.; Tinahones, F. J.; Rao, P. V.; Tsoukas, G. M.; Thomsen, A. B.; Kaltoft, M. S.; Maislos, M.; Efficacy and safety of switching from sitagliptin to liraglutide in subjects with type 2 diabetes (LIRA-SWITCH): a randomized, double-blind, double-dummy, active-controlled 26-week trial; Diabetes Obes Metab; 2016; vol. 18 (no. 12); 1191-1198

29.1. Study details

Secondary publication of another included study- see primary study for details	No additional information.
Other publications associated with this study included in review	No additional information.
Trial name / registration number	NCT01907854. LIRA-SWITCH.
Study type	Randomised controlled trial (RCT)
Study location	Multicentre trial.
Study setting	Outpatient follow-up.
Study dates	December 2013 to June 2015.
Sources of funding	Funded by Novo Nordisk.
Inclusion criteria	Type 2 diabetes; age at least 18 years; HbA1c 7.5-9.5%; BMI at least 20kg/m2; previous treatment with stable doses of sitagliptin (100mg/day) and metformin (at least 1500mg/day or maximum tolerated dose at least 1000mg/day) for at least 90 days.
Exclusion criteria	Treatment with glucose-lowering agents other than those stated in the inclusion criteria in a period of 90 days prior to screening; women likely to become pregnant or to breast-feed; history of pancreatitis; screening calcitonin at least 50 ng/L; personal or family history of medullary thyroid carcinoma or multiple endocrine syndrome type 2; diagnosed with

	malignant neoplasm in the previous 5 years; impaired liver or renal function; significant cardiovascular event within 90 days prior to screening; heart failure (NYHA class IV); systolic blood pressure at least 180 mmHg and or diastolic blood pressure at least 100 mmHg.
Recruitment / selection of participants	No additional information.
Intervention(s)	Liraglutide N=202 Liraglutide 0.6mg/day subcutaneously with weekly dose escalations of 0.6mg/day until the maintenance dose of 1.8mg/day was reached plus once-daily sitagliptin placebo tablets.
Cointervention	Concomitant therapy: Everyone received sitagliptin 100 mg/day and metformin (at least 1500mg/day or maximum tolerated dose of at least 1000 mg/day for at least 90 days before the main phase of the trial before. The metformin was continued during the main phase of the trial.
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear Excluded "heart failure (New York Heart Association class IV)", unclear if excluded all heart failure. No information in baseline characteristics.
Strata 2: People with atherosclerotic cardiovascular disease	Not stated/unclear Excluded "significant cardiovascular event within 90 days prior to screening", unclear prior to this. No information in baseline characteristics.
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	People without chronic kidney disease Excluded "impaired renal function".
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	Not stated/unclear
Subgroup 1: People with moderate or severe frailty	Not stated/unclear

Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear
Subgroup 3: People with non-alcoholic fatty liver disease	Not stated/unclear
Subgroup 4: People with obesity	Not stated/unclear
Subgroup 5: eGFR category at baseline	Not stated/unclear
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Population subgroups	No additional information.
Comparator	Sitagliptin N=204 Sitagliptin 100mg/day orally plus liraglutide placebo (subcutaneously) mirroring the dose escalation of the active liraglutide arm.
Number of participants	406
Duration of follow-up	26 weeks
Indirectness	No additional information.
Method of analysis	ACA
Additional comments	No additional information.

29.2. Study arms

29.2.1. Liraglutide (N = 202)

Liraglutide 0.6mg/day subcutaneously with weekly dose escalations of 0.6mg/day until the maintenance dose of 1.8mg/day was reached plus once-daily sitagliptin placebo tablets. Concomitant therapy: Everyone received sitagliptin 100 mg/day and metformin (at least 1500mg/day or maximum tolerated dose of at least 1000 mg/day for at least 90 days before the main phase of the trial before. The metformin was continued during the main phase of the trial.

29.2.2. Sitagliptin (N = 204)

Sitagliptin 100mg/day orally plus liraglutide placebo (subcutaneously) mirroring the dose escalation of the active liraglutide arm. Concomitant therapy: Everyone received sitagliptin 100 mg/day and metformin (at least 1500mg/day or maximum tolerated dose of at least 1000 mg/day for at least 90 days before the main phase of the trial before. The metformin was continued during the main phase of the trial.

29.3. Characteristics

29.3.1. Arm-level characteristics

Characteristic	Liraglutide (N = 202)	Sitagliptin (N = 204)
% Male Sample size	n = 117 ; % = 58	n = 124 ; % = 61
Mean age (SD) (years) Mean (SD)	56.3 (10.6)	56.5 (9.7)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA
Comorbidities Sample size	n = NA ; % = NA	n = NA ; % = NA
Presence of frailty Sample size	n = NA ; % = NA	n = NA ; % = NA
Time since type 2 diabetes diagnosed (years) Mean (SD)	7.9 (5.7)	7.6 (6.2)
Cardiovascular risk factors Sample size	n = NR ; % = NR	n = NR ; % = NR
Smoking status	n = NR ; % = NR	n = NR ; % = NR

Characteristic	Liraglutide (N = 202)	Sitagliptin (N = 204)
Sample size		
Alcohol consumption Sample size	n = NR ; % = NR	n = NR ; % = NR
Presence of severe mental illness Sample size	n = NR ; % = NR	n = NR ; % = NR
People with significant cognitive impairment Sample size	n = NR ; % = NR	n = NR ; % = NR
People with a learning disability Sample size	n = NR ; % = NR	n = NR ; % = NR
Number of people with obesity Sample size	n = NR ; % = NR	n = NR ; % = NR
Other antidiabetic medication used Sample size	n = NR ; % = NR	n = NR ; % = NR
Blood pressure-lowering medication used Sample size	n = NR ; % = NR	n = NR ; % = NR
Statins/lipid-lowering medication used Sample size	n = NR ; % = NR	n = NR ; % = NR
Other treatment being received Sample size	n = NR ; % = NR	n = NR ; % = NR

30. Bain, 2019

Bibliographic Reference	Bain, Stephen C; Mosenzon, Ofri; Arechavaleta, Rosario; Bogdanski, Pawel; Comlekci, Abdurrahman; Consoli, Agostino; Deerochanawong, Chaicharn; Dungan, Kathleen; Faingold, Maria C; Farkouh, Michael E; Franco, Denise R; Gram, Jeppe; Guja, Cristian; Joshi, Pankaj; Malek, Rachid; Merino-Torres, Juan F; Nauck, Michael A; Pedersen, Sue D; Sheu, Wayne H-H; Silver, Robert J; Tack, Cees J; Tandon, Nikhil; Jeppesen, Ole K; Strange, Mette; Thomsen, Mette; Husain, Mansoor; Cardiovascular safety of oral semaglutide in patients with type 2 diabetes: Rationale, design and patient baseline characteristics for the PIONEER 6 trial.; Diabetes, obesity & metabolism; 2019; vol. 21 (no. 3); 499-508

30.1. Study details

Secondary publication of another included study- see primary study for details	PIONEER-6 trial. Husain, Mansoor, Birkenfeld Andreas, L, Donsmark, Morten et al. (2019) Oral Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes. The New England journal of medicine 381(9): 841-851
Other publications associated with this study included in review	NA
Trial name / registration number	PIONEER6- ClinicalTrials.gov number, NCT02692716

31. Bajaj, 2014

Bibliographic Reference	Bajaj, M.; Gilman, R.; Patel, S.; Kempthorne-Rawson, J.; Lewis-D'Agostino, D.; Woerle, H. J.; Linagliptin improved glycaemic control without weight gain or hypoglycaemia in patients with Type 2 diabetes inadequately controlled by a combination of metformin and pioglitazone: A 24-week randomized, double-blind study; Diabet Med; 2014; vol. 31 (no. 12); 1505-1514

31.1. Study details

Trial name / registration number	NCT 00996658
Study location	52 trial centres in Asia, Europe and North America
Study setting	NR
Study dates	NR
Sources of funding	Boehringer Ingelheim. The funders participated in the study design, data collection and data analysis.
Inclusion criteria	Type 2 diabetes mellitus inadequately controlled by a combination of metformin and pioglitazone. Male and female patients with Type 2 diabetes, who were aged ≥ 18 and < 80 years, with a BMI ≤ 45 kg/m2 and HbA1c ≥ 58 mmol/mol (7.5%) and ≤ 86 mmol/mol (10.0%) despite receiving a dose of ≥ 1500 mg/day of metformin (or the maximum tolerated dose, if lower) and a dose of 45 mg/day of pioglitazone (or the maximum clinically acceptable dose in the investigators' opinion). Both doses of metformin and pioglitazone were to be unchanged for 12 weeks before informed consent.
Exclusion criteria	Uncontrolled hyperglycaemia with a glucose level > 13.3 mmol/l (240 mg/dl) after an overnight fast or > 22.2 mmol/l (400 mg/dl) in a randomly performed measurement during placebo run-in and confirmed by a second measurement on a different day; myocardial infarction, stroke or transient ischaemic attack within 3 months before informed consent; impaired hepatic function; or previous gastric bypass surgery; known hypersensitivity or allergy to the investigational products; misuse of metformin or pioglitazone; alcohol or drug abuse within 3 months before informed consent that would interfere with trial participation; treatment with systemic steroids at the time of informed consent or change in dosage of thyroid hormones within 6 weeks before informed consent; and participation in another trial with an investigational drug within 2 months before informed consent; treated with rosiglitazone, DPP-4 inhibitors, GLP-1 analogues, insulin or anti-obesity drugs within 3 months of enrolment; pre-menopausal women who were nursing, pregnant or not practising an acceptable method of birth control.

Recruitment / selection of participants	NR
Intervention(s)	Linagliptin
Cointervention	Metformin + pioglitazone (on at recruitment and throughout). Rescue medication was permitted during the randomized period if a patient met the following criteria: a confirmed fasting plasma glucose level of > 11.1 mmol/l or a glucose level > 22.2 mmol/l in a randomly performed measurement during the first 12 weeks; or a confirmed fasting plasma glucose level of > 11.1 mmol/l or a glucose level > 22.2 mmol/l in a randomly performed measurement during weeks 13–24. These results were confirmed by two measurements on separate days.
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear Not an inclusion/exclusion criteria. No information in baseline characteristics.
Strata 2: People with atherosclerotic cardiovascular disease	Not stated/unclear Excluded "myocardial infarction, stroke or transient ischaemic attack within 3 months before informed consent", unclear prior to this. No information in baseline characteristics.
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear Not an inclusion/exclusion criteria. eGFR categories given in baseline characteristics but not CKD diagnosis.
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	Not stated/unclear
Subgroup 1: People with moderate or severe frailty	Not stated/unclear

Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear
Subgroup 3: People with non-alcoholic fatty liver disease	Not stated/unclear
Subgroup 4: People with obesity	Not stated/unclear
Subgroup 5: eGFR category at baseline	Not stated/unclear
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Comparator	Placebo
Number of participants	272
Duration of follow-up	24 weeks
Indirectness	None
Method of analysis	Other
Additional comments	The primary endpoint was evaluated using analysis of covariance (ANCOVA), with 'treatment' as a fixed classification effect, 'baseline HbA1c' as a linear covariate and 'centre' as a random effect. The analysis was conducted on the full analysis set, comprising all randomized participants who were treated with ≥ 1 dose of study medication, had a baseline HbA1c measurement and ≥ 1 on-treatment HbA1c measurement. Secondary endpoints were assessed in the full analysis set using an ANCOVA model

31.2. Study arms

31.2.1. Linagliptin (N = 183)

Linagliptin 5 mg orally once daily. As an add-on to metformin + pioglitazone (on at recruitment and throughout).

31.2.2. Placebo (N = 89)

Placebo. As an add-on to metformin + pioglitazone (on at recruitment and throughout).

31.3. Characteristics

31.3.1. Arm-level characteristics

Characteristic	Linagliptin (N = 183)	Placebo (N = 89)
% Male Sample size	n = 83 ; % = 45.4	n = 49 ; % = 55.1
Mean age (SD) Mean (SD)	53.1 (9.7)	55.2 (8.4)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA
American-Indian/Alaska Native Sample size	n = 0 ; % = 0	n = 1 ; % = 1.1
Asian Sample size	n = 125 ; % = 68.3	n = 62 ; % = 69.7
Black or African American Sample size	n = 9 ; % = 4.9	n = 2 ; % = 2.2
White Sample size	n = 49 ; % = 26.8	n = 24 ; % = 27
Comorbidities Sample size	n = NR ; % = NR	n = NR ; % = NR
Presence of frailty Sample size	n = NR ; % = NR	n = NR ; % = NR
Time since type 2 diabetes diagnosed Sample size	n = NA ; % = NA	n = NA ; % = NA

Characteristic	Linagliptin (N = 183)	Placebo (N = 89)
<1 year Sample size	n = 84 ; % = 46.9	n = 38 ; % = 42.7
>1 to 5 years Sample size	n = 73 ; % = 40.8	n = 45 ; % = 50.6
5+ years Sample size	n = 22 ; % = 12.3	n = 6 ; % = 6.7
Cardiovascular risk factors Sample size	n = NR ; % = NR	n = NR ; % = NR
Smoking status Sample size	n = NR ; % = NR	n = NR ; % = NR
Alcohol consumption Mean (SD)	NR (NR)	NR (NR)
Presence of severe mental illness Sample size	n = NR ; % = NR	n = NR ; % = NR
People with significant cognitive impairment Sample size	n = NR ; % = NR	n = NR ; % = NR
People with a learning disability Sample size	n = NR ; % = NR	n = NR ; % = NR
Number of people with obesity Sample size	n = NR ; % = NR	n = NR ; % = NR
Other antidiabetic medication used Sample size	n = NA ; % = NA	n = NA ; % = NA
Metformin + Pioglitazone Sample size	n = 183 ; % = 100	n = 89 ; % = 100
Blood pressure-lowering medication used Sample size	n = NR ; % = NR	n = NR ; % = NR
Statins/lipid-lowering medication used Sample size	n = NR ; % = NR	n = NR ; % = NR
Other treatment being received Sample size	n = NR ; % = NR	n = NR ; % = NR

32. Barnett, 2012

Bibliographic Reference	Barnett, A. H.; Charbonnel, B.; Donovan, M.; Fleming, D.; Chen, R.; Effect of saxagliptin as add-on therapy in patients with poorly controlled type 2 diabetes on insulin alone or insulin combined with metformin; Curr Med Res Opin; 2012; vol. 28 (no. 4); 513-23

32.1. Study details

Secondary publication of another included study- see primary study for details	Primary study
Other publications associated with this study included in review	Barnett AH, Charbonnel B, Li J, Donovan M, Fleming D, Iqbal N. Saxagliptin add-on therapy to insulin with or without metformin for type 2 diabetes mellitus: 52-week safety and efficacy. Clin Drug Investig. 2013 Oct;33(10):707-17. doi: 10.1007/s40261-013-0107-8.
Trial name / registration number	NCT00757588; CV181-057
Study type	Randomised controlled trial (RCT)
Study location	72 sites in 10 countries
Study dates	13 November 2008 to 8 November 2010
Sources of funding	Funding was provided by Bristol-Myers Squibb and AstraZeneca. Authors declare numerous grants and honoraria for multiple pharmaceutical companies.
Inclusion criteria	Men and women aged 18–78 years inclusive with inadequately controlled T2D (HbA1c ≥7.5% and ≤11%), on a stable dose of insulin (≥30 U/day and ≤150 U/day with ≤20% variation from patient's mean in total daily dose, alone or combined with a stable dose of metformin for ≥8 weeks before screening) were eligible. Patients also had to have a BMI of 45 kg/m2 and a fasting C-peptide level of ≥0.8 ng/mL (≥0.3 nmol/L). Permitted insulin types were intermediate acting, long acting, or pre-mixed, which could include short- or rapid-acting insulin as one component.
Exclusion criteria	Patients were excluded if they had symptoms of poorly controlled diabetes, including but not limited to; marked polyuria and polydipsia with >10% weight loss during the 3 months prior to screening, a history of diabetic ketoacidosis, or hyperosmolar nonketotic coma. Other major exclusion criteria included a major cardiovascular event within 6 months before

	screening; New York Heart Association class III/ IV congestive heart failure and/or known left ventricular ejection fraction <40%; serum creatinine ≥1.5 mg/dL (132.6 mmol/L) for men and ≥1.4 mg/dL (123.8 mmol/L) for women or calculated serum creatinine clearance 560 mL/min; history of unstable renal disease or hemoglobinopathies; alcohol or drug abuse within the year prior to screening; unstable, major psychiatric disorders; active liver disease; or clinically significant abnormalities on screening tests for hepatic or renal function, free T4, or anemia. Patients also were excluded if they received any antihyperglycemic therapy, other than insulin and metformin, for more than 3 consecutive days or 7 non-consecutive days during the 8 weeks before screening or were treated with potent systemic cytochrome P450 3A4 inducers. Those who were immunocompromised or had chronic or repeated intermittent corticosteroid use were ineligible.
Intervention(s)	Saxagliptin (n=304) Participants received 5mg Saxagliptin daily for 52 weeks
Cointervention	Concomitant therapy; Participants continued baseline line therapy throughout the study with insulin or insulin plus metformin
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear Excluded "New York Heart Association class III/ IV congestive heart failure and/or known left ventricular ejection fraction <40%", unclear if all heart failure excluded. No information in baseline characteristics.
Strata 2: People with atherosclerotic cardiovascular disease	Not stated/unclear
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	People without chronic kidney disease Excluded "history of unstable renal disease". Also excluded "clinically significant abnormalities on screening tests for renal function".
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	Not stated/unclear
Subgroup 1: People with moderate or severe frailty	Not stated/unclear

Subgroup 3: People with non-alcoholic fatty liver disease	Not stated/unclear
Subgroup 4: People with obesity	Not stated/unclear
Subgroup 5: eGFR category at baseline	Not stated/unclear
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Population subgroups	No additional information
Comparator	Placebo (n=151). Daily oral tablet for 52 weeks
Number of participants	455
Duration of follow-up	52 weeks
Indirectness	No additional information
Method of analysis	Other
Additional comments	Changes from baseline HbA1c, mean total daily insulin dose, body weight, and BMI at post-baseline visits were analysed using a repeated-measures model that contained terms for treatment group, baseline measurement, metformin use at baseline, time (weeks), and time by treatment group. Repeated-measures analysis also took into account missing data. In addition, analysis of covariance (ANCOVA) was performed on the continuous efficacy end points, using last observation carried forward (LOCF), with treatment group as an effect and baseline value and metformin use at baseline as covariates. ANCOVA with observed values was also used to describe the changes from baseline in HbA1c and mean total daily insulin dose. This analysis method differs from the primary analysis used for the 24-week phase (ANCOVA, including only data before rescue). Because insulin dosage was flexible after rescue in the initial 24-week phase and throughout the 28-week extension, the current efficacy and safety analyses were conducted without regard for changes in insulin dosage. Adjusted mean change from baseline HbA1c was compared between groups; this was performed as a post hoc analysis without formal control for type I error. The proportion of patients achieving HbA1c <7 %

	(LOCF) at selected visits was summarized for each treatment group using counts and percentages. The 95 % confidence intervals for the difference in proportions between treatment groups were calculated based on the Mantel–Haenszel method. Analyses carried out for each metformin use stratum included change in HbA1c from baseline to week 52, change in mean total daily dose of insulin from baseline to week 52, and proportion of patients achieving a therapeutic glycemic response of HbA1c <7 %. The incidence of AEs, including AEs of special interest was captured for all treated patients and summarized using proportions for all randomized and treated patients regardless of insulin dose. AEs were also summarized for each metformin use stratum.

32.2. Study arms

32.2.1. Saxagliptin (N = 304)

Saxagliptin 5 mg was administered once daily for 24 weeks. Prior to randomisation to intervention, all participants initially undertook a 4-week, single-blind, placebo, dietary and exercise lead-in period, during which baseline therapy was maintained and alongside a diet and exercise program and the use of a home glucose monitor and diary for recording glucose values and daily insulin doses. Participants were advised to keep insulin therapy as stable as possible. However, insulin could be down-titrated at the discretion of the investigator. A patient with poor glycemic control, based on a single, high FPG value (4240 mg/dL [413.3 mmol/L] at weeks 4 or 6;4220 mg/dL [412.2 mmol/L] at week 8; or 4200 mg/dL [411.1 mmol/L] at weeks 12, 16, or 20) was rescued. Additionally, a patient with mean total daily insulin dose exceeding the baseline dose by 20% was rescued. Each patient who was rescued had a rescue visit with a meal tolerance test to measure PPG and was subsequently allowed to change their dose and/or type of insulin, based on guidelines of the American Diabetes Association or country-specific guidelines. Changes in metformin dose or addition of other antihyperglycemic medications were prohibited. During the extension phase up to 52 weeks, participants continued to take the same blinded study medication assigned during the initial 24-week phase.

32.2.2. Placebo (N = 151)

Placebo was administered once daily for 24 weeks. Prior to randomisation to intervention, all participants initially undertook a 4-week, single-blind, placebo, dietary and exercise lead-in period, during which baseline therapy was maintained and alongside a diet and exercise program and the use of a home glucose monitor and diary for recording glucose values and daily insulin doses. Participants were advised to keep insulin therapy as stable as possible. However, insulin could be down-titrated at the discretion of the investigator. A patient with poor glycemic control, based on a single, high FPG value (4240 mg/dL [413.3 mmol/L] at weeks 4 or 6;4220 mg/dL [412.2 mmol/L] at week 8; or 4200 mg/dL [411.1 mmol/L] at weeks 12, 16, or 20) was rescued. Additionally, a patient with mean total daily insulin dose exceeding the baseline dose by 20% was rescued. Each patient who was rescued had a rescue visit with a meal tolerance test to measure PPG and was subsequently allowed to

change their dose and/or type of insulin, based on guidelines of the American Diabetes Association or country-specific guidelines. Changes in metformin dose or addition of other antihyperglycemic medications were prohibited. During the extension phase up to 52 weeks, participants continued to take the same blinded study medication assigned during the initial 24-week phase.

32.3. Characteristics

32.3.1. Arm-level characteristics

Characteristic	Saxagliptin (N = 304)	Placebo (N = 151)
% Male Sample size	n = 120 ; % = 40	n = 68 ; % = 45
Mean age (SD) (Years (mean, SD)) Mean (SD)	57.2 (9.43)	57.3 (9.27)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA
White Sample size	n = 237 ; % = 78	n = 118 ; % = 78
Asian Sample size	n = 40 ; % = 13	n = 19 ; % = 13
Black/African American Sample size	n = 13 ; % = 4	n = 9 ; % = 6
Other Sample size	n = 14 ; % = 5	n = 5 ; % = 3
Comorbidities Sample size	n = NA ; % = NA	n = NA ; % = NA
Presence of frailty Sample size	n = NR ; % = NR	n = NR ; % = NR
Time since type 2 diabetes diagnosed (Years (mean, SD)) Mean (SD)	11.8 (6.9)	12.2 (7.4)
Smoking status Sample size	n = NR ; % = NR	n = NR ; % = NR

Characteristic	Saxagliptin (N = 304)	Placebo (N = 151)
Alcohol consumption Sample size	n = NR ; % = NR	n = NR ; % = NR
Presence of severe mental illness Sample size	n = NR ; % = NR	n = NR ; % = NR
People with significant cognitive impairment Sample size	n = NR ; % = NR	n = NR ; % = NR
People with a learning disability Sample size	n = NR ; % = NR	n = NR ; % = NR
Number of people with obesity Sample size	n = NR ; % = NR	n = NR ; % = NR
Cholesterol and lipid levels Sample size	n = NR ; % = NR	n = NR ; % = NR
Other antidiabetic medication used Sample size	n = NA ; % = NA	n = NA ; % = NA
Insulin use Sample size	n = 304 ; % = 100	n = 151 ; % = 100
Metformin use Sample size	n = 209 ; % = 68.6	n = 105 ; % = 69.5
Blood pressure-lowering medication used Sample size	n = NR ; % = NR	n = NR ; % = NR
Statins/lipid-lowering medication used Sample size	n = NR ; % = NR	n = NR ; % = NR

33. Barnett, 2013

Bibliographic Reference	Barnett, A. H.; Huisman, H.; Jones, R.; Eynatten, M.; Patel, S.; Woerle, H. J.; Linagliptin for patients aged 70 years or older with type 2 diabetes inadequately controlled with common antidiabetes treatments: a randomised, double-blind, placebo-controlled trial; Lancet; 2013; vol. 382 (no. 9902); 1413-23

33.1. Study details

Secondary publication of another included study- see primary study for details	NA
Other publications associated with this study included in review	NA
Trial name / registration number	NCT01084005, and the European Clinical Trials database (EudractCT), number 2009–015255–25
Study type	Randomised controlled trial (RCT)
Study location	33 clinics in five countries
Study setting	"Clinic"
Study dates	March 10, 2010, to June 22, 2011
Sources of funding	Sponsored by Boehringer Ingelheim
Inclusion criteria	Type 2 diabetes; aged 70 years or older; had insufficient glycaemic control (HbA1c ≥7·0%), and had been receiving stable doses of metformin, sulfonylureas, or basal insulin, or combinations of these drugs, for at least 8 weeks.
Exclusion criteria	Fasting plasma glucose (FPG) greater than 13·3 mmol/L; impaired hepatic function (serum concentrations of alanine transaminase [ALT], aspartate transaminase [AST], or alkaline phosphatase [ALP] more than three times the upper limit of normal); myocardial infarction, stroke, or transient ischaemic attack within 3 months before the study; previous bariatric surgery; present treatment with rapid acting or premixed insulin or

	systemic steroids; treatment within the previous 3 months with a thiazolidinedione, α-glucosidase inhibitor, meglitinide, GLP1 analogue, DPP4 inhibitor, or anti-obesity drug
Recruitment / selection of participants	NR
Intervention(s)	Linagliptin
Cointervention	Metformin, sulfonylureas, or basal insulin, or combinations of these drugs
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear Not an inclusion/exclusion criteria. No information in baseline characteristics.
Strata 2: People with atherosclerotic cardiovascular disease	Not stated/unclear Excluded "myocardial infarction, stroke, or transient ischaemic attack within 3 months before the study", unclear prior to this. 87% had "macrovascular disease", however this could include "coronary artery disease, peripheral artery disease, cerebrovascular disease, and hypertension" - as this definition included hypertension, unable to determine the % of people with CV disease as per review protocol.
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear Not an inclusion/exclusion criteria. Number of people with renal impairment given by eGFR categories but not bey CKD diagnosis.
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	Not stated/unclear
Subgroup 1: People with moderate or severe frailty	Not stated/unclear
Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear

Subgroup 3: People with non-alcoholic fatty liver disease	Not stated/unclear
Subgroup 4: People with obesity	Not stated/unclear
Subgroup 5: eGFR category at baseline	eGFR ≥30mL/min/1.73m2
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Comparator	Placebo
Number of participants	241
Duration of follow-up	24 weeks
Indirectness	None
Method of analysis	ACA Modified ITT
Additional comments	The primary efficacy analysis, change in HbA1c from baseline to week 24, was done with the full analysis set (all randomised patients who received at least one dose of study medication, and who had a baseline and at least one on-treatment HbA1c measurement), using a last observation-carried-forward approach to impute missing data. Safety data were generally analysed descriptively for the treated set, which consisted of all randomised patients who received at least one dose of study drug.

33.2. Study arms

33.2.1. Linagliptin (N = 162)

Once-daily oral treatment with linagliptin 5 mg, in addition to their existing glucose-lowering treatment. All patients had a 2 week, open-label, placebo run-in period. Doses of background treatments were maintained for the first 12 weeks of randomised treatment, after which dose adjustments were permitted. Rescue medication for hyperglycaemia (confirmed glucose level: fasting >13·3 mmol/L in weeks 1–12, >11·1 mmol/L in weeks 13–24; or random test >22·2 mmol/L; two or

more measurements on different days, one done after an overnight fast) was permitted during randomised treatment.

33.2.2. Placebo (N = 79)

Once-daily placebo, in addition to their existing glucose-lowering treatment. All patients had a 2 week, open-label, placebo run-in period. Doses of background treatments were maintained for the first 12 weeks of randomised treatment, after which dose adjustments were permitted. Rescue medication for hyperglycaemia (confirmed glucose level: fasting >13·3 mmol/L in weeks 1–12, >11·1 mmol/L in weeks 13–24; or random test >22·2 mmol/L; two or more measurements on different days, one done after an overnight fast) was permitted during randomised treatment.

33.3. Characteristics

33.3.1. Arm-level characteristics

Characteristic	Linagliptin (N = 162)	Placebo (N = 79)
% Male Sample size	n = 116 ; % = 71.6	n = 49 ; % = 62
Mean age (SD) Mean (SD)	74.9 (4.4)	74.9 (4.2)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA
White Sample size	n = 157 ; % = 96.9	n = 76 ; % = 96.2
Asian Sample size	n = 3 ; % = 1.9	n = 2 ; % = 2.5
Black Sample size	n = 2 ; % = 1.2	n = 1 ; % = 1.3
Comorbidities Sample size	n = NR ; % = NR	n = NR ; % = NR
Presence of frailty Sample size	n = NR ; % = NR	n = NR ; % = NR
Time since type 2 diabetes diagnosed Sample size	n = NA ; % = NA	n = NA ; % = NA

Characteristic	Linagliptin (N = 162)	Placebo (N = 79)
<1 year Sample size	n = 3 ; % = 1.9	n = 0 ; % = 0
>1 to 5 years Sample size	n = 20 ; % = 12.5	n = 7 ; % = 9
>5 to 10 years Sample size	n = 48 ; % = 30	n = 29 ; % = 37.2
10 years Sample size	n = 89 ; % = 55.6	n = 42 ; % = 53.8
Cardiovascular risk factors Sample size	n = NR ; % = NR	n = NR ; % = NR
Smoking status Sample size	n = NR ; % = NR	n = NR ; % = NR
Alcohol consumption Mean (SD)	NR (NR)	NR (NR)
Presence of severe mental illness Sample size	n = NR ; % = NR	n = NR ; % = NR
People with significant cognitive impairment Sample size	n = NR ; % = NR	n = NR ; % = NR
People with a learning disability Sample size	n = NR ; % = NR	n = NR ; % = NR
Number of people with obesity Sample size	n = NR ; % = NR	n = NR ; % = NR
eGFR mL/min/1.73m2 Sample size	n = NA ; % = NA	n = NA ; % = NA
Normal (≥90 ml/min/1.73 m2) Sample size	n = 36 ; % = 22.2	n = 15 ; % = 19
Mild impairment (60 to <90) Sample size	n = 83 ; % = 51.2	n = 42 ; % = 53.2
Moderate impairment (30 to <60) Sample size	n = 41 ; % = 25.3	n = 21 ; % = 26.6

Characteristic	Linagliptin (N = 162)	Placebo (N = 79)
Severe impairment (<30) Sample size	n = 2 ; % = 1.2	n = 1 ; % = 1.3
Other antidiabetic medication used Sample size	n = NA ; % = NA	n = NA ; % = NA
Metformin Sample size	n = 133 ; % = 83.1	n = 69 ; % = 88.5
Sulfonylurea Sample size	n = 94 ; % = 58.8	n = 42 ; % = 55.1
Insulin Sample size	n = 35 ; % = 21.9	n = 15 ; % = 19.2
Meglitinide Sample size	n = 1 ; % = 0.6	n = 0 ; % = 0
Alpha glucosidase inhibitors Sample size	n = 1 ; % = 0.6	n = 0 ; % = 0
Blood pressure-lowering medication used Sample size	n = NR ; % = NR	n = NR ; % = NR
Statins/lipid-lowering medication used Sample size	n = NR ; % = NR	n = NR ; % = NR
Other treatment being received Sample size	n = NA ; % = NA	n = NA ; % = NA
Concomitant drugs (non-diabetes): 1 or more Sample size	n = 159 ; % = 98.1	n = 77 ; % = 97.5
Concomitant drugs (non-diabetes): 3 or more Sample size	n = 141 ; % = 87	n = 67 ; % = 84.8
Concomitant drugs (non-diabetes): 5 or more Sample size	n = 96 ; % = 59.3	n = 54 ; % = 68.4

34. Barnett, 2014

Bibliographic Reference	Barnett, A. H.; Mithal, A.; Manassie, J.; Jones, R.; Rattunde, H.; Woerle, H. J.; Broedl, U. C.; Efficacy and safety of empagliflozin added to existing antidiabetes treatment in patients with type 2 diabetes and chronic kidney disease: A randomised, double-blind, placebo-controlled trial; Lancet Diabetes Endocrinol; 2014; vol. 2 (no. 5); 369-384

34.1. Study details

Secondary publication of another included study- see primary study for details	Not applicable
Other publications associated with this study included in review	Not applicable
Trial name / registration number	EMPA-REG RENAL trial NCT01164501
Study type	Randomised controlled trial (RCT)
Study location	127 centres in 15 countries (Canada, France, Hong Kong, India, Malaysia, Philippines, Poland, Portugal, Russia, Slovakia, South Africa, Spain, Netherlands, the UK, and the USA)
Study setting	Not reported
Study dates	3rd September 2010 and 26th July 2012
Sources of funding	Boehringer Ingelheim, Eli Lilly
Inclusion criteria	• 18 years or older • BMI of less than or equal to 45 kg/m² • HbA1c of 7–10% (53–86 mmol/mol) • Estimated glomerular filtration rate (eGFR) less than 90 mL/min per 1.73 m² as established during screening and a 2 week placebo run-in period. • Patients receiving anti-diabetes drugs (excluding SGLT2 inhibitors) were required to be on an unchanged dose (or, for insulin, within 10% of the dose at randomisation) or the maximum tolerated dose

	(or maximum dose according to local label) for 12 weeks or longer before randomisation.
Exclusion criteria	• Uncontrolled hyperglycaemia (glucose level >13.3 mmol/L after an overnight fast) • Renal transplant; eGFR less than 15 mL/min per 1.73 m² • Requirement for chronic or acute dialysis • History of acute coronary syndrome, stroke, or transient ischaemic attack within 3 months of screening • Liver disease • Cancer within the past 5 years • Gastrointestinal surgery in the past 2 years • Treatment with anti-obesity drugs within 3 months of screening or any intervention leading to unstable bodyweight at screening.
Recruitment / selection of participants	Not reported
Intervention(s)	• 10 mg empagliflozin • 25 mg empagliflozin [Add-on to existing anti-diabetes treatment, given orally, once-daily in the morning, for 52 weeks]
Cointervention	• Background anti-diabetes medication was not changed for the first 24 weeks. After this, it could be altered by the investigator to control glucose values and HbA1c. • Diet and exercise counselling • Rescue therapy if a patient had a confirmed glucose level greater than 13.3 mmol/L after an overnight fast between weeks 1 and 12, or if a patient had a confirmed glucose level greater than 11.1 mmol/L after an overnight fast between weeks 12 and 24. • Rescue medication was given at the discretion of the investigator, and adjustment of background anti-diabetes medication between weeks 24 and 52 was not deemed rescue medication.
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear Not an inclusion/exclusion criteria. No information in baseline characteristics.
Strata 2: People with atherosclerotic cardiovascular disease	Not stated/unclear Excluded "history of acute coronary syndrome, stroke, or transient ischaemic attack within 3 months of screening", unclear prior to this. No information in baseline characteristics.
Strata 3: People with	People with chronic kidney disease Included people with stage 2-4 CKD.

type 2 diabetes mellitus and chronic kidney disease	
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	Not stated/unclear
Subgroup 1: People with moderate or severe frailty	Not stated/unclear
Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear
Subgroup 3: People with non-alcoholic fatty liver disease	Not stated/unclear
Subgroup 4: People with obesity	Not stated/unclear
Subgroup 5: eGFR category at baseline	Mixed population Randomisation stratified and results presented according to eGFR
Subgroup 6: Albuminuria category at baseline	Mixed population
Population subgroups	• Stage 2 CKD - eGFR ≥60 and <90 mL/min per 1.73m2 • Stage 3 CKD - eGFR ≥30 and <60 mL/min per 1.73m2 • Stage 4 CKD - eGFR ≥15 and <30 mL/min per 1.73m2
Comparator	Placebo
Number of participants	Stage 2 CKD (n=292)

	• Placebo - 97 assigned, 87 completed 52-week treatment period, 95 included in full analysis set • 10 mg empagliflozin - 98 assigned - 88 completed 52-week treatment period, 98 included in full analysis set • 25 mg empagliflozin - 97 assigned - 89 completed 52-week treatment period, 97 included in full analysis set Stage 3 CKD (n=375) • Placebo - 187 assigned, 166 completed 52-week treatment period, 187 in full analysis set • 25 mg empagliflozin - 188 assigned, 165 completed 52-week treatment period, 187 included in full analysis set Stage 4 CKD (n=74) • Placebo - 37 assigned, 25 completed 52-week treatment period, 37 included in full analysis set • 25 mg empagliflozin - 37 assigned, 26 completed 52-week treatment period, 37 included in full analysis set
Duration of follow-up	• 24 weeks • 52 weeks
Indirectness	Directly applicable
Method of analysis	ITT Described as the full analysis set in the report. This included patients treated with one or more doses of study drug who had a HbA1c value. The last observation carried forward approach was used to impute missing data. The effects of methods for handling missing data and important protocol violations in the primary analyses were analysed by means of sensitivity analyses, including restricted maximum likelihood based mixed model repeated measures (MMRM) analyses in the full analysis set, and ANCOVA analyses in the per-protocol set (patients in the full analysis set without important protocol violations leading to exclusion). Safety analyses were done on the treated set (patients treated with one or more doses of a study drug). Descriptive statistics for eGFR and urine albumin to creatinine ratio were assessed in the treated set and in patients in the full analysis set who completed 52 weeks of treatment.
Additional comments	• Double-blind, parallel-group trial to assess the efficacy and safety of empagliflozin as an add-on treatment. • Analysis of patients with stage 4 CKD was intended to be exploratory only. • For patients with stage 2 CKD, it was calculated that 85 patients per group were needed to provide 83% power to detect a 0.5% treatment difference in HbA1c for each empagliflozin group

	compared with placebo, assuming an SD of 1.1% and α (type I error) at 5%. • For patients with stage 3 CKD, 167 patients per group were needed to provide 70% power to detect a 0·3% treatment difference in HbA1c for empagliflozin 25 mg compared with placebo, assuming an SD of 1·1%.

34.2. Study arms

34.2.1. Stage 2 CKD - Placebo (N = 97)

Participants with eGFR ≥60 and <90 mL/min per 1.73m2

34.2.2. Stage 2 CKD - Empagliflozin 10 mg (N = 98)

Participants with eGFR ≥60 and <90 mL/min per 1.73m2

34.2.3. Stage 2 CKD - Empagliflozin 25 mg (N = 97)

Participants with eGFR ≥60 and <90 mL/min per 1.73m2

34.2.4. Stage 3 CKD - Placebo (N = 187)

Participants with eGFR ≥30 and <60 mL/min per 1.73m2

34.2.5. Stage 3 CKD - Empagliflozin 25 mg (N = 188)

Participants with eGFR ≥30 and <60 mL/min per 1.73m2

34.2.6. Stage 4 CKD - Placebo (N = 37)

Participants with eGFR ≥15 and <30 mL/min per 1.73m2

34.2.7. Stage 4 CKD - Empagliflozin 25 mg (N = 37)

Participants with eGFR ≥15 and <30 mL/min per 1.73m2

34.3. Characteristics

34.3.1. Arm-level characteristics

Characteristic	Stage 2 CKD - Placebo (N = 97)	Stage 2 CKD - Empagliflozin 10 mg (N = 98)	Stage 2 CKD - Empagliflozin 25 mg (N = 97)	Stage 3 CKD - Placebo (N = 187)	Stage 3 CKD - Empagliflozin 25 mg (N = 188)	Stage 4 CKD - Placebo (N = 37)	Stage 4 CKD - Empagliflozin 25 mg (N = 37)
% Male Sample size	n = 56 ; % = 58.9	n = 60 ; % = 61.2	n = 61 ; % = 62.9	n = 106 ; % = 56.7	n = 107 ; % = 57.2	n = 19 ; % = 51.4	n = 21 ; % = 56.8
Mean age (SD) Mean (SD)	62.6 (8.1)	63.2 (8.5)	62 (8.4)	65.1 (8.2)	64.6 (8.9)	62.9 (11.9)	65.4 (10.2)
White Sample size	n = 65 ; % = 68.4	n = 69 ; % = 70.4	n = 64 ; % = 66	n = 108 ; % = 57.8	n = 102 ; % = 54.5	n = 18 ; % = 48.6	n = 19 ; % = 51.4
Asian Sample size	n = 26 ; % = 27.4	n = 25 ; % = 25.5	n = 27 ; % = 27.8	n = 74 ; % = 39.6	n = 79 ; % = 42.2	n = 19 ; % = 51.4	n = 16 ; % = 43.2
Black/African-American Sample size	n = 4 ; % = 4.2	n = 3 ; % = 3.1	n = 6 ; % = 6.2	n = 2 ; % = 1.1	n = 5 ; % = 2.7	n = 0 ; % = 0	n = 2 ; % = 5.4
Other Sample size	n = 0 ; % = 0	n = 1 ; % = 1	n = 0 ; % = 0	n = 3 ; % = 1.6	n = 1 ; % = 0.5	n = 0 ; % = 0	n = 0 ; % = 0
Comorbidities Nominal	NR	NR	NR	NR	NR	NR	NR
Presence of frailty Nominal	NR	NR	NR	NR	NR	NR	NR
Less than or equal to 1 year Sample size	n = 1 ; % = 1.1	n = 0 ; % = 0	n = 2 ; % = 2.1	n = 1 ; % = 0.5	n = 2 ; % = 1.1	n = 0 ; % = 0	n = 0 ; % = 0

Characteristic	Stage 2 CKD - Placebo (N = 97)	Stage 2 CKD - Empagliflozin 10 mg (N = 98)	Stage 2 CKD - Empagliflozin 25 mg (N = 97)	Stage 3 CKD - Placebo (N = 187)	Stage 3 CKD - Empagliflozin 25 mg (N = 188)	Stage 4 CKD - Placebo (N = 37)	Stage 4 CKD - Empagliflozin 25 mg (N = 37)
>1 to 5 years Sample size	n = 19 ; % = 20	n = 18 ; % = 18.4	n = 14 ; % = 14.4	n = 25 ; % = 13.4	n = 21 ; % = 11.2	n = 6 ; % = 16.2	n = 4 ; % = 10.8
>5 to 10 years Sample size	n = 29 ; % = 30.5	n = 22 ; % = 22.4	n = 33 ; % = 34	n = 38 ; % = 20.3	n = 35 ; % = 18.7	n = 8 ; % = 21.6	n = 6 ; % = 16.2
10 years Sample size	n = 46 ; % = 48.4	n = 58 ; % = 59.2	n = 48 ; % = 49.5	n = 123 ; % = 65.8	n = 129 ; % = 69	n = 23 ; % = 6.2	n = 27 ; % = 73
HbA1c Mean (SD)	8.09 (0.8)	8.02 (0.84)	7.96 (0.73)	8.09 (0.8)	8.02 (0.84)	8.16 (0.99)	8.06 (1.05)
Cardiovascular risk factors Nominal	NR	NR	NR	NR	NR	NR	NR
Blood pressure (mmHg) Systolic blood pressure Mean (SD)	134.7 (17)	137.4 (15)	133.7 (17.7)	134.7 (17)	137.4 (15)	146.2 (22)	145 (20.6)
Smoking status Nominal	NR	NR	NR	NR	NR	NR	NR
Presence of severe mental illness Nominal	NR	NR	NR	NR	NR	NR	NR
People with significant cognitive impairment	NR	NR	NR	NR	NR	NR	NR

Characteristic	Stage 2 CKD - Placebo (N = 97)	Stage 2 CKD - Empagliflozin 10 mg (N = 98)	Stage 2 CKD - Empagliflozin 25 mg (N = 97)	Stage 3 CKD - Placebo (N = 187)	Stage 3 CKD - Empagliflozin 25 mg (N = 188)	Stage 4 CKD - Placebo (N = 37)	Stage 4 CKD - Empagliflozin 25 mg (N = 37)
Nominal							
People with a learning disability Nominal	NR	NR	NR	NR	NR	NR	NR
Weight (kg) Mean (SD)	86 (20)	92.1 (21.4)	88.1 (21.7)	82.5 (18)	83.2 (19.5)	84.1 (21.1)	77.9 (16.4)
BMI (kg/m2) Mean (SD)	30.8 (5.6)	32.4 (5.4)	31.3 (5.8)	30.3 (5.3)	30.2 (5.3)	31.8 (6)	29 (4.9)
Number of people with obesity Nominal	NR	NR	NR	NR	NR	NR	NR
Cholesterol and lipid levels (mmol/L) Total cholesterol Mean (SE)	4.24 (0.1)	4.04 (0.1)	4.36 (0.11)	4.46 (0.08)	4.36 (0.07)	4.71 (0.18)	4.58 (0.24)
eGFR mL/min/1.73 m2 Mean (SD)	71.8 (10.2)	70.8 (10.3)	72.3 (11.2)	44.3 (10.3)	45.4 (10.2)	22 (4.4)	24.4 (5.2)
Metformin monotherapy Sample size	n = 16 ; % = 16.8	n = 13 ; % = 13.3	n = 8 ; % = 8.2	n = 16 ; % = 8.6	n = 13 ; % = 7	n = 0 ; % = 0	n = 0 ; % = 0
Insulin monotherapy Sample size	n = 11 ; % = 11.6	n = 12 ; % = 12.2	n = 5 ; % = 5.2	n = 51 ; % = 27.3	n = 44 ; % = 23.5	n = 19 ; % = 51.4	n = 22 ; % = 59.2

Characteristic	Stage 2 CKD - Placebo (N = 97)	Stage 2 CKD - Empagliflozin 10 mg (N = 98)	Stage 2 CKD - Empagliflozin 25 mg (N = 97)	Stage 3 CKD - Placebo (N = 187)	Stage 3 CKD - Empagliflozin 25 mg (N = 188)	Stage 4 CKD - Placebo (N = 37)	Stage 4 CKD - Empagliflozin 25 mg (N = 37)
Sulfonylurea only Sample size	n = 0 ; % = 0	n = 0 ; % = 0	n = 0 ; % = 0	n = 13 ; % = 7	n = 15 ; % = 8	n = 3 ; % = 8.1	n = 4 ; % = 10.8
Metformin plus sulfonylurea Sample size	n = 20 ; % = 21.1	n = 25 ; % = 25.5	n = 23 ; % = 23.7	n = 27 ; % = 14.4	n = 25 ; % = 13.4	n = 2 ; % = 5.4	n = 1 ; % = 2.7
Metformin plus insulin Sample size	n = 14 ; % = 14.7	n = 23 ; % = 23.5	n = 23 ; % = 23.7	n = 25 ; % = 13.4	n = 27 ; % = 14.4	n = 2 ; % = 5.4	n = 0 ; % = 0
Sulfonylurea plus insulin Sample size	n = 0 ; % = 0	n = 0 ; % = 0	n = 0 ; % = 0	n = 0 ; % = 0	n = 0 ; % = 0	n = 3 ; % = 8.1	n = 3 ; % = 8.1
Other therapy Sample size	n = 34 ; % = 35.8	n = 25 ; % = 25.5	n = 38 ; % = 39.2	n = 55 ; % = 29.4	n = 63 ; % = 33.7	n = 8 ; % = 21.6	n = 7 ; % = 18.9
Blood pressure-lowering medication used Sample size	n = 83 ; % = 87.4	n = 86 ; % = 87.8	n = 83 ; % = 85.6	n = 170 ; % = 90.9	n = 174 ; % = 93	n = 36 ; % = 97.3	n = 37 ; % = 100
Diuretics Sample size	n = 32 ; % = 33.7	n = 33 ; % = 33.7	n = 27 ; % = 27.8	n = 71 ; % = 38	n = 73 ; % = 39	n = 22 ; % = 59.5	n = 24 ; % = 64.9
Loop diuretics Sample size	n = 6 ; % = 6.3	n = 8 ; % = 8.2	n = 4 ; % = 4.1	n = 36 ; % = 19.3	n = 32 ; % = 17.1	n = 19 ; % = 51.4	n = 15 ; % = 40.5
Thiazides Sample size	n = 22 ; % = 23.2	n = 14 ; % = 14.3	n = 17 ; % = 17.5	n = 20 ; % = 10.7	n = 29 ; % = 15.5	n = 4 ; % = 10.8	n = 6 ; % = 16.2

Characteristic	Stage 2 CKD - Placebo (N = 97)	Stage 2 CKD - Empagliflozin 10 mg (N = 98)	Stage 2 CKD - Empagliflozin 25 mg (N = 97)	Stage 3 CKD - Placebo (N = 187)	Stage 3 CKD - Empagliflozin 25 mg (N = 188)	Stage 4 CKD - Placebo (N = 37)	Stage 4 CKD - Empagliflozin 25 mg (N = 37)
β-blocking drugs Sample size	n = 30 ; % = 31.6	n = 27 ; % = 27.6	n = 23 ; % = 23.7	n = 65 ; % = 34.8	n = 84 ; % = 44.9	n = 16 ; % = 43.2	n = 16 ; % = 43.2
Calcium-channel blockers Sample size	n = 24 ; % = 25.3	n = 33 ; % = 33.7	n = 30 ; % = 30.9	n = 76 ; % = 40.6	n = 84 ; % = 44.9	n = 22 ; % = 59.5	n = 24 ; % = 64.9
ACE inhibitors or angiotensin-receptor blockers Sample size	n = 74 ; % = 77.9	n = 74 ; % = 75.5	n = 73 ; % = 75.3	n = 134 ; % = 71.7	n = 145 ; % = 77.5	n = 23 ; % = 62.2	n = 23 ; % = 62.2
Statins/lipid-lowering medication used Nominal	NR	NR	NR	NR	NR	NR	NR
Other treatment being received Nominal	NR	NR	NR	NR	NR	NR	NR
Blood pressure (mmHg) Diastolic blood pressure Mean (SD)	77.5 (9.4)	76.5 (8.9)	76.7 (9)	77.5 (9.4)	76.5 (8.9)	77.9 (11.9)	77.2 (8.9)
Cholesterol and lipid levels (mmol/L) HDL-cholesterol Mean (SE)	4.24 (0.1)	4.04 (0.1)	4.36 (0.11)	1.26 (0.02)	1.26 (0.03)	1.23 (0.07)	1.2 (0.05)

Characteristic	Stage 2 CKD - Placebo (N = 97)	Stage 2 CKD - Empagliflozin 10 mg (N = 98)	Stage 2 CKD - Empagliflozin 25 mg (N = 97)	Stage 3 CKD - Placebo (N = 187)	Stage 3 CKD - Empagliflozin 25 mg (N = 188)	Stage 4 CKD - Placebo (N = 37)	Stage 4 CKD - Empagliflozin 25 mg (N = 37)
Cholesterol and lipid levels (mmol/L) LDL-cholesterol Mean (SE)	2.22 (0.09)	2.03 (0.09)	2.29 (0.08)	2.31 (0.06)	2.25 (0.06)	2.51 (0.17)	2.23 (0.13)
Cholesterol and lipid levels (mmol/L) Triglycerides Mean (SE)	1.67 (0.12)	1.63 (0.1)	1.63 (0.09)	1.86 (0.08)	1.9 (0.09)	2.15 (0.18)	2.69 (0.62)

35. Barnett, 2013

Bibliographic Reference	Barnett, Anthony H; Charbonnel, Bernard; Li, Jia; Donovan, Mark; Fleming, Douglas; Iqbal, Nayyar; Saxagliptin add-on therapy to insulin with or without metformin for type 2 diabetes mellitus: 52-week safety and efficacy.; Clinical drug investigation; 2013; vol. 33 (no. 10); 707-17

35.1. Study details

Secondary publication of another included study- see primary study for details	Parent study Barnett 2012 (population strata details there) Barnett AH, Charbonnel B, Donovan M, Fleming D, Chen R. Effect of saxagliptin as add-on therapy in patients with poorly controlled type 2 diabetes on insulin alone or insulin combined with metformin. Curr Med Res Opin. 2012 Apr;28(4):513-23. doi: 10.1185/03007995.2012.665046.
Other publications associated with this study included in review	NA
Trial name / registration number	NCT00757588; CV181-057

36. Bergenstal, 2010

Bibliographic Reference	Bergenstal, R. M.; Wysham, C.; Macconell, L.; Malloy, J.; Walsh, B.; Yan, P.; Wilhelm, K.; Malone, J.; Porter, L. E.; Efficacy and safety of exenatide once weekly versus sitagliptin or pioglitazone as an adjunct to metformin for treatment of type 2 diabetes (DURATION-2): a randomised trial; Lancet; 2010; vol. 376 (no. 9739); 431-9

36.1. Study details

Secondary publication of another included study- see primary study for details	N/A
Other publications associated with this study included in review	Jennie H. Best, Richard R. Rubin, Mark Peyrot, Yan Li, Ping Yan, Jaret Malloy, Louis P. Garrison; Weight-Related Quality of Life, Health Utility, Psychological Well-Being, and Satisfaction With Exenatide Once Weekly Compared With Sitagliptin or Pioglitazone After 26 Weeks of Treatment. *Diabetes Care* 1 February 2011; 34 (2): 314–319. https://doi.org/10.2337/dc10-1119 EPPI ID = 13722476
Trial name / registration number	NCT00637273
Study location	USA, India and Mexico.
Study setting	72 hospitals and clinics.
Study dates	Patients recruited between 22 January and 6 August 2008.
Sources of funding	Amylin Pharmaceuticals and Eli Lilly
Inclusion criteria	• People with type 2 diabetes aged 18 years and older, otherwise healthy, treated with a stable metformin regimen for at least 2 months prior to screening. • HbA1c of 7.1-11.0% • Body mass index of 25-45 kg/m2 • Stable body weight (not varying by >3% for at least 3 months prior to screening) • Fasting plasma glucose concentration <280 mg/dL (15.5 mmol/L) at screening visit

	• Either not treated with or has been on a stable treatment regimen with any of the following medications for a minimum of 2 months: hormone replacement therapy, oral contraceptives, anti-hypertensive agents, lipid-lowering agents, thyroid replacement therapy, anti-depressive agents, drugs known to affect bodyweight; male or female and not pregnant or lactating, using birth control for study duration if of childbearing potential); clinical laboratory test values assessed as not clinically significant by the investigator at screening; physical examination and electrocardiogram results judged as not clinically significant at visit 2; able to provide informed consent, answer study questionnaires and comply with the study protocol.
Exclusion criteria	• Clinically significant medical condition, including: hepatic disease or alanine aminotransferase or aspartate aminotransferase value of > 3 times upper limit of normal; renal disease (corresponding to serum creatinine levels of >1.5 mg/dL in men and >1.4 mg/dL in women; cardiovascular disease, including significant oedema, congestive heart failure or New York Heart Association Class III or IV status; gastroparesis; clinically significant malignant disease (excluding basal and squamous skin cell carcinoma) within 5 years of screening; macula oedema; known or suspected infections (e.g., HIV, TB). • Current or previous history of drug or alcohol abuse • Fasting triglyceride concentration ≥600 mg/dL at screening • Previous exposure to exenatide LAR • Donated blood within previous 60 days of screening or planned donation during study period • Major surgery or blood transfusion within 2 months of screening • Current or expected treatment with any of the following medications: Exenatide or any DPP-4 inhibitor, sulfonylurea, thiazolidinedione, or GLP-1 analogue within 3 months prior to screening; alpha-glucosidase inhibitor, meglitinide, nateglinide, or pramlintide within 30 days of screening; insulin within 2 weeks of screening or for more than 1 week within 3 months of screening; systemic corticosteroids by oral, intravenous, or intramuscular route; or potent, inhaled, or intrapulmonary steroids known to have a high rate of systemic absorption; drugs interacting with the CYP2C8 enzyme system. • Received any investigational drug within 1 month (or five half lives of investigational drug, whichever is greater) of screening. • Known allergies or hypersensitivity to any component of study treatment (including PLG and Microsphere Diluent) • Previously experienced a clinically significant adverse event related to TZD or DPP-4 inhibitor use • An immediate family member of personnel directly affiliated with the study at the clinical study site, or is directly affiliated with the study at the clinical study site • Employed by Amylin Pharmaceuticals, Inc (Amylin), Eli Lilly and Company, or Alkermes, Inc • Pregnancy or lactation

Recruitment / selection of participants	No further information
Intervention(s)	1) Exenatide 2 mg once weekly self-administered subcutaneous injection plus oral placebo once daily 2) Sitagliptin 100 mg once daily oral plus placebo once weekly subcutaneous injection
Cointervention	Stable metformin regimen for at least 2 months prior to screening.
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear The study states that "people with T2D but otherwise healthy" were recruited. "Cardiovascular disease, including significant oedema, congestive heart failure, or New York Heart Association Class III or Class IV cardiac status" stated as exclusion criteria. No information about class II. No information in baseline characteristics.
Strata 2: People with atherosclerotic cardiovascular disease	Not stated/unclear The study states that "people with T2D but otherwise healthy" were recruited. "Cardiovascular disease, including significant oedema, congestive heart failure, or New York Heart Association Class III or Class IV cardiac status" stated as exclusion criteria. No information in baseline characteristics.
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear Stated recruited "people with T2D but otherwise healthy". Exclusion criteria state "Renal disease (corresponding to serum creatinine levels of >1.5 mg/dL in men and >1.4 mg/dL in women)"; CKD not stated as an exclusion criteria. No information in baseline characteristics.
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	Not stated/unclear
Subgroup 1: People with moderate or severe frailty	Not stated/unclear
Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear

Subgroup 3: People with non-alcoholic fatty liver disease	People without non-alcoholic fatty liver disease Exclusion criteria state "Hepatic disease or an alanine aminotransferase or aspartate aminotransferase value of >3 times the upper limit of normal"
Subgroup 4: People with obesity	Not stated/unclear
Subgroup 5: eGFR category at baseline	Not stated/unclear
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Comparator	3) Pioglitazone 45 mg oral once daily plus placebo once weekly subcutaneous injection
Number of participants	514 enrolled and entered into randomisation
Duration of follow-up	26 weeks
Method of analysis	Modified ITT
Additional comments	The authors describe the analysis as intention-to-treat. The definition is "all randomised patients who received at least one dose of study drug". 491 entered into the intention-to-treat analysis (514 originally randomised).

36.2. Study arms

36.2.1. Exenatide (N = 160)

Exenatide 2 mg once weekly self-administered subcutaneous injection plus oral placebo once daily.

36.2.2. Sitagliptin (N = 166)

Sitagliptin 100 mg once daily oral plus placebo once weekly subcutaneous injection.

36.2.3. Pioglitazone (N = 165)

Pioglitazone 45 mg oral once daily plus placebo once weekly subcutaneous injection

36.3. Characteristics

36.3.1. Arm-level characteristics

Characteristic	Exenatide (N = 160)	Sitagliptin (N = 166)	Pioglitazone (N = 165)
% Male Sample size	n = 89 ; % = 56	n = 86 ; % = 52	n = 79 ; % = 48
Mean age (SD) (years) Mean (SD)	52 (10)	52 (11)	53 (10)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
White Sample size	n = 53 ; % = 33	n = 50 ; % = 30	n = 65 ; % = 39
Black Sample size	n = 19 ; % = 12	n = 20 ; % = 12	n = 13 ; % = 8
Hispanic Sample size	n = 50 ; % = 31	n = 49 ; % = 30	n = 44 ; % = 27
Asian Sample size	n = 37 ; % = 23	n = 42 ; % = 25	n = 40 ; % = 24
Native American Sample size	n = 0 ; % = 0	n = 3 ; % = 2	n = 0 ; % = 0
Other Sample size	n = 1 ; % = 1	n = 2 ; % = 1	n = 3 ; % = 2
Comorbidities Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Presence of frailty Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Time since type 2 diabetes diagnosed (years) Mean (SD)	6 (5)	5 (4)	6 (5)

Characteristic	Exenatide (N = 160)	Sitagliptin (N = 166)	Pioglitazone (N = 165)
HbA1c (%) Mean (SD)	8.6 (1.2)	8.5 (1.2)	8.5 (1.1)
Cardiovascular risk factors Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Heart rate Mean (SD)	NR (NR)	NR (NR)	NR (NR)
Smoking status Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Alcohol consumption Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Presence of severe mental illness Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
People with significant cognitive impairment Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
People with a learning disability Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Weight (kg) Mean (SD)	89 (20)	87 (20)	88 (20)
BMI (kg/m²) Mean (SD)	32 (5)	32 (5)	32 (6)
Number of people with obesity Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Cholesterol and lipid levels Mean (SD)	NA (NA)	NA (NA)	NA (NA)
Total cholesterol Mean (SD)	4.5 (1)	4.6 (1.1)	4.9 (1.1)
LDL cholesterol Mean (SD)	2.7 (0.8)	2.7 (0.9)	2.9 (1)

Characteristic	Exenatide (N = 160)	Sitagliptin (N = 166)	Pioglitazone (N = 165)
HDL cholesterol Mean (SD)	1.1 (0.2)	1.1 (0.3)	1.1 (0.3)
Triglycerides Mean (SD)	1.9 (1.1)	1.9 (1.3)	2.2 (1.3)
Albumin creatinine ratio Mean (SD)	NR (NR)	NR (NR)	NR (NR)
eGFR mL/min/1.73m2 Mean (SD)	NR (NR)	NR (NR)	NR (NR)
Other antidiabetic medication used Mean (SD)	NA (NA)	NA (NA)	NA (NA)
Metformin dose (daily) Mean (SD)	1504 (586)	1583 (510)	1480 (559)
Blood pressure-lowering medication used (mg) Mean (SD)	NA (NA)	NA (NA)	NA (NA)
Systolic blood pressure Mean (SD)	126 (14)	126 (14)	127 (14)
Statins/lipid-lowering medication used Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Other treatment being received Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR

37. Bergenstal, 2009

Bibliographic Reference	Bergenstal, R.; Lewin, A.; Bailey, T.; Chang, D.; Gylvin, T.; Roberts, V.; Efficacy and safety of biphasic insulin aspart 70/30 versus exenatide in subjects with type 2 diabetes failing to achieve glycemic control with metformin and a sulfonylurea; Curr Med Res Opin; 2009; vol. 25 (no. 1); 65-75

37.1. Study details

Secondary publication of another included study- see primary study for details	N/A
Other publications associated with this study included in review	N/A
Trial name / registration number	NCT00097877
Study type	Randomised controlled trial (RCT)
Study location	102 sites in the USA
Study setting	No additional information
Study dates	No information
Sources of funding	The study was supported by Novo Nordisk.
Inclusion criteria	• People aged between ≥18 years and ≤ 80 years with type 2 diabetes for > 6 months (according to the American Diabetes Association criteria) • HbA1c ≥8% • Insulin naïve (patients not on insulin, who had received no insulin for more than 2 weeks of daily use within 6 months preceding the trial)

	• Received therapy with metformin (at least 1500 mg daily) and a sulfonylurea (at least half of the maximal dose) for 3 months before screening
Exclusion criteria	• Significant heart disease defined as: New York Heart Association (NHYA) class III or IV congestive heart failure, unstable angina, and/or myocardial infarction within 12 months prior to the study • Hepatic insufficiency (liver function tests ≥ 2.5 times upper reference limit) • Renal insufficiency (serum creatinine ≥ 1.3 mg/dL for males and ≥ 1.2 mg/dL for females). • Use of thiazolidinedione, alpha-glucosidase inhibitor or meglintide within 6 months prior to the study • History of eating disorder or receiving current treatment with a weight-reducing diet.
Recruitment / selection of participants	No further information
Intervention(s)	Exenatide therapy was initiated at 5 µg dose twice daily for the initial 4 weeks. After the initial 4 weeks, the dose was escalated to 10 µg twice daily for the remaining 20 weeks.
Cointervention	Metformin (at least 1500 mg/day) and sulfonylurea (at least half the maximal dose) for at least 3 moths prior to screening. Doses of metformin and sulfonylurea remained fixed following randomisation.
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear Excluded "significant cardiac disease (New York Heart Association [NYHA] class III or IV congestive heart failure, unstable angina, and/or myocardial infarction) within 12 months prior to study", other heart failure unclear. No information in baseline characteristics.
Strata 2: People with atherosclerotic cardiovascular disease	Not stated/unclear Excluded "significant cardiac disease (New York Heart Association [NYHA] class III or IV congestive heart failure, unstable angina, and/or myocardial infarction) within 12 months prior to study", prior events unclear. No information in baseline characteristics.
Strata 3: People with type 2 diabetes mellitus and	Not stated/unclear Excluded "renal insufficiency (serum creatinine 1.3 mg/dL for males; 1.2 mg/dL for females)", but CKD diagnosis unclear. No information in baseline characteristics.

chronic kidney disease	
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	Not stated/unclear
Subgroup 1: People with moderate or severe frailty	Not stated/unclear
Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear Participants had to have had type 2 diabetes for at least 6 months to be eligible for the study. Only mean duration of diabetes reported in baseline characteristics.
Subgroup 3: People with non-alcoholic fatty liver disease	Not stated/unclear Hepatic insufficiency an exclusion criteria (defined as liver function tests ≥ 2.5 times upper reference limit). No further information.
Subgroup 4: People with obesity	Not stated/unclear Number of people with obesity not reported. Only mean BMI reported in baseline characteristics.
Subgroup 5: eGFR category at baseline	Not stated/unclear
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Comparator	Insulin therapy was initiated with 12 U before supper. Participants were instructed to adjust their insulin dose every 3-4 days based on an insulin titration algorithm. Insulin dos titration based on SMBG results for the prior 3 days unless hypoglycemia occurred. In the event of hypoglycaemia occurred, titration was postponed and the insulin dose remained the same.
Number of participants	Overall participants in the study N= 372

	Included in the review N = 248 (exenatide group N= 124; insulin once daily group N= 124; insulin twice daily group excluded due to different cointervention)
Duration of follow-up	24 weeks
Method of analysis	Per protocol Per protocol analysis used to evaluate the primary efficacy endpoint - HbA1c change at 24 weeks. Per protocol population defined as subjects who completed the study without protocol violations. Modified ITT ITT analysis used to analyse primary and secondary efficacy outcomes. ITT defined as participants who took at least one dose of study medication and had one post-dosing ad post-baseline efficacy measurement. Other Safety population was comprised of participants randomised to treatment.
Additional comments	Authors report that ITT analysis was used to analyse primary and secondary efficacy outcomes. ITT defined as participants who took at least one dose of study medication and had one post-dosing and post-baseline efficacy measurement.

37.2. Study arms

37.2.1. Exenatide twice daily (N = 124)

37.2.2. Biphasic insulin aspart once daily (N = 124)

37.3. Characteristics

37.3.1. Arm-level characteristics

Characteristic	Exenatide twice daily (N = 124)	Biphasic insulin aspart once daily (N = 124)
% Male Sample size	n = 60 ; % = 48.4	n = 60 ; % = 48.4
Mean age (SD) (years) Mean (SD)	52.5 (10.62)	51.8 (10.9)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA
Hispanic or Latino Sample size	n = 44 ; % = 35.5	n = 36 ; % = 29
Not hispanic or latino Sample size	n = 80 ; % = 64.5	n = 88 ; % = 71
Comorbidities Sample size	n = NR ; % = NR	n = NR ; % = NR
Presence of frailty Sample size	n = NR ; % = NR	n = NR ; % = NR
Time since type 2 diabetes diagnosed (years) Mean (SD)	8.6 (5.9)	8.4 (6.3)
HbA1c (%) Mean (SD)	10.2 (1.52)	10.1 (1.79)
Cardiovascular risk factors Sample size	n = NR ; % = NR	n = NR ; % = NR
Blood pressure Mean (SD)	NR (NR)	NR (NR)
Heart rate Mean (SD)	NR (NR)	NR (NR)
Smoking status Sample size	n = NR ; % = NR	n = NR ; % = NR

Characteristic	Exenatide twice daily (N = 124)	Biphasic insulin aspart once daily (N = 124)
Alcohol consumption Sample size	n = NR ; % = NR	n = NR ; % = NR
Presence of severe mental illness Sample size	n = NR ; % = NR	n = NR ; % = NR
People with significant cognitive impairment Sample size	n = NR ; % = NR	n = NR ; % = NR
People with a learning disability Sample size	n = NR ; % = NR	n = NR ; % = NR
Weight (kg) Mean (SD)	96.6 (24)	96.9 (25)
BMI (kg/m²) Mean (SD)	34.2 (7.1)	33.7 (7.1)
Number of people with obesity Sample size	n = NR ; % = NR	n = NR ; % = NR
Cholesterol and lipid levels Mean (SD)	NR (NR)	NR (NR)
Albumin creatinine ratio Mean (SD)	NR (NR)	NR (NR)
eGFR mL/min/1.73m2 Mean (SD)	NR (NR)	NR (NR)
Other antidiabetic medication used Sample size	n = NA ; % = NA	n = NA ; % = NA
Blood pressure-lowering medication used Sample size	n = NR ; % = NR	n = NR ; % = NR
Statins/lipid-lowering medication used Sample size	n = NR ; % = NR	n = NR ; % = NR
Other treatment being received Sample size	n = NR ; % = NR	n = NR ; % = NR

Characteristic	Exenatide twice daily (N = 124)	Biphasic insulin aspart once daily (N = 124)
Race Sample size	n = NA ; % = NA	n = NA ; % = NA
American-Indian/Alaska Native Sample size	n = 13 ; % = 10.5	n = 10 ; % = 8.1
Asian Sample size	n = 2 ; % = 1.6	n = 3 ; % = 2.4
Black or African-American Sample size	n = 24 ; % = 19.4	n = 23 ; % = 18.5
White Sample size	n = 79 ; % = 63.7	n = 84 ; % = 67.7
Other Other race includes Greek, Hawaiian/Chinese, Mexican, Mexican-American, or Puerto Rican Sample size	n = 6 ; % = 4.8	n = 4 ; % = 3.2

38. Berndt-Zipfel, 2013

Bibliographic Reference	Berndt-Zipfel, C.; Michelson, G.; Dworak, M.; Mitry, M.; Loffler, A.; Pfutzner, A.; Forst, T.; Vildagliptin in addition to metformin improves retinal blood flow and erythrocyte deformability in patients with type 2 diabetes mellitus - results from an exploratory study; Cardiovasc Diabetol; 2013; vol. 12 (no. 1); 59

38.1. Study details

Secondary publication of another included study- see primary study for details	N/A
Other publications associated with this study included in review	N/A
Trial name / registration number	N/A
Study type	Randomised controlled trial (RCT)
Study location	Not stated
Study setting	No information
Study dates	Not stated
Sources of funding	Not stated
Inclusion criteria	• People with type 2 diabetes aged 30 to 80 years • Pre-treated with metformin • HbA1c in the range 6.6 to 9.5%
Exclusion criteria	• Myocardial infarction or stroke within 6 months prior to study enrolment • Impaired hepatic or renal function • Moderate or proliferative diabetic retinopathy • More than one unexplained episode of severe hypoglycaemia within 6 months

	• Pre-treatment with anti-diabetic medication other than metformin within the last 3 months • Uncontrolled hypertension, defined as systolic blood pressure >160 mmHg and /or diastolic blood pressure >90 mmHg.
Recruitment / selection of participants	No additional information
Intervention(s)	Vildagliptin 50 mg twice daily
Cointervention	Metformin (participants were already being treated with metformin).
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear Not an inclusion/exclusion criteria. No information in baseline characteristics.
Strata 2: People with atherosclerotic cardiovascular disease	Not stated/unclear Excluded "myocardial infarction or stroke within 6 months prior to study enrolment", prior to this unclear. No information in baseline characteristics.
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear Excluded "impaired renal function", otherwise unclear. No information in baseline characteristics.
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	Not stated/unclear
Subgroup 1: People with moderate or severe frailty	Not stated/unclear
Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear Only mean duration of diabetes reported in the baseline characteristics.

Subgroup 3: People with non-alcoholic fatty liver disease	Not stated/unclear "Impaired hepatic function" was an exclusion criterion. No further detail.
Subgroup 4: People with obesity	Not stated/unclear
Subgroup 5: eGFR category at baseline	Not stated/unclear
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Population subgroups	N/A
Comparator	Glimepiride was administered in the morning with individual dose titration in the range 0.5 to 4 mg to achieve the best possible glycaemic control, according to investigator judgement.
Number of participants	44
Duration of follow-up	24 weeks
Indirectness	N/A
Method of analysis	Not stated/unclear The manuscript states "44 patients were included in the final analysis"; however the method of analysis is not explicitly stated as ITT. It is unclear how many patients were initially randomised and there is no CONSORT flow diagram available.
Additional comments	Exploratory study. No power calculation performed to determine sample size.

38.2. Study arms

38.2.1. Vildagliptin (N = 22)

Vildagliptin 50 mg twice daily

38.2.2. Glimepiride (N = 22)

Glimepiride administered in the morning with individual dose titration in the range 0.5 to 4 mg to achieve best possible glycaemic control as judged by the investigator.

38.3. Characteristics

38.3.1. Arm-level characteristics

Characteristic	Vildagliptin (N = 22)	Glimepiride (N = 22)
% Male Sample size	n = 13 ; % = 59	n = 15 ; % = 68
Mean age (SD) (years) Mean (SD)	60 (7)	57 (9)
Ethnicity Sample size	n = NR ; % = NR	n = NR ; % = NR
Comorbidities Sample size	n = NR ; % = NR	n = NR ; % = NR
Presence of frailty Sample size	n = NR ; % = NR	n = NR ; % = NR
Time since type 2 diabetes diagnosed (years) Mean (SD)	6.1 (4.4)	8.4 (9)
HbA1c (%) Mean (SD)	7.3 (0.6)	7.4 (0.7)
Cardiovascular risk factors Sample size	n = NR ; % = NR	n = NR ; % = NR
Blood pressure Mean (SD)	NR (NR)	NR (NR)
Heart rate Mean (SD)	NR (NR)	NR (NR)
Smoking status Sample size	n = NR ; % = NR	n = NR ; % = NR

Characteristic	Vildagliptin (N = 22)	Glimepiride (N = 22)
Alcohol consumption Mean (SD)	NR (NR)	NR (NR)
Presence of severe mental illness Sample size	n = NR ; % = NR	n = NR ; % = NR
People with significant cognitive impairment Sample size	n = NR ; % = NR	n = NR ; % = NR
People with a learning disability Sample size	n = NR ; % = NR	n = NR ; % = NR
Weight Mean (SD)	99.3 (14.9)	93.7 (19.6)
BMI (kg/m²) Mean (SD)	33.3 (6.7)	34.6 (5.9)
Number of people with obesity Sample size	n = NR ; % = NR	n = NR ; % = NR
Cholesterol and lipid levels Mean (SD)	NR (NR)	NR (NR)
Albumin creatinine ratio Mean (SD)	NR (NR)	NR (NR)
eGFR mL/min/1.73m2 Mean (SD)	NR (NR)	NR (NR)
Other antidiabetic medication used Sample size	n = NA ; % = NA	n = NA ; % = NA
Blood pressure-lowering medication used Sample size	n = NR ; % = NR	n = NR ; % = NR
Statins/lipid-lowering medication used Sample size	n = NR ; % = NR	n = NR ; % = NR
Other treatment being received Sample size	n = NR ; % = NR	n = NR ; % = NR

39. Best, 2011

Bibliographic Reference	Best, Jennie H; Rubin, Richard R; Peyrot, Mark; Li, Yan; Yan, Ping; Malloy, Jaret; Garrison, Louis P; Weight-related quality of life, health utility, psychological well-being, and satisfaction with exenatide once weekly compared with sitagliptin or pioglitazone after 26 weeks of treatment.; Diabetes care; 2011; vol. 34 (no. 2); 314-9

39.1. Study details

Secondary publication of another included study- see primary study for details	N/A
Other publications associated with this study included in review	N/A
Trial name / registration number	N/A
Study location	USA, India and Mexico
Study setting	No further information
Study dates	Recruitment took place between February and August 2008.
Sources of funding	Not specified
Inclusion criteria	• People with type 2 diabetes aged 18 years and over treated with metformin (stable regimen of metformin monotherapy for a minimum of 2 months prior to screening). • HbA1c 7.1-11.0% • BMI 25-45kg/m2
Exclusion criteria	• Pregnancy

Recruitment / selection of participants	No further information
Intervention(s)	1) Exenatide 2mg once weekly self-administered subcutaneous injection plus placebo oral capsule each morning. 2) Sitagliptin 100mg once daily oral plus placebo subcutaneous injection self-administered once weekly.
Cointervention	Stable regimen of metformin monotherapy for at least 2 months prior to screening.
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear Not an inclusion/exclusion criteria. No information in baseline characteristics.
Strata 2: People with atherosclerotic cardiovascular disease	Not stated/unclear Not an inclusion/exclusion criteria. No information in baseline characteristics.
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear Not an inclusion/exclusion criteria. No information in baseline characteristics.
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	Not stated/unclear No information
Subgroup 1: People with moderate or severe frailty	Not stated/unclear
Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear

Subgroup 3: People with non-alcoholic fatty liver disease	Not stated/unclear
Subgroup 4: People with obesity	Not stated/unclear
Subgroup 5: eGFR category at baseline	Not stated/unclear
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Comparator	Pioglitazone 45mg one daily oral plus subcutaneous injection self-administered once weekly.
Number of participants	491
Duration of follow-up	26 weeks
Indirectness	
Method of analysis	Modified ITT Authors describe the analysis as intention-to-treat, with the following definition: "all randomised subjects who received at least one dose of randomised study medication"

39.2. Study arms

39.2.1. Exenatide (N = 160)

Exenatide 2mg once weekly self-administered subcutaneous injection plus placebo oral capsule each morning

39.2.2. Sitagliptin (N = 166)

Sitagliptin 100mg once daily oral plus placebo subcutaneous injection self-administered once weekly

39.2.3. Pioglitazone (N = 165)

Pioglitazone 45mg one daily oral plus subcutaneous injection self-administered once weekly

39.3. Characteristics

39.3.1. Arm-level characteristics

Characteristic	Exenatide (N = 160)	Sitagliptin (N = 166)	Pioglitazone (N = 165)
% Male Sample size	n = 89 ; % = 56	n = 86 ; % = 52	n = 79 ; % = 48
Mean age (SD) Mean (SD)	52 (10)	52 (11)	53 (10)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
White Sample size	n = 53 ; % = 33	n = 50 ; % = 30	n = 65 ; % = 39
Black Sample size	n = 19 ; % = 12	n = 20 ; % = 12	n = 13 ; % = 8
Hispanic Sample size	n = 50 ; % = 31	n = 49 ; % = 30	n = 44 ; % = 27
Asian Sample size	n = 37 ; % = 23	n = 42 ; % = 25	n = 40 ; % = 24
Other Sample size	n = 1 ; % = 1	n = 5 ; % = 3	n = 3 ; % = 2
Comorbidities Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Presence of frailty Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Time since type 2 diabetes diagnosed Mean (SD)	NR (NR)	NR (NR)	NR (NR)

Characteristic	Exenatide (N = 160)	Sitagliptin (N = 166)	Pioglitazone (N = 165)
HbA1c (%) Mean (SD)	8.6 (1.2)	8.5 (1.2)	8.5 (1.1)
Cardiovascular risk factors Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Blood pressure Mean (SD)	NR (NR)	NR (NR)	NR (NR)
Heart rate Mean (SD)	NR (NR)	NR (NR)	NR (NR)
Smoking status Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Alcohol consumption Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Presence of severe mental illness Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
People with significant cognitive impairment Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
People with a learning disability Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Weight (kg) Mean (SD)	89 (20)	87 (20)	88 (21)
BMI (kg/m2) Mean (SD)	32 (5)	32 (5)	33 (5.5)
Number of people with obesity Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Cholesterol and lipid levels Mean (SD)	NR (NR)	NR (NR)	NR (NR)
Albumin creatinine ratio Mean (SD)	NR (NR)	NR (NR)	NR (NR)

Characteristic	Exenatide (N = 160)	Sitagliptin (N = 166)	Pioglitazone (N = 165)
eGFR mL/min/1.73m2 Mean (SD)	NR (NR)	NR (NR)	NR (NR)
Other antidiabetic medication used Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
Blood pressure-lowering medication used Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Statins/lipid-lowering medication used Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Other treatment being received Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR

40. Bethel M, 2019

Bibliographic Reference	Bethel M, A; Engel S, S; Stevens S, R; Lokhnygina, Y; Ding, J; Josse R, G; Alvarsson, M; Hramiak, I; Green J, B; Peterson E, D; Holman R, R; Progression of glucose-lowering diabetes therapy in TECOS; Endocrinology, Diabetes and Metabolism; 2019; vol. 2 (no. 1); e00053

40.1. Study details

Secondary publication of another included study- see primary study for details	TECOS trial. Green et al (2015) Effect of Sitagliptin on Cardiovascular Outcomes in Type 2 Diabetes. The New England journal of medicine; 2015; vol. 373 (no. 3); 232-42
Other publications associated with this study included in review	Green, Jennifer B, Bethel, M Angelyn, Paul, Sanjoy K et al. (2013) Rationale, design, and organization of a randomized, controlled Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS) in patients with type 2 diabetes and established cardiovascular disease. American heart journal 166(6): 983-989e7 Nauck Michael, A, McGuire Darren, K, Pieper Karen, S et al. (2019) Sitagliptin does not reduce the risk of cardiovascular death or hospitalization for heart failure following myocardial infarction in patients with diabetes: observations from TECOS. Cardiovascular diabetology 18(1): 116 McGuire, Darren K, Van de Werf, Frans, Armstrong, Paul W et al. (2016) Association Between Sitagliptin Use and Heart Failure Hospitalization and Related Outcomes in Type 2 Diabetes Mellitus: Secondary Analysis of a Randomized Clinical Trial. JAMA cardiology 1(2): 126-35
Trial name / registration number	TECOS ClinicalTrials.gov number NCT00790205
Study type	Randomised controlled trial (RCT)
Study location	See parent study
Study setting	See parent study
Study dates	See parent study

Sources of funding	See parent study
Inclusion criteria	See parent study
Exclusion criteria	See parent study
Recruitment / selection of participants	See parent study
Intervention(s)	Sitagliptin 100 mg daily (or 50 mg daily if the baseline eGFR was ≥30 and <50 ml per minute per 1.73 m2). Concomitant therapy: open label antihyperglycemic agents encourages as required with the aim of achieving individually appropriate HbA1c targets in all patients.
Strata 1: People with type 2 diabetes mellitus and heart failure	People without heart failure 18% of study participants had prior congestive heart failure (80% rule in protocol - over 80% did not have prior congestive heart failure)
Strata 2: People with atherosclerotic cardiovascular disease	People with atherosclerotic cardiovascular diseases Patients had established CVD (defined as a history of major coronary artery disease, ischemic cerebrovascular disease or atherosclerotic peripheral arterial disease)
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	People at higher risk of developing cardiovascular disease Patients had established CVD (defined as a history of major coronary artery disease, ischemic cerebrovascular disease or atherosclerotic peripheral arterial disease)
Subgroup 1: People with	Not stated/unclear

moderate or severe frailty	
Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear
Subgroup 3: People with non-alcoholic fatty liver disease	Not stated/unclear
Subgroup 4: People with obesity	Not stated/unclear
Subgroup 5: eGFR category at baseline	eGFR ≥30mL/min/1.73m2
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Population subgroups	Mean HbA1c difference, severe adverse events and severe hypoglycemic events also reported by baseline diabetes medication.
Comparator	Matching placebo. Concomitant therapy: open label antihyperglycemic agents encouraged as required with the aim of achieving individually appropriate HbA1c targets in all patients.
Number of participants	14671
Duration of follow-up	Median 3.0 years FUP
Indirectness	No concerns
Method of analysis	ITT
Additional comments	ITT

40.2. Study arms

40.2.1. Sitagliptin (N = 7332)

100 mg daily (or 50 mg daily if the baseline eGFR was ≥30 and <50 ml per minute per 1.73 m2). Concomitant therapy: open label antihyperglycemic agents encourages as required with the aim of achieving individually appropriate HbA1c targets in all patients.

40.2.2. Placebo (N = 7339)

Matching placebo Concomitant therapy: open label antihyperglycemic agents encouraged as required with the aim of achieving individually appropriate HbA1c targets in all patients.

41. Betteridge, 2005

Bibliographic Reference	Betteridge, D J; Verges, B; Long-term effects on lipids and lipoproteins of pioglitazone versus gliclazide addition to metformin and pioglitazone versus metformin addition to sulphonylurea in the treatment of type 2 diabetes.; Diabetologia; 2005; vol. 48 (no. 12); 2477-81

41.1. Study details

Secondary publication of another included study- see primary study for details	For pioglitazone v metformin trial, see: • Hanefeld, M., Brunetti, P., Schernthaner, G. H., Matthews, D. R., Charbonnel, B. H., & QUARTET Study Group. (2004). One-year glycemic control with a sulfonylurea plus pioglitazone versus a sulfonylurea plus metformin in patients with type 2 diabetes. *Diabetes care*, *27*(1), 141-147. For pioglitazone v gliclazide trial, see: • Matthews, D. R., Charbonnel, B. H., Hanefeld, M., Brunetti, P., & Schernthaner, G. (2005). Long-term therapy with addition of pioglitazone to metformin compared with the addition of gliclazide to metformin in patients with type 2 diabetes: a randomized, comparative study. *Diabetes/metabolism research and reviews*, *21*(2), 167-174.
Other publications associated with this study included in review	For 2-year efficacy results of both trials, see: • Charbonnel, B., Schernthaner, G., Brunetti, P., Matthews, D. R., Urquhart, R., Tan, M. H., & Hanefeld, M. (2005). Long-term efficacy and tolerability of add-on pioglitazone therapy to failing monotherapy compared with addition of gliclazide or metformin in patients with type 2 diabetes. *Diabetologia*, *48*, 1093-1104.
Trial name / registration number	Not reported
Study type	Randomised controlled trial (RCT) Both double-blind parallel group RCTs

42. Billings, 2018

Bibliographic Reference	Billings, Liana K; Doshi, Ankur; Gouet, Didier; Oviedo, Alejandra; Rodbard, Helena W; Tentolouris, Nikolaos; Gron, Randi; Halladin, Natalie; Jodar, Esteban; Efficacy and Safety of IDegLira Versus Basal-Bolus Insulin Therapy in Patients With Type 2 Diabetes Uncontrolled on Metformin and Basal Insulin: The DUAL VII Randomized Clinical Trial.; Diabetes care; 2018; vol. 41 (no. 5); 1009-1016

42.1. Study details

Secondary publication of another included study- see primary study for details	N/A
Other publications associated with this study included in review	Patient-reported outcomes reported in: Miller, E., Doshi, A., Grøn, R., Jódar, E., Őrsy, P., Ranthe, M. F., ... & Billings, L. K. (2019). IDegLira improves patient-reported outcomes while using a simple regimen with fewer injections and dose adjustments compared with basal–bolus therapy. *Diabetes, Obesity and Metabolism*, *21*(12), 2643-2650.
Trial name / registration number	NCT02420262
Study type	Randomised controlled trial (RCT)
Study location	Multinational study conducted at 89 sites in 12 countries: Argentina, Czech Republic, France, Greece, Hungary, Israel, Mexico, Russian Federation, Slovakia, Spain, Turkey, United States.
Study setting	No additional information
Study dates	July 2015 to October 2016
Sources of funding	Trial funded by Novo Nordisk
Inclusion criteria	• Male or female aged ≥ 18 years at the time of signing informed consent. • Patients with type 2 diabetes (diagnosed clinically) ≥ 6 months prior to screening. • HbA_{1c} 7.0 to 10.0% inclusive (53-86 mmol/mol inclusive) by central laboratory analysis

	• Current treatment with insulin glargine 100 units/mL for at least 90 days prior to screening • Stable dose of insulin glargine 100 units/mL between 20 units and 50 units inclusive for at least 56 days prior to screening Individual fluctuations of +/-10% within the 56 days were acceptable; one the day of screening total daily dose should be within the 20-50 units range. • Stable daily dose of metformin (≥1500 mg or maximum tolerated dose) for at least 90 days prior to screening. • Body mass index ≤ 40 kg/m² • Willing and able to adhere to protocol including performing self-measured plasma glucose profiles, to keep a trial diary and use pre-filled pen device.
Exclusion criteria	• Known or suspected hypersensitivity to trial products or related products. • Previous participation in this trial (defined as signed informed consent). • Female who is pregnant, breast feeding, or intends to become pregnant or is of child-bearing potential not using adequate contraception method. • Receipt of any investigational medicinal product within 30 days of screening. • Treatment with any medication for the indication of diabetes or obesity other than stated in the inclusion criteria in a period of 90 days before screening. • Anticipated initiation of, or change to, concomitant medication for more than 14 days known to affect weight or glucose metabolism (e.g. sibutramine, orlistat, thyroid hormones, corticosteroids). • Impaired liver function defined as alanine transaminase ≥2.5 times upper limit of normal. • Renal impairment defined as eGFR <60 mL/min/1.73 m² as per Chronic Kidney Disease Epidemiology Collaboration guidelines. • Screening calcitonin ≥50 ng/L. • History of acute or chronic pancreatitis. • Personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia type 2. • Patients presently classified as being in New York Heart Association Class IV. • Myocardial infarction, stroke, transient ischaemic attack, hospitalisation for heart failure and /or unstable angina within the past 180 days. • Current planned coronary, carotid or peripheral artery revascularisation. • Inadequately treated blood pressure defined as Class 2 hypertension or higher (systolic ≥160 mmHG or diastolic ≥100 mgHg). • Proliferative retinopathy or maculopathy requiring acute treatment. verified by fundus photography. • Diagnosis of malignant neoplasms within the past 5 years (except basal and squamous cell skin cancer, polyps and in-situ carcinoma. • Any condition which in the opinion of the investigator might jeopardise patient safety or compliance with the protocol.

Recruitment / selection of participants	No additional information.
Intervention(s)	IDegLira (insulin degludec 100 units/mL and liraglutide 3.6 mg/mL) in a prefilled FlexTouch pen for subcutaneous injection. Administered once daily at any time, regardless of meals, repeated at approximately the same time each day. Patients were initiated on 16 units degludec/0.58 mg liraglutide and titrated twice weekly, aiming for a mean pre-breakfast self-monitored plasma glucose target range of 4.0 - 5.0 mmol/L (72-90 mg/dL). The maximum dose of IDegLira was 50 units degludec/1.8 mg liraglutide.
Cointervention	Metformin continued at pre-trial dose.
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear Excluded "New York Heart Association Class IV", other HF unclear. No information in baseline characteristics.
Strata 2: People with atherosclerotic cardiovascular disease	Not stated/unclear Excluded "myocardial infarction, stroke or hospitalization for unstable angina and/or transient ischemic attack within 180 days", prior to this unclear. No information in baseline characteristics.
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear Excluded people with "renal impairment (estimated glomerular filtration rate <60 mL/min/1.73 m2)", unclear by CKD diagnosis. No information in baseline characteristics.
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	Not stated/unclear
Subgroup 1: People with moderate or severe frailty	Not stated/unclear
Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear Only mean duration reported in baseline characteristics

Subgroup 3: People with non-alcoholic fatty liver disease	Not stated/unclear Excluded people with "impaired liver function defined as alanine transaminase ≥2.5 times upper limit of normal". No further information about liver disease.
Subgroup 4: People with obesity	Not stated/unclear Body mass index ≤ 40 kg/m² in the inclusion criteria. Only mean weight and BMI reported for each group in baseline characteristics.
Subgroup 5: eGFR category at baseline	eGFR ≥30mL/min/1.73m2 Renal impairment defined as eGFR <60 mL/min/1.73 m² in the exclusion criteria.
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Comparator	Insulin glargine 100 units/mL solution in a pre-filled 3 mL Solostar pen for subcutaneous injection and insulin aspart 100 units/mL solution in a 3 mL prefilled FlexPen for subcutaneous injection. Insulin glargine was administered once daily according to local labelling and was initiated at a dose equivalent to the pre-trial dose, titrated using the same algorithm as IDegLira. Insulin aspart was initiated from the day of randomisation at a starting dose of 4 units per main meal (≤ 4 times per day) and titrated twice weekly, aiming for a mean pre-prandial and bedtime SMPG target range of 4.0 - 6.0 mmol/L (72-108 mg/dL). The principal investigator at each study site could adjust the titration according to clinical judgement. No protocols given to patients regarding meal size or constituents.
Number of participants	N=506
Duration of follow-up	26 week treatment period with 4 week follow-up period
Indirectness	Partially applicable for the nocturnal hypoglycaemia outcome. Nocturnal hypoglycaemia outcome includes only people experiencing severe hypoglycaemia episodes at night (comprising severe hypoglycemia requiring third party assistance and blood-glucose confirmed symptomatic hypoglycaemia [SMBG <31.mmol/L) overnight, and does not include any people who had non-severe hypoglycaemia episodes at night.

Method of analysis	ITT Efficacy outcomes analysed using the full analysis set, defined as all randomised patients. Modified ITT
Additional comments	"All efficacy end points were summarised using the full analysis set (FAS), and safety end points were summarised using the safety analysis set (SAS). All statistical analyses of efficacy and safety end points were based on the FAS." FAS defined as all patients randomised. SAS defined as all patients randomised who took at least one dose of study medication. Sensitivity analyses were performed to assess the robustness of primary and confirmatory secondary analyses. Sensitivity analyses included MMRM (mixed model for repeated measurement), multiple imputation and LOCF (last observation carried forward).

42.2. Study arms

42.2.1. Insulin degludec and liraglutide fixed-ratio combination (N = 252)

Other publications associated with this study included in review	N/A

IDegLira (insulin degludec 100 units/mL and liraglutide 3.6 mg/mL in a 3 mL prefilled FlexTouch pen)

42.2.2. Basal-bolus insulin (Insulin glargine and insulin aspart) (N = 254)

Other publications associated with this study included in review	N/A

Insulin glargine (100 units/mL solution) in a 3 mL prefilled Solostar pen for subcutaneous injection and insulin aspart (100 units/mL solution) in a 3 mL prefilled FlexPen for subcutaneous injection.

42.3. Characteristics

42.3.1. Arm-level characteristics

Characteristic	Insulin degludec and liraglutide fixed-ratio combination (N = 252)	Basal-bolus insulin (Insulin glargine and insulin aspart) (N = 254)
% Male Sample size	n = 110 ; % = 43.7	n = 117 ; % = 46.1
Mean age (SD) (years) Mean (SD)	58.6 (9)	58 (8.6)
Ethnicity Sample size	n = NR ; % = NR	n = NR ; % = NR
Comorbidities Sample size	n = NR ; % = NR	n = NR ; % = NR
Presence of frailty Sample size	n = NR ; % = NR	n = NR ; % = NR
Time since type 2 diabetes diagnosed Mean (SD)	NR (NR)	NR (NR)
HbA1c Mean (SD)	8.2 (0.8)	8.2 (0.8)
Cardiovascular risk factors Sample size	n = NR ; % = NR	n = NR ; % = NR
Blood pressure Sample size	n = NR ; % = NR	n = NR ; % = NR
Heart rate Mean (SD)	NR (NR)	NR (NR)
Smoking status Sample size	n = NR ; % = NR	n = NR ; % = NR

Characteristic	Insulin degludec and liraglutide fixed-ratio combination (N = 252)	Basal-bolus insulin (Insulin glargine and insulin aspart) (N = 254)
Alcohol consumption Mean (SD)	NR (NR)	NR (NR)
Presence of severe mental illness Sample size	n = NR ; % = NR	n = NR ; % = NR
People with significant cognitive impairment Sample size	n = NR ; % = NR	n = NR ; % = NR
People with a learning disability Sample size	n = NR ; % = NR	n = NR ; % = NR
Weight (kg) Mean (SD)	87.2 (16)	88.2 (17.2)
BMI (kg/m²) Mean (SD)	31.7 (4.4)	31.7 (4.5)
Number of people with obesity Sample size	n = NR ; % = NR	n = NR ; % = NR
Cholesterol and lipid levels Mean (SD)	NR (NR)	NR (NR)
Albumin creatinine ratio Mean (SD)	NR (NR)	NR (NR)
eGFR mL/min/1.73m2 Mean (SD)	NR (NR)	NR (NR)
Other antidiabetic medication used Mean (SD)	NA (NA)	NA (NA)
Metformin Daily metformin dose (mg) Mean (SD)	2049 (456)	2091 (458.3)

Characteristic	Insulin degludec and liraglutide fixed-ratio combination (N = 252)	Basal-bolus insulin (Insulin glargine and insulin aspart) (N = 254)
Insulin Daily insulin dose (units) Mean (SD)	34 (10.7)	33 (10.4)
Blood pressure-lowering medication used Sample size	n = NR ; % = NR	n = NR ; % = NR
Statins/lipid-lowering medication used Sample size	n = NR ; % = NR	n = NR ; % = NR
Other treatment being received Sample size	n = NR ; % = NR	n = NR ; % = NR

43. Bizino, 2019

Bibliographic Reference	Bizino, M. B.; Jazet, I. M.; Westenberg, J. J. M.; Van Eyk, H. J.; Paiman, E. H. M.; Smit, J. W. A.; Lamb, H. J.; Effect of liraglutide on cardiac function in patients with type 2 diabetes mellitus: randomized placebo-controlled trial; Cardiovasc Diabetol; 2019; vol. 18 (no. 1); 55

43.1. Study details

Secondary publication of another included study- see primary study for details	N/A - primary study for MAGNA VICTORIA trial
Other publications associated with this study included in review	van Eyk HJ, Paiman EHM, Bizino MB, IJzermans SL, Kleiburg F, Boers TGW, Rappel EJ, Burakiewicz J, Kan HE, Smit JWA, Lamb HJ, Jazet IM, Rensen PCN. Liraglutide decreases energy expenditure and does not affect the fat fraction of supraclavicular brown adipose tissue in patients with type 2 diabetes. Nutr Metab Cardiovasc Dis. 2020 Apr 12;30(4):616-624. doi: 10.1016/j.numecd.2019.12.005. Epub 2019 Dec 13. PMID: 32127340. EPPI ID = 13676344
Trial name / registration number	NCT01761318
Study location	Trial conducted at Leiden University Medical Centre, Leiden, Netherlands
Study setting	No additional information
Study dates	Participants were enrolled between December 2013 and September 2015, with the last patient visit in March 2016.
Sources of funding	Novo Nordisk funded the study.
Inclusion criteria	Inclusion criteria: • men and women with type 2 diabetes aged 18-69 years • BMI 25 kg/m2 or above • HbA1c level of 7.0 to 10.0% (53-86 mmol/mol) despite use of maximum tolerable dose of metformin, with or without sulfonylurea and /or insulin, with stable dosage in the 3 months before study entry

	• blood pressure <150/85 mmHg and stable for at least 1 month
Exclusion criteria	Exclusion criteria: • use of glucose-lowering therapies other than those specified in the inclusion criteria • history or presence of renal, hepatic or cardiovascular disease • gastric bypass surgery • chronic pancreatitis or previous acute pancreatitis • pregnant or lactating women • contra-indications for MRI
Recruitment / selection of participants	Patients underwent pre-screening by telephone to assess eligibility based on drug use, medical history and anthropometric measures. Potentially eligible patients attended a subsequent screening visit with detailed history taking (including cardiovascular symptoms, presence of neuropathy, nephropathy and retinopathy), physical examination and ECG and blood tests. .
Intervention(s)	Liraglutide once daily subcutaneous injection. Liraglutide was up-titrated from 0.6 mg in the first week, 1.2 mg in the second week and 1.8 mg from week 3. Study drug dose was reduced if necessitated by adverse events.
Cointervention	Metformin with or without sulfonylurea and / or insulin
Strata 1: People with type 2 diabetes mellitus and heart failure	People without heart failure Excluded "history or presence of cardiovascular disease". The nonattendance of cardiovascular disease was defined as absence of symptoms related to coronary artery disease and heart failure and normal ECG.
Strata 2: People with atherosclerotic cardiovascular disease	People without atherosclerotic cardiovascular diseases Excluded "history or presence of cardiovascular disease". "The nonattendance of cardiovascular disease was defined as absence of symptoms related to coronary artery disease and heart failure and normal ECG." Only 9% had cerebrovascular or peripheral artery disease.
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Mixed population Excluded "history or presence of renal disease" but baseline characteristics show 26% had nephropathy.

Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	Not stated/unclear
Subgroup 1: People with moderate or severe frailty	Not stated/unclear
Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear Only mean age and mean duration of diabetes reported.
Subgroup 3: People with non-alcoholic fatty liver disease	People without non-alcoholic fatty liver disease Hepatic disease an exclusion criteria.
Subgroup 4: People with obesity	Not stated/unclear Only mean BMI at baseline reported
Subgroup 5: eGFR category at baseline	Not stated/unclear
Subgroup 6: Albuminuria category at baseline	Not stated/unclear Only mean UACR at baseline reported. No information in inclusion/exclusion criteria.
Comparator	Placebo once daily subcutaneous injection added to pharmacologic treatment at study entry.
Number of participants	N= 49
Duration of follow-up	26 weeks
Indirectness	
Method of analysis	ITT Authors describe analysis as ITT population. 50 people were randomised, 49 people were included in the analysis.

43.2. Study arms

43.2.1. Liraglutide (N = 23)

Other publications associated with this study included in review	Bizino 2021

Liraglutide 1.8 mg once daily subcutaneous administration

43.2.2. Placebo (N = 26)

Once daily subcutaneous injection

43.3. Characteristics

43.3.1. Arm-level characteristics

Characteristic	Liraglutide (N = 23)	Placebo (N = 26)
% Male Sample size	n = 14 ; % = 61	n = 15 ; % = 58
Mean age (SD) (years) Mean (SD)	60 (6)	59 (7)
Ethnicity Sample size	n = NR ; % = NR	n = NR ; % = NR
Comorbidities Sample size	n = NA ; % = NA	n = NA ; % = NA
Retinopathy Sample size	n = 4 ; % = 17	n = 2 ; % = 8
Nephropathy Sample size	n = 2 ; % = 9	n = 11 ; % = 42
Neuropathy Sample size	n = 10 ; % = 44	n = 7 ; % = 2

Characteristic	Liraglutide (N = 23)	Placebo (N = 26)
Macrovascular complications cerebrovascular or peripheral artery disease Sample size	n = 2 ; % = 9	n = 0 ; % = 0
Presence of frailty Sample size	n = NR ; % = NR	n = NR ; % = NR
Time since type 2 diabetes diagnosed (years) Mean (SD)	11 (6)	11 (7)
HbA1c (%) Mean (SD)	8.4 (1.1)	8.2 (1)
Cardiovascular risk factors Sample size	n = NA ; % = NA	n = NA ; % = NA
Blood pressure (mmHg) Mean (SD)	NA (NA)	NA (NA)
Diastolic blood pressure Mean (SD)	86 (6)	87 (11)
Systolic blood pressure Mean (SD)	141 (14)	141 (15)
Heart rate Mean (SD)	NR (NR)	NR (NR)
Smoking status Sample size	n = NA ; % = NA	n = NA ; % = NA
Never smoked Sample size	n = 10 ; % = 44	n = 8 ; % = 31
Current smoker Sample size	n = 4 ; % = 17	n = 5 ; % = 19
Ex-smoker Sample size	n = 9 ; % = 39	n = 13 ; % = 50
Alcohol consumption Mean (SD)	NR (NR)	NR (NR)
Presence of severe mental illness	n = NR ; % = NR	n = NR ; % = NR

Characteristic	Liraglutide (N = 23)	Placebo (N = 26)
Sample size		
People with significant cognitive impairment Sample size	n = NR ; % = NR	n = NR ; % = NR
People with a learning disability Sample size	n = NR ; % = NR	n = NR ; % = NR
Weight (kg) Mean (SD)	98 (14)	94 (13)
BMI (kg/m2) Mean (SD)	32.6 (4.4)	31.6 (3.4)
Number of people with obesity Sample size	n = NR ; % = NR	n = NR ; % = NR
Cholesterol and lipid levels (mmol/L) Mean (SD)	NA (NA)	NA (NA)
Triglycerides Mean (SD)	2.2 (1.5)	2.1 (1.1)
HDL cholesterol Mean (SD)	1.2 (0.2)	1.3 (0.4)
LDL cholesterol Mean (SD)	2.6 (0.9)	2.5 (0.9)
Albumin creatinine ratio (mmol/µg) Mean (SD)	1 (1.3)	5 (8.9)
eGFR mL/min/1.73m2 Mean (SD)	NR (NR)	NR (NR)
Other antidiabetic medication used Sample size	n = NA ; % = NA	n = NA ; % = NA
Sulfonlyurea Sample size	n = 6 ; % = 26	n = 8 ; % = 31
Insulin Sample size	n = 15 ; % = 65	n = 17 ; % = 65

Characteristic	Liraglutide (N = 23)	Placebo (N = 26)
Metformin Sample size	n = 23 ; % = 100	n = 26 ; % = 100
Blood pressure-lowering medication used Sample size	n = 18 ; % = 78	n = 20 ; % = 77
Statins/lipid-lowering medication used Sample size	n = 21 ; % = 91	n = 19 ; % = 73
Other treatment being received Sample size	n = NA ; % = NA	n = NA ; % = NA
Metformin dose (g/day) Mean (SD)	2.1 (0.7)	2 (0.5)

44. Blonde, 2020

Bibliographic Reference	Blonde, L.; Belousova, L.; Fainberg, U.; Garcia-Hernandez, P. A.; Jain, S. M.; Kaltoft, M. S.; Mosenzon, O.; Nafach, J.; Palle, M. S.; Rea, R.; Liraglutide as add-on to sodium-glucose co-transporter-2 inhibitors in patients with inadequately controlled type 2 diabetes: LIRA-ADD2SGLT2i, a 26-week, randomized, double-blind, placebo-controlled trial; Diab Obes Metab; 2020

44.1. Study details

Secondary publication of another included study- see primary study for details	N/A
Other publications associated with this study included in review	N/A
Trial name / registration number	LIRA-ADD2SGLT2i / NCT02964247
Study type	Randomised controlled trial (RCT)
Study location	Multicentre, multinational trial at 74 sites in Brazil, India, Israel, Mexico, the Russian Federation and the United States.
Study setting	No additional information.
Study dates	3 March 2017 to 8 May 2018.
Sources of funding	Novo Nordisk
Inclusion criteria	• Adults ≥ 18 years with type 2 diabetes and HbA1c 7.0% to 9.5% • BMI ≥20 kg/m2 • On a stable dose of an SGLT2i for at least 90 days as monotherapy or combined with a stable metformin dose (≥1500 mg or maximum tolerated dose)
Exclusion criteria	• History of diabetic ketoacidosis while being treated with SGLT2is

	• Family or personal history of multiple endocrine neoplasia type 2 or medullary thyroid carcinoma • History of acute or chronic pancreatitis • Estimated glomerular filtration rate <60 mL/min/1.73 m2
Recruitment / selection of participants	No additional information.
Intervention(s)	Liraglutide once daily subcutaneous injection 1.8 mg maintenance dose after initial dose escalation delivered via a prefilled pen injector. Dose escalation started with a dose of 0.6 mg during week 1, increasing to 1.2 mg during week 2 and 1.8 mg during weeks 3–26 depending on patient tolerance. Escalation from 0.6 to 1.2 mg/day, then 1.8 mg/day could have been extended by 7 days in total if patients did not tolerate an increase in dose, at the discretion of the investigator. Maintenance dose of 1.8 mg/day should have remained unchanged throughout the remainder of the trial. In rare situations where a dose of 1.8 mg/day despite all efforts was not tolerated (e.g. using extra time for dose escalation and discussing with/informing patients that gastrointestinal adverse events in general are transient and subside over time), the dose could have been reduced to 1.2 mg/day, again at the discretion of the investigator.
Cointervention	Pre-existing SGLT2 inhibitor with or without metformin (≥1500 mg or maximum tolerated dose)
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear Not an inclusion/exclusion criteria. No information in baseline characteristics.
Strata 2: People with atherosclerotic cardiovascular disease	Not stated/unclear Not an inclusion/exclusion criteria. No information in baseline characteristics.
Strata 3: People with type 2	Not stated/unclear Excluded "eGFR< 60 mL/min/1.73 m2", otherwise unclear. Baseline characteristics give eGFR categories but not CKD diagnosis.

diabetes mellitus and chronic kidney disease	
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	Not stated/unclear
Subgroup 1: People with moderate or severe frailty	Not stated/unclear
Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear Only mean duration of diabetes reported in baseline characteristics.
Subgroup 3: People with non-alcoholic fatty liver disease	Not stated/unclear
Subgroup 4: People with obesity	Mixed population Baseline data for BMI shows number of people in each category. 60% of people in the trial had a BMI ≥30.
Subgroup 5: eGFR category at baseline	eGFR ≥30mL/min/1.73m2 eGFR <60 mL/min/1.73 m2 an exclusion criterion
Subgroup 6: Albuminuria category at baseline	Mixed population 23% of participants had UACR >30 mg/g
Population subgroups	N/A
Comparator	Placebo once daily subcutaneous injection using a prefilled pen injector (identical to the pen injector used in the intervention group).
Number of participants	303

Duration of follow-up	26 weeks
Indirectness	
Method of analysis	ITT Statistical approach described as the 'treatment policy estimand' was used to evaluate the average treatment effect in all randomised patients, regardless of adherence to treatment or use of rescue therapy.

44.2. Study arms

44.2.1. Liraglutide (N = 203)

Liraglutide once daily subcutaneous injection 1.8 mg maintenance dose after initial dose escalation.

44.2.2. Placebo (N = 100)

Placebo once daily subcutaneous injection 1.8 mg maintenance dose after initial dose escalation.

44.3. Characteristics

44.3.1. Arm-level characteristics

Characteristic	Liraglutide (N = 203)	Placebo (N = 100)
% Male Sample size	n = 125 ; % = 62	n = 58 ; % = 58
Mean age (SD) (years) Mean (SD)	54.7 (10.1)	56 (9.9)
Ethnicity Sample size	n = NR ; % = NR	n = NR ; % = NR
Comorbidities Sample size	n = NR ; % = NR	n = NR ; % = NR
Presence of frailty Sample size	n = NR ; % = NR	n = NR ; % = NR

Characteristic	Liraglutide (N = 203)	Placebo (N = 100)
Time since type 2 diabetes diagnosed (years) Mean (SD)	10.1 (7.2)	9.6 (6.7)
HbA1c (%) Mean (SD)	8 (0.7)	8 (0.6)
Cardiovascular risk factors Sample size	n = NR ; % = NR	n = NR ; % = NR
Blood pressure Mean (SD)	NA (NA)	NA (NA)
Systolic blood pressure mmHg Mean (SD)	127.5 (12.7)	128.5 (14.4)
Diastolic blood pressure mmHg Mean (SD)	79.2 (9)	79.3 (8.9)
Heart rate Mean (SD)	NR (NR)	NR (NR)
Smoking status Sample size	n = NR ; % = NR	n = NR ; % = NR
Alcohol consumption Mean (SD)	NR (NR)	NR (NR)
Presence of severe mental illness Sample size	n = NR ; % = NR	n = NR ; % = NR
People with significant cognitive impairment Sample size	n = NR ; % = NR	n = NR ; % = NR
People with a learning disability Sample size	n = NR ; % = NR	n = NR ; % = NR
Weight (kg) Mean (SD)	91 (21)	91.4 (21.4)
BMI (kg/m²) Mean (SD)	32 (6)	32.6 (6.5)

Characteristic	Liraglutide (N = 203)	Placebo (N = 100)
Number of people with obesity (kg/m²) Sample size	n = NA ; % = NA	n = NA ; % = NA
BMI <25 Sample size	n = 13 ; % = 6.4	n = 14 ; % = 14
BMI 25 to 30 Sample size	n = 72 ; % = 35.5	n = 22 ; % = 22
BMI 30 to <35 Sample size	n = 64 ; % = 31.5	n = 34 ; % = 34
BMI 35 to <40 Sample size	n = 34 ; % = 16.7	n = 20 ; % = 20
BMI ≥40 Sample size	n = 20 ; % = 9.9	n = 10 ; % = 10
Cholesterol and lipid levels Mean (SD)	NR (NR)	NR (NR)
Albumin creatinine ratio (mg/g) UACR >30 mg/g Sample size	n = 51 ; % = 25.9	n = 18 ; % = 18.6
eGFR mL/min/1.73m2 (ml/min/1.73 m2) Sample size	n = NA ; % = NA	n = NA ; % = NA
Normal (>=90) Sample size	n = 149 ; % = 73.4	n = 72 ; % = 72
Mildly decreased (60 to 90) Sample size	n = 53 ; % = 26.1	n = 28 ; % = 28
Other antidiabetic medication used Sample size	n = NA ; % = NA	n = NA ; % = NA
Dapagliflozin Sample size	n = 96 ; % = 47.3	n = 54 ; % = 54
Empagliflozin Sample size	n = 55 ; % = 27.1	n = 23 ; % = 23

Characteristic	Liraglutide (N = 203)	Placebo (N = 100)
Canagliflozin Sample size	n = 52 ; % = 25.6	n = 23 ; % = 23
Metformin Sample size	n = 191 ; % = 94.1	n = 95 ; % = 95
Blood pressure-lowering medication used Sample size	n = NR ; % = NR	n = NR ; % = NR
Statins/lipid-lowering medication used Sample size	n = NR ; % = NR	n = NR ; % = NR
Other treatment being received Sample size	n = NR ; % = NR	n = NR ; % = NR
Race Sample size	n = NA ; % = NA	n = NA ; % = NA
White Sample size	n = 131 ; % = 64.5	n = 59 ; % = 59
Black or African American Sample size	n = 12 ; % = 5.9	n = 5 ; % = 5
Asian Sample size	n = 38 ; % = 18.7	n = 15 ; % = 15
Other Includes American Indian or Alaska Native, Native Hawaiian, or other Pacific Islander, and others Sample size	n = 22 ; % = 10.8	n = 21 ; % = 21

45. Blonde, 2015

Bibliographic Reference	Blonde, L.; Jendle, J.; Gross, J.; Woo, V.; Jiang, H.; Fahrbach, J. L.; Milicevic, Z.; Once-weekly dulaglutide versus bedtime insulin glargine, both in combination with prandial insulin lispro, in patients with type 2 diabetes (AWARD-4): a randomised, open-label, phase 3, non-inferiority study; Lancet; 2015; vol. 385 (no. 9982); 2057-66

45.1. Study details

Secondary publication of another included study- see primary study for details	N/A
Other publications associated with this study included in review	N/A
Trial name / registration number	NCT01191268
Study type	Randomised controlled trial (RCT)
Study location	105 sites in 15 countries: Argentina, Australia, Belgium, Brazil, Canada, Denmark, Greece, Hungary, Mexico, Poland, Russia, Spain, Sweden, Taiwan and the USA.
Study dates	Random assignment of patients took place between 9 December 2010 and 21 September 2012.
Sources of funding	Eli Lilly and Company
Inclusion criteria	• Male and female (not pregnant or breast feeding) adults aged ≥ 18 years old with type 2 diabetes r • Screening HbA1c concentration of 7.0% or more (≥53 mmol/mol) and 11.0% or less (≤97 mmol/mol) • Treated for ≥3 months with a conventional insulin regimen: one or two stable daily insulin doses (any combination of basal, basal with prandial, or premixed insulin [excluding any prandial insulin only regimen], with or without oral antihyperglycaemic medications). Eligible patients must have been on stable doses of insulin (to confirm that intensification of therapy was needed).

	• Stable body weight and BMI of 23 - 45 kg/m2 for ≥3 months prior to screening. • Provided written informed consent.
Exclusion criteria	• Diagnosis of type 1 diabetes. • Multiple daily injection insulin regimen (≥3 insulin doses per day). • Serious diabetes-related or other health concerns or risks including: cardiovascular conditions such as acute myocardial infarction, New York Heart Association class III/IV heart failure, or stroke within 2 months prior to study visit 1; significant gastric emptying abnormality; acute or chronic hepatitis or symptoms of liver disease; acute or chronic pancreatitis; GFR ≤30 mL/min/1.73m2 at screening; significant uncontrolled endocrine abnormality; type 2A or 2B multiple endocrine neoplasia or self or family history of medullary C-cell hyperplasia, focal hyperplasia, or carcinoma; serum calcitonin level of ≥20 pg/mL at visit 1; organ transplantation other than corneal transplants. • GLP-1 receptor agonist treatment within 3 months prior to visit 1. • Treatment with weight loss medication within 3 months of visit 1 or chronic (>2 weeks) systemic glucocorticoid therapy (excluding topical, intra-ocular, intranasal, or inhaled preparations) or such treatment within1 month of visit 1.
Recruitment / selection of participants	
Intervention(s)	1) Dulaglutide 1.5 mg daily subcutaneous injection plus insulin lispro at 50% of the pre-randomisation insulin dose. Insulin dose adjusted twice weekly according to a treatment algorithm. 2) Dulaglutide 0.75 mg daily by subcutaneous injection plus insulin lispro at 50% of the pre-randomisation insulin dose. Insulin dose adjusted twice weekly according to a treatment algorithm.
Cointervention	Metformin was allowed. Patients receiving metformin were to have used 1500 mg per day or more by week 2 of the lead-in period. The dose remained stable for at least 6 weeks before randomisation and during the treatment period. Other oral glucose-lowering drugs were discontinued.
Strata 1: People with type 2	Not stated/unclear

diabetes mellitus and heart failure	People with New York heart Association Heart failure class III and IV within 2 months prior to visit 1 were excluded. No information class II or heart failure before the 2 months pre-visit 1. No information in baseline characteristics.
Strata 2: People with atherosclerotic cardiovascular disease	Not stated/unclear Not an inclusion/exclusion criteria. No information in baseline characteristics.
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear Not an inclusion/exclusion criteria. No information in baseline characteristics.
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	Not stated/unclear
Subgroup 1: People with moderate or severe frailty	Not stated/unclear
Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear Duration of type 2 diabetes reported in baseline characteristics, but no information about age of onset.
Subgroup 3: People with non-alcoholic fatty liver disease	Not stated/unclear "Symptoms of liver disease" an exclusion criteria' no further information.
Subgroup 4: People with obesity	Not stated/unclear Only mean weight reported at baseline; number of people with obesity is unclear.
Subgroup 5: eGFR category at baseline	eGFR ≥30mL/min/1.73m2 People with GFR ≤30 mL/min/1·73 m2 at screening were excluded

Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Population subgroups	Not in the inclusion or exclusion criteria. No information in baseline characteristics.
Comparator	Insulin glargine once daily subcutaneous injection at bed time in accordance with treatment algorithm (treat-to-target strategy) plus daily pre-meal insulin lispro subcutaneous injections according to treatment algorithm. Glargine was commenced at 50% of the pre-randomisation dose of total daily insulin; the remaining 50% was applied to lispro.
Number of participants	N=884
Duration of follow-up	52 weeks
Method of analysis	ITT

45.2. Study arms

45.2.1. Duaglutide 1.5 mg (N = 295)

Once weekly dulaglutide subcutaneous injection plus daily pre-meal insulin lispro subcutaneous injections according to treatment algorithm

45.2.2. Dulaglutide 0.75 mg (N = 293)

Once weekly dulaglutide 0.75 mg subcutaneous injection plus daily pre-meal insulin lispro subcutaneous injections according to treatment algorithm

45.2.3. Insulin glargine (N = 296)

Insulin glargine once daily subcutaneous injection at bed time in accordance with treatment algorithm (treat-to-target strategy) plus daily pre-meal insulin lispro subcutaneous injections according to treatment algorithm

45.3. Characteristics

45.3.1. Arm-level characteristics

Characteristic	Duaglutide 1.5 mg (N = 295)	Dulaglutide 0.75 mg (N = 293)	Insulin glargine (N = 296)
% Male Sample size	n = 160 ; % = 54	n = 148 ; % = 50	n = 165 ; % = 56
Mean age (SD) (years) Mean (SD)	58.9 (9.6)	59.3 (9)	59.9 (9.1)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
Hispanic or Latino Sample size	n = 102 ; % = 35	n = 101 ; % = 34	n = 100 ; % = 34
Comorbidities Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Presence of frailty Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Time since type 2 diabetes diagnosed (years) Mean (SD)	12.8 (7.2)	12.4 (6.9)	13 (6.8)
HbA1c (%) Mean (SD)	8.46 (1.08)	8.4 (1.03)	8.53 (1.03)
Cardiovascular risk factors Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Blood pressure mmHg Mean (SD)	NA (NA)	NA (NA)	NA (NA)
Systolic blood pressure Mean (SD)	133.3 (16.6)	134 (15.9)	133.3 (17)
Diastolic blood pressure Mean (SD)	77.3 (9.7)	77.6 (9)	77.2 (10.4)
Heart rate	NR (NR)	NR (NR)	NR (NR)

Characteristic	Duaglutide 1.5 mg (N = 295)	Dulaglutide 0.75 mg (N = 293)	Insulin glargine (N = 296)
Mean (SD)			
Smoking status Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Alcohol consumption Mean (SD)	NR (NR)	NR (NR)	NR (NR)
Presence of severe mental illness Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
People with significant cognitive impairment Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
People with a learning disability Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Weight (kg) Mean (SD)	91 (18.2)	91.7 (18)	90.8 (18.9)
BMI (kg/m²) Mean (SD)	32 (5.1)	33.1 (5.2)	32.4 (5.3)
Number of people with obesity Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Cholesterol and lipid levels Mean (SD)	NR (NR)	NR (NR)	NR (NR)
Albumin creatinine ratio Mean (SD)	NR (NR)	NR (NR)	NR (NR)
eGFR mL/min/1.73m2 Mean (SD)	NR (NR)	NR (NR)	NR (NR)
Other antidiabetic medication used Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA

Characteristic	Duaglutide 1.5 mg (N = 295)	Dulaglutide 0.75 mg (N = 293)	Insulin glargine (N = 296)
Basal insulin regimen Sample size	n = 182 ; % = 62	n = 181 ; % = 62	n = 181 ; % = 61
Basal and prandial insulin regimen Sample size	n = 113 ; % = 38	n = 112 ; % = 38	n = 115 ; % = 39
Oral drugs Sample size	n = 236 ; % = 80	n = 237 ; % = 81	n = 234 ; % = 79
Alpha-glucosidase inhibitors Sample size	n = 1 ; % = 0.34	n = 2 ; % = 1	n = 5 ; % = 2
Biguanides Sample size	n = 216 ; % = 73	n = 212 ; % = 72	n = 214 ; % = 72
DPP-4 inhibitors Sample size	n = 10 ; % = 3	n = 16 ; % = 72	n = 214 ; % = 72
Glinides Sample size	n = 3 ; % = 1	n = 1 ; % = 0.34	n = 4 ; % = 1
Sulfonylureas Sample size	n = 80 ; % = 27	n = 92 ; % = 31	n = 87 ; % = 29
Thiazolidinediones Sample size	n = 16 ; % = 5	n = 14 ; % = 5	n = 17 ; % = 6
Blood pressure-lowering medication used Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Statins/lipid-lowering medication used Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Other treatment being received Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Race Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA

Characteristic	Duaglutide 1.5 mg (N = 295)	Dulaglutide 0.75 mg (N = 293)	Insulin glargine (N = 296)
American Indian or Alaska Native Sample size	n = 16 ; % = 5	n = 13 ; % = 4	n = 17 ; % = 6
Asian Sample size	n = 9 ; % = 3	n = 12 ; % = 4	n = 14 ; % = 5
Black or African American Sample size	n = 32 ; % = 11	n = 27 ; % = 9	n = 26 ; % = 9
Multiple Sample size	n = 7 ; % = 2	n = 6 ; % = 2	n = 7 ; % = 2
Native Hawaiian or other Pacific Islander Sample size	n = 0 ; % = 0	n = 0 ; % = 0	n = 1 ; % = 0.34
White Sample size	n = 231 ; % = 78	n = 235 ; % = 80	n = 231 ; % = 78
Total daily insulin dose (IU) Mean (SD)	55.2 (32.2)	59.11 (38.1)	53.93 (30.7)

46. Bode, 2013

Bibliographic Reference	Bode, B.; Stenlöf, K.; Sullivan, D.; Fung, A.; Usiskin, K.; Efficacy and safety of canagliflozin treatment in older subjects with type 2 diabetes mellitus: a randomized trial; Hosp Pract (1995); 2013; vol. 41 (no. 2); 72-84

46.1. Study details

Secondary publication of another included study- see primary study for details	N/A
Other publications associated with this study included in review	Bode 2015 (78 week extension period, reporting 104 week outcomes) Bode B, Stenlöf K, Harris S, Sullivan D, Fung A, Usiskin K, Meininger G. Long-term efficacy and safety of canagliflozin over 104 weeks in patients aged 55-80 years with type 2 diabetes. Diabetes Obes Metab. 2015 Mar;17(3):294-303. doi: 10.1111/dom.12428. Epub 2015 Jan 12. PMID: 25495720. EPPI ID = 13681674
Trial name / registration number	NCT01106651
Study type	Randomised controlled trial (RCT)
Study location	17 countries
Study setting	Study conducted at 90 study centres in 17 countries. No further information.
Study dates	April 2010 to November 2011 (primary study) , followed by a 78 week extension period (subsidiary study Bode 2015)
Sources of funding	Study sponsored by Janssen Research & Development
Inclusion criteria	• Men and women with type 2 diabetes aged 55 to 80 years, who had inadequate glycaemic control (HbA1c levels ≥ 7.0% to ≤ 10.0%) on no blood glucose-lowering agent, or on a stable regimen of blood glucose-lowering agents/s as monotherapy or combination

	therapy (including metformin, sulfonylurea, dipeptidyl peptidase-4 [DPP-4] inhibitor, alpha-glucosidase inhibitor, glucagon-like peptide-1 [GLP-1] agonist, or insulin [for ≥ 12 weeks prior to screening] or pioglitazone [for ≥ 6 months prior to screening]) used in accordance with local prescribing information. • Body mass index between 20 - 40 kg/m² • Fasting plasma glucose (FPG) level < 270 mg/dL (15.0 mmol/L) at week -2 (start of the single-blind, placebo run-in period) • Fasting fingerstick blood glucose level ≥ 110 mg/dL (6.1 mmol/L) and < 270 mg/dL (15.0 mmol/L at baseline)
Exclusion criteria	• History of type 1 diabetes • Repeated FPG level ≥ 270 mg/dL (15.0 mmol/L) during the pretreatment phase • History of myocardial infarction, unstable angina, revascularisation procedure, or cerebrovascular accident within 3 months before screening • History of New York Heart Association Class III-IV cardiac disease • Uncontrolled hypertension • Estimated glomerular filtration rate (eGFR) < 50 mL/min/1.73 m² • People on background metformin therapy were excluded if they had serum creatinine levels ≥ 1.4 mg/dL (124 µmol/L) for men and ≥ 1.3 mg/dL (115 µmol/L) for women, or any contraindication to the use of metformin (including low eGFR) based on the label for the country of the investigational site.
Recruitment / selection of participants	No further information
Intervention(s)	Canagliflozin 100 mg once daily before first meal in addition to existing therapy for type 2 diabetes Canagliflozin 300 mg once daily before first meal in addition to existing therapy for type 2 diabetes
Cointervention	Most participants were on a pre-existing stable regimen of blood glucose-lowering therapy as monotherapy or combination therapy (including metformin, sulfonylurea, DPP-4 inhibitor, α-glucosidase inhibitor, GLP-1 agonist, insulin or pioglitazone). Some participants were not on any pre-existing glucose-lowering therapy. Glycaemic rescue therapy (up-titration of current blood glucose-lowering medicine/s, or step-wise addition of blood glucose-lowering medicines) was initiated in accordance with prespecified criteria.
Strata 1: People with type 2	Not stated/unclear Excluded "history of New York Heart Association Class III–IV cardiac disease", otherwise unclear. No information in baseline characteristics.

diabetes mellitus and heart failure	
Strata 2: People with atherosclerotic cardiovascular disease	Not stated/unclear Excluded "history of myocardial infarction, unstable angina, revascularization procedure, or cerebrovascular accident within 3 months before screening", prior to this unclear. No information in baseline characteristics.
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear Excluded "eGFR , 50 mL/min/1.73 m2", otherwise unclear. No information in baseline characteristics.
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	Not stated/unclear
Subgroup 1: People with moderate or severe frailty	Not stated/unclear
Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear Only mean duration of type 2 diabetes reported
Subgroup 3: People with non-alcoholic fatty liver disease	Not stated/unclear
Subgroup 4: People with obesity	Not stated/unclear Only mean BMI reported
Subgroup 5: eGFR category at baseline	eGFR ≥30mL/min/1.73m2 eGFR < 50 ml/min/1.73m² an exclusion criteria
Subgroup 6: Albuminuria	Not stated/unclear

category at baseline	
Population subgroups	
Comparator	Placebo once daily before first meal in addition to existing therapy for type 2 diabetes
Number of participants	N=714
Duration of follow-up	104 weeks
Indirectness	2.7% of participants were not on glucose-lowering drug therapy at randomisation.
Method of analysis	Modified ITT Efficacy endpoints reported in the manuscript based on mITT analysis (mITT defined as all randomised patients who received ≥ one dose of double-blinded study medication). Efficacy endpoints also reported extension mITT analysis (all patients in the mITT population who entered the extension treatment period, took ≥ dose of extension double-blind study medication and did not receive any rescue therapy before entering the extension period). Other Completers analysis also reported for HbA1c change

46.2. Study arms

46.2.1. Canagliflozin 100 mg (N = 241)

Canagliflozin 100 mg daily before the first meal, in addition to pre-existing treatment regimen.

46.2.2. Canagliflozin 300 mg (N = 236)

Canagliflozin 300 mg daily before the first meal, in addition to pre-existing treatment regimen.

46.2.3. Placebo (N = 237)

Placebo once daily before the first meal, in addition to pre-existing treatment regimen.

46.3. Characteristics

46.3.1. Arm-level characteristics

Characteristic	Canagliflozin 100 mg (N = 241)	Canagliflozin 300 mg (N = 236)	Placebo (N = 237)
% Male Sample size	n = 124 ; % = 51.5	n = 129 ; % = 54.7	n = 143 ; % = 60.3
Mean age (SD) (years) Mean (SD)	64.3 (6.5)	63.4 (6)	63.2 (6.2)
Ethnicity Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Comorbidities Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Presence of frailty Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Time since type 2 diabetes diagnosed (years) Mean (SD)	12.3 (7.8)	11.3 (7.2)	11.4 (7.3)
HbA1c (%) Mean (SD)	7.8 (0.8)	7.7 (0.8)	7.8 (0.8)
Cardiovascular risk factors Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Blood pressure Mean (SD)	NR (NR)	NR (NR)	NR (NR)
Heart rate Mean (SD)	NR (NR)	NR (NR)	NR (NR)
Smoking status Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Alcohol consumption Mean (SD)	NR (NR)	NR (NR)	NR (NR)

Characteristic	Canagliflozin 100 mg (N = 241)	Canagliflozin 300 mg (N = 236)	Placebo (N = 237)
Presence of severe mental illness Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
People with significant cognitive impairment Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
People with a learning disability Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Weight (kg) Mean (SD)	88.4 (15.6)	88.8 (17.1)	91.1 (17.5)
BMI (kg/m²) Mean (SD)	31.4 (4.4)	31.5 (4.6)	31.8 (4.8)
Number of people with obesity Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Cholesterol and lipid levels Mean (SD)	NR (NR)	NR (NR)	NR (NR)
Albumin creatinine ratio Mean (SD)	NR (NR)	NR (NR)	NR (NR)
eGFR mL/min/1.73m2 (ml/min/1.73 m²) Mean (SD)	77.6 (17)	78.7 (16.4)	76.1 (16.3)
Other antidiabetic medication used Alone or in combination Sample size	n = 231 ; % = 95.9	n = 233 ; % = 98.7	n = 232 ; % = 97.9
Metformin Sample size	n = 207 ; % = 85.9	n = 209 ; % = 88.6	n = 193 ; % = 81.4
Sulfonylureas Sample size	n = 121 ; % = 50.2	n = 117 ; % = 49.6	n = 110 ; % = 46.4
Thiazolinediones Sample size	n = 28 ; % = 11.6	n = 28 ; % = 11.9	n = 31 ; % = 13.1
DPP4-inhibitors	n = 24 ; % = 10	n = 20 ; % = 8.5	n = 21 ; % = 8.9

Characteristic	Canagliflozin 100 mg (N = 241)	Canagliflozin 300 mg (N = 236)	Placebo (N = 237)
Sample size			
Other blood glucose-lowering agents Including α-glucosidase inhibitors, GLP-1 agonists, glinides, and other blood glucose-lowering agents Sample size	n = 16 ; % = 6.6	n = 13 ; % = 5.5	n = 19 ; % = 8
Blood pressure-lowering medication used Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Statins/lipid-lowering medication used Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Other treatment being received Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Race Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
White Sample size	n = 194 ; % = 80.5	n = 173 ; % = 73.3	n = 185 ; % = 78.1
Black or African American Sample size	n = 18 ; % = 7.5	n = 19 ; % = 8.1	n = 20 ; % = 8.4
Asian Sample size	n = 15 ; % = 6.2	n = 15 ; % = 6.2	n = 21 ; % = 8.9
Other Sample size	n = 14 ; % = 5.8	n = 19 ; % = 8.1	n = 11 ; % = 4.6
Other antidiabetic medication used - combinations Subset of participants on combinations of the blood glucose-lowering agents listed above Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
Metformin + sulfonlyurea Sample size	n = 109 ; % = 45.2	n = 106 ; % = 44.9	n = 96 ; % = 40.5

Characteristic	Canagliflozin 100 mg (N = 241)	Canagliflozin 300 mg (N = 236)	Placebo (N = 237)
Metformin + insulin Sample size	n = 73 ; % = 30.3	n = 53 ; % = 22.5	n = 54 ; % = 22.9
Sulfonylurea + insulin Sample size	n = 28 ; % = 11.6	n = 14 ; % = 5.9	n = 13 ; % = 5.5
Other blood glucose-lowering agent + insulin Including α-glucosidase inhibitors, thiazolidinediones, DPP-4 inhibitors, GLP-1 agonists, glinides, and other blood glucose-lowering agents Sample size	n = 17 ; % = 7.1	n = 13 ; % = 5.5	n = 15 ; % = 6.3

47. Bode, 2015

Bibliographic Reference	Bode, B; Stenlof, K; Harris, S; Sullivan, D; Fung, A; Usiskin, K; Meininger, G; Long-term efficacy and safety of canagliflozin over 104 weeks in patients aged 55-80 years with type 2 diabetes.; Diabetes, obesity & metabolism; 2015; vol. 17 (no. 3); 294-303

47.1. Study details

Secondary publication of another included study- see primary study for details	Parent study Bode 2013 Bode B, Stenlöf K, Sullivan D, Fung A, Usiskin K. Efficacy and safety of canagliflozin treatment in older subjects with type 2 diabetes mellitus: a randomized trial. Hosp Pract (1995). 2013 Apr;41(2):72-84. doi: 10.3810/hp.2013.04.1020. PMID: 23680739. EPPI ID =13722509
Other publications associated with this study included in review	NA
Trial name / registration number	NCT01106651

48. Bolinder, 2012

Bibliographic Reference	Bolinder, J.; Ljunggren, Ö; Kullberg, J.; Johansson, L.; Wilding, J.; Langkilde, A. M.; 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; J Clin Endocrinol Metab; 2012; vol. 97 (no. 3); 1020-31

48.1. Study details

Secondary publication of another included study- see primary study for details	NA
Other publications associated with this study included in review	Bolinder 2014, Grandy 2014, Ljunggren 2012
Trial name / registration number	NCT00855166
Study type	Randomised controlled trial (RCT)
Study location	Conducted at 40 sites in Bulgaria, Czech Republic, Hungary, Poland, and Sweden
Study setting	NA
Study dates	February 13, 2009 to 2012
Sources of funding	AstraZeneca and Bristol-Myers Squibb
Inclusion criteria	patients with T2DM; women aged 55–75 yr who were postmenopausal for a period of at least 5 yr or men aged 30 –75 yr; hemoglobin A1c (HbA1c) 6.5– 8.5%; fasting plasma glucose (FPG) less than or equal to 240 mg/dl (<13.2 mmol/liter); body mass index (BMI) of 25 kg/m2 or higher; body weight no higher than 120 kg ;and treatment exclusively with metformin at a stable dose of at least 1500 mg/d for at least 12 weeks before enrolment
Exclusion criteria	type 1 diabetes; diabetes insipidus; corticosteroid induced type 2 diabetes; history of diabetic ketoacidosis or hyperosmolar non-ketotic coma; poorly controlled diabetes characterized by polyuria/polydipsia with >5% weight loss; use of insulin within 6 months of the first study visit,

	except a temporary period of insulin use for ≤7 days. General exclusion criteria included: body weight change >5% within 3 months of enrolment; calculated creatinine clearance <60 mL/min; urine albumin: creatinine ratio >1800 mg/g (>203.4 mg/mmol); aspartate aminotransferase and/or alanine aminotransferase and/or creatine kinase ≥3 X upper limit of normal range; serum total bilirubin >34 µmol/L; hemoglobin (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, bilateral hip replacement, spinal deformity or spinal surgery; metabolic bone disease or disease known to significantly influence bone metabolism or use of medication known to significantly influence bone metabolism within 6 months of enrolment; T-score less than −2.0 for bone mineral density at lumbar spine, femoral neck, or total hip at baseline DXA measurement; 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, hematological, 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
Recruitment / selection of participants	
Intervention(s)	Dapagliflozin 10mg taken once daily in the morning before or together with meal for 24 weeks (with extension of 78 weeks).
Cointervention	Metformin
Strata 1: People with type 2 diabetes mellitus and heart failure	People without heart failure Excluded "congestive heart failure".
Strata 2: People with atherosclerotic cardiovascular disease	Mixed population Excluded "cardiovascular event within 6 months of enrolment", prior to this unclear. Baseline characteristics show around 25% had history of CVD (excluded hypertension alone).
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear Excluded "significant renal disorders", unclear if all CKD. Baseline characteristics give eGFR categories but not CKD. <1% had nephropathy but other CKD unclear.
Strata 4: People with	People at higher risk of developing cardiovascular disease Over 80% also had hypertension

type 2 diabetes mellitus and high cardiovascular risk	
Subgroup 1: People with moderate or severe frailty	Not stated/unclear
Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear
Subgroup 3: People with non-alcoholic fatty liver disease	Not stated/unclear
Subgroup 4: People with obesity	Not stated/unclear
Subgroup 5: eGFR category at baseline	eGFR ≥30mL/min/1.73m2
Subgroup 6: Albuminuria category at baseline	Mixed population
Population subgroups	NA
Comparator	Placebo + Metformin
Number of participants	180
Duration of follow-up	24 weeks (extension of 78 weeks in subsidiary study)
Indirectness	None
Method of analysis	Other

Additional comments	Continuous endpoints were evaluated using analysis of covariance, with treatment and sex as fixed effects and baseline value as covariate. Primary, key secondary, and exploratory endpoints were analysed using the full analysis set. For glycemic variables, observations after initiation of rescue therapy were excluded from the analysis, with these and other missing values for glycemic and nonglycemic variables at week 24 replaced using the last observation carried forward (LOCF) method.

48.2. Study arms

48.2.1. Dapagliflozin + Metformin (N = 89)

Dapagliflozin is 10 mg taken once daily in the morning before or together with meal for 24 weeks (with extension of 78 weeks). Minimum does of metformin is 1500mg/dl for at least 12 weeks.

48.2.2. Placebo + Metformin (N = 91)

48.3. Characteristics

48.3.1. Arm-level characteristics

Characteristic	Dapagliflozin + Metformin (N = 89)	Placebo + Metformin (N = 91)
% Male Sample size	n = 49 ; % = 55.1	n = 51 ; % = 56
Mean age (SD) (yrs) Mean (SD)	60.6 (8.2)	60.8 (6.9)
Caucasian / white Sample size	n = 89 ; % = 100	n = 91 ; % = 100
Time since type 2 diabetes diagnosed (yrs) Mean (SD)	6 (4.5)	5.5 (5.3)
<30 ml/min Sample size	n = 0 ; % = 0	n = 0 ; % = 0
>30 and <60 ml/min	n = 5 ; % = 5.5	n = 1 ; % = 1.1

Characteristic	Dapagliflozin + Metformin (N = 89)	Placebo + Metformin (N = 91)
Sample size		
>60 and <90 ml/min Sample size	n = 56 ; % = 61.5	n = 54 ; % = 60.7
>90 ml/min Sample size	n = 30 ; % = 33	n = 34 ; % = 38.2
BMI >27 kg/m2 Sample size	n = 78 ; % = 87.6	n = 79 ; % = 86.8
BMI >30 kg/m2 Sample size	n = 60 ; % = 67.4	n = 60 ; % = 65.9
Hypertension Sample size	n = 77 ; % = 86.5	n = 75 ; % = 82.4
Dyslipidaemia Sample size	n = 51 ; % = 57.3	n = 53 ; % = 58.2
History of CVD Sample size	n = 21 ; % = 23.6	n = 26 ; % = 28.6
Microalbuminuria Sample size	n = 4 ; % = 4.5	n = 3 ; % = 3.3
Nephropathy Sample size	n = 0 ; % = 0	n = 1 ; % = 1.1
Retinopathy Sample size	n = 1 ; % = 1.1	n = 4 ; % = 4.4
Neuropathy Sample size	n = 7 ; % = 7.9	n = 4 ; % = 4.4
Diuretic use at randomization Sample size	n = 36 ; % = 39.6	n = 41 ; % = 45.1
less than 1500 mg per day Sample size	n = 0 ; % = 0	n = 0 ; % = 0
1500-2000 mg per day Sample size	n = 36 ; % = 39.6	n = 41 ; % = 45.1

Characteristic	Dapagliflozin + Metformin (N = 89)	Placebo + Metformin (N = 91)
more than 2000 mg per day Sample size	n = 55 ; % = 60.4	n = 50 ; % = 54.7
Waist circumference (cm) Mean (SD)	105.6 (10.1)	104.5 (12.3)
Fasting plasma glucose (mg/dL) Mean (SD)	148 (24.7)	149.6 (25.1)

49. Bolinder, 2014

Bibliographic Reference	Bolinder, J; Ljunggren, O; Johansson, L; Wilding, J; Langkilde, A M; Sjostrom, C D; Sugg, J; Parikh, S; Dapagliflozin maintains glycaemic control while reducing weight and body fat mass over 2 years in patients with type 2 diabetes mellitus inadequately controlled on metformin.; Diabetes, obesity & metabolism; 2014; vol. 16 (no. 2); 159-69

49.1. Study details

Secondary publication of another included study- see primary study for details	Parent study Bolinder et al., (2012). 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. J Clin Endocrinol Metab; 2012; vol. 97 (no. 3); 1020-31
Other publications associated with this study included in review	Ljunggren 2012, Grady 2014,
Trial name / registration number	NCT00855166

50. Bolli, 2014

Bibliographic Reference	Bolli, G. B.; Munteanu, M.; Dotsenko, S.; Niemoeller, E.; Boka, G.; Wu, Y.; Hanefeld, M.; Efficacy and safety of lixisenatide once daily vs. placebo in people with Type 2 diabetes insufficiently controlled on metformin (GetGoal-F1); Diabetic Med; 2014; vol. 31 (no. 2); 176-184

50.1. Study details

Secondary publication of another included study- see primary study for details	NA
Other publications associated with this study included in review	NA
Trial name / registration number	GetGoal-F1/ NCT00763451
Study location	Worldwide. Conducted at 75 centres across 15 countries
Study setting	NA
Study dates	September 2008 - January 2011
Sources of funding	Sanofi
Inclusion criteria	Men and women, aged 24–79 years, with Type 2 diabetes > 1 year since diagnosis) currently receiving at least 1.5 g/ day of metformin as monotherapy (for at least 3 months) and with HbA1c 53-86 mmol/ mol (7–10%)
Exclusion criteria	use of injectable or oral glucose-lowering agents (other than metformin) within 3 months prior to the time of screening; fasting plasma glucose at screening > 13.9 mmol/l (250 mg/dl); history of unexplained pancreatitis, chronic pancreatitis, pancreatectomy, stomach/gastric surgery or inflammatory bowel disease
Recruitment / selection of participants	NA

Intervention(s)	Lixisenatide 10-20 micro grams
Cointervention	Metformin (existing therapy)
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear Not an inclusion/exclusion criteria. No information in baseline characteristics
Strata 2: People with atherosclerotic cardiovascular disease	Not stated/unclear Not an inclusion/exclusion criteria. No information in baseline characteristics
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear Not an inclusion/exclusion criteria. No information in baseline characteristics
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	People at higher risk of developing cardiovascular disease
Subgroup 1: People with moderate or severe frailty	Not stated/unclear
Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear
Subgroup 3: People with non-alcoholic fatty liver disease	Not stated/unclear

Subgroup 4: People with obesity	Not stated/unclear
Subgroup 5: eGFR category at baseline	Not stated/unclear
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Population subgroups	NA
Comparator	Placebo
Number of participants	Total number of participants= 322
Duration of follow-up	76 weeks
Indirectness	None
Method of analysis	Modified ITT
Additional comments	

50.2. Study arms

50.2.1. Lixisenatide one-step dose increase (N = 161)

Lixisenatide one-step dose increase (10 micro gram once daily for 2 weeks then 20 micro gram once daily; n = 161)

50.2.2. Lixisenatide two-step dose increase (N = 161)

Lixisenatide two-step dose increase (10 micro gram once daily for 1 week, 15 micro gram once daily for 1 week then 20 micro gram once daily; n = 161)

50.2.3. Placebo (N = 160)

50.3. Characteristics

50.3.1. Arm-level characteristics

Characteristic	Lixisenatide one-step dose increase (N = 161)	Lixisenatide two-step dose increase (N = 161)	Placebo (N = 160)
% Male Sample size	n = 71 ; % = 44	n = 73 ; % = 45	n = 72 ; % = 45
Mean age (SD) (years) Mean (SD)	55.4 (8.9)	54.6 (8.9)	58 (9.8)
Ethnicity number of Caucasian Sample size	n = 142 ; % = 88	n = 147 ; % = 91	n = 149 ; % = 93
Time since type 2 diabetes diagnosed (years (mean)) Mean (SD)	5.8 (3.9)	6 (4.6)	6.2 (4.7)
Duration of metformin treatment (years) Mean (SD)	3.3 (2.6)	3.7 (3.4)	3.6 (3.1)
Daily metformin dose (mg) Mean (SD)	1968 (404)	2036 (427)	1943 (399)

51. Bolli, 2009

Bibliographic Reference	Bolli, G.; Dotta, F.; Colin, L.; Minic, B.; Goodman, M.; Comparison of vildagliptin and pioglitazone in patients with type 2 diabetes inadequately controlled with metformin; Diabetes Obes Metab; 2009; vol. 11 (no. 6); 589-95

51.1. Study details

Secondary publication of another included study- see primary study for details	Parent Study Bolli 2008
Other publications associated with this study included in review	

52. Bolli, 2008

Bibliographic Reference	Bolli, G; Dotta, F; Rochotte, E; Cohen, S E; Efficacy and tolerability of vildagliptin vs. pioglitazone when added to metformin: a 24-week, randomized, double-blind study.; Diabetes, obesity & metabolism; 2008; vol. 10 (no. 1); 82-90

52.1. Study details

Secondary publication of another included study- see primary study for details	NA
Other publications associated with this study included in review	Bolli 2009
Trial name / registration number	NCT 00237237
Study location	Worldwide. Study conducted at 118 centres; Germany (26), UK (25), USA (24), Spain (16), Italy (12), Switzerland (5), Austria (4), South Africa (3) and Australia (3).
Study setting	NA
Study dates	22/09/2005 to 22/02/2007
Sources of funding	Novartis Pharmaceuticals Corporation
Inclusion criteria	Participants with T2DM and A1C of 7.5–11.0% at the screening visit while receiving a stable dose of metformin >1500 mg/day were included. Male and female (non-fertile or of childbearing potential using a medically approved birth control method), patients aged 18–77 years, inclusive, with a body mass index (BMI) of 22–45 kg/m2, and with fasting plasma glucose (FPG) of <15 mmol/l were eligible to participate.
Exclusion criteria	history of type 1 or secondary forms of diabetes, acute metabolic diabetic complications, myocardial infarction, unstable angina or coronary artery bypass surgery within the previous 6 months. Congestive heart failure (New York Heart Association [NYHA] classes I–IV) and liver disease such

	as cirrhosis or chronic active hepatitis also precluded participation. Patients with any of the following laboratory abnormalities were also excluded: alanine aminotransferase or aspartate aminotransferase greater than 2.5 times the upper limit of normal (ULN), direct bilirubin >1.3 times the ULN, serum creatinine levels >132 micro mol / l (males) or >125 micro mol/l (females), clinically significant abnormal thyroid-stimulating hormone or fasting triglycerides (TG) >7.9 micro mol/l.
Recruitment / selection of participants	Eligible patients were randomized at visit 2 (baseline, week 0) to receive vildagliptin (100 mg daily, given as two equally divided doses) or pioglitazone (30 mg daily, given as a single q.d. dose). Efficacy and tolerability were assessed during four additional visits at weeks 4, 12, 16 and 24 of treatment
Intervention(s)	Vildagliptin vs. Pioglitazone
Cointervention	Metformin
Strata 1: People with type 2 diabetes mellitus and heart failure	People without heart failure Excluded "Congestive heart failure (New York Heart Association [NYHA] classes I–IV)"
Strata 2: People with atherosclerotic cardiovascular disease	Not stated/unclear Excluded "myocardial infarction, unstable angina or coronary artery bypass surgery within the previous 6 months" prior unclear. No information in baseline characteristics.
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear Not an inclusion/exclusion criteria. No information in baseline characteristics.
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	Not stated/unclear
Subgroup 1: People with moderate or severe frailty	Not stated/unclear

Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear
Subgroup 3: People with non-alcoholic fatty liver disease	Not stated/unclear
Subgroup 4: People with obesity	Not stated/unclear
Subgroup 5: eGFR category at baseline	Not stated/unclear
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Population subgroups	NA
Comparator	Pioglitazone
Number of participants	576
Duration of follow-up	24 weeks
Indirectness	NA
Method of analysis	Per protocol
Additional comments	Per protocol and LOCF

52.2. Study arms

52.2.1. Vildagliptin 100 mg (N = 295)

vildagliptin 100 mg daily, given as two equally divided doses

52.2.2. Pioglitazone 30mg (N = 281)

30 mg daily, given as a single q.d dose

52.3. Characteristics

52.3.1. Arm-level characteristics

Characteristic	Vildagliptin 100 mg (N = 295)	Pioglitazone 30mg (N = 281)
% Male Sample size	n = 182 ; % = 61.7	n = 180 ; % = 64.1
Mean age (SD) Mean (SD)	56.3 (9.3)	57 (9.7)
Caucasian Sample size	n = 243 ; % = 82.4	n = 230 ; % = 81.9
Hispanic or Latino Sample size	n = 25 ; % = 8.5	n = 29 ; % = 10.3
Asia (non-indian subcontinent) Sample size	n = 12 ; % = 4.1	n = 11 ; % = 3.9
Black Sample size	n = 9 ; % = 3	n = 7 ; % = 2.5
All others Sample size	n = 6 ; % = 2	n = 4 ; % = 1.4
Comorbidities Sample size	n = NR ; % = NR	n = NR ; % = NR
Presence of frailty Sample size	n = NR ; % = NR	n = NR ; % = NR
Time since type 2 diabetes diagnosed (years) Mean (SD)	6.4 (4.9)	6.4 (5.2)
Cardiovascular risk factors Sample size	n = NR ; % = NR	n = NR ; % = NR
Blood pressure	NR (NR)	NR (NR)

Characteristic	Vildagliptin 100 mg (N = 295)	Pioglitazone 30mg (N = 281)
Mean (SD)		
Heart rate Mean (SD)	NR (NR)	NR (NR)
Smoking status Custom value	NR	NR

53. Bosi, 2007

Bibliographic Reference	Bosi, E.; Camisasca, R. P.; Collober, C.; Rochotte, E.; Garber, A. J.; Effects of vildagliptin on glucose control over 24 weeks in patients with type 2 diabetes inadequately controlled with metformin; Diabetes Care; 2007; vol. 30 (no. 4); 890-5

53.1. Study details

Secondary publication of another included study- see primary study for details	NA
Other publications associated with this study included in review	NA
Trial name / registration number	NCT00099892
Study location	East Hanover, New Jersey, United States. Study was conducted at 109 centres in the U.S, France, Italy and Sweden.
Study setting	NA
Study dates	NA
Sources of funding	Novartis Pharmaceuticals Corporation
Inclusion criteria	The study enrolled patients with type 2 diabetes who had been treated with metformin monotherapy for at least 3 months and who had been on a stable dose of >1,500 mg daily for a minimum of 4 weeks before visit 1. Participants were required to have A1C in the range of 7.5–11.0% at the screening visit, and, if they were not at that time receiving their maximum-tolerated dose, they agreed to increase their metformin dose to 2,000 mg daily at visit 1. Male and female patients (unfertile or of childbearing potential using a medically approved birth control method) aged 18–78 years were included. People with BMI in the range of 22–45 kg/m2 and with FPG <15 mmol/l were eligible to participate

Exclusion criteria	History of type 1 diabetes; other secondary forms of diabetes; history of type 1 or secondary forms of diabetes; acute metabolic diabetes complications within the past 6 months; history of congestive heart failure requiring pharmacologic treatment; history of myocardial infarction, unstable angina, or coronary artery bypass surgery within the previous 6 months; people with Liver disease such as cirrhosis or chronic active hepatitis, renal disease or renal dysfunction as suggested by elevated serum creatinine levels≥132 micro mol/l for male and ≥123 micro mol/l for female subjects
Recruitment / selection of participants	NA
Intervention(s)	Vildagliptin 50 mg and 100 mg added to standard metformin care
Cointervention	Metformin
Strata 1: People with type 2 diabetes mellitus and heart failure	People without heart failure Excluded "congestive heart failure requiring pharmacologic treatment"
Strata 2: People with atherosclerotic cardiovascular disease	Not stated/unclear Excluded "myocardial infarction, unstable angina, or coronary artery bypass surgery within the previous 6 months", unclear prior to this. No information in baseline characteristics.
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	People without chronic kidney disease Excluded "renal disease".
Subgroup 1: People with moderate or severe frailty	Not stated/unclear
Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear
Subgroup 3: People with non-alcoholic	Not stated/unclear

fatty liver disease	
Subgroup 4: People with obesity	Not stated/unclear
Subgroup 5: eGFR category at baseline	Not stated/unclear
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Population subgroups	
Comparator	Vildagliptin 50mg vs. 100mg
Number of participants	544
Duration of follow-up	24 weeks
Indirectness	NA
Method of analysis	Modified ITT
Additional comments	

53.2. Study arms

53.2.1. Vildagliptin 50 mg (N = 177)

receive 50 mg vildagliptin daily once daily along with the standard metformin therapy

53.2.2. Vildagliptin 100 mg (N = 185)

receive 100 mg vildagliptin daily (as equally divided doses) along with standard metformin therapy

53.2.3. Placebo (N = 182)

Placebo + standard metformin therapy

53.3. Characteristics

53.3.1. Arm-level characteristics

Characteristic	Vildagliptin 50 mg (N = 177)	Vildagliptin 100 mg (N = 185)	Placebo (N = 182)
% Male Sample size	n = 82 ; % = 57.3	n = 88 ; % = 61.5	n = 69 ; % = 53.1
Mean age (SD) (years) Mean (SD)	54.3 (9.7)	53.9 (9.5)	54.4 (10.3)
Caucasian Sample size	n = 106 ; % = 74.1	n = 106 ; % = 74.1	n = 95 ; % = 73.1
Hispanic or Latino Sample size	n = 24 ; % = 16.8	n = 19 ; % = 13.3	n = 24 ; % = 18.5
Black Sample size	n = 9 ; % = 6.3	n = 13 ; % = 9.1	n = 9 ; % = 6.9
Others Sample size	n = 4 ; % = 2.8	n = 5 ; % = 3.5	n = 2 ; % = 1.5
Comorbidities Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Presence of frailty Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Time since type 2 diabetes diagnosed (years) Mean (SD)	6.8 (5.5)	5.8 (4.7)	6.2 (5.3)
Cardiovascular risk factors Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Blood pressure Mean (SD)	NR (NR)	NR (NR)	NR (NR)
Heart rate Mean (SD)	NR (NR)	NR (NR)	NR (NR)

Characteristic	Vildagliptin 50 mg (N = 177)	Vildagliptin 100 mg (N = 185)	Placebo (N = 182)
Smoking status Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Alcohol consumption Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Presence of severe mental illness Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
People with significant cognitive impairment Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
People with a learning disability Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Number of people with obesity Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Cholesterol and lipid levels Mean (SD)	NR (NR)	NR (NR)	NR (NR)
Albumin creatinine ratio Mean (SD)	NR (NR)	NR (NR)	NR (NR)
eGFR mL/min/1.73m2 Mean (SD)	NR (NR)	NR (NR)	NR (NR)
Other antidiabetic medication used Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Blood pressure-lowering medication used Mean (SD)	NR (NR)	NR (NR)	NR (NR)
Statins/lipid-lowering medication used Mean (SD)	NR (NR)	NR (NR)	NR (NR)

Characteristic	Vildagliptin 50 mg (N = 177)	Vildagliptin 100 mg (N = 185)	Placebo (N = 182)
Other treatment being received Mean (SD)	NR (NR)	NR (NR)	NR (NR)
Metformin dose (mg/day) Mean (SD)	2126 (298)	2099 (328)	2102 (320)
Duration of metformin (Months) Mean (SD)	17.8 (23.2)	17.9 (23)	15.9 (16.7)

54. Brown, 2020

Bibliographic Reference	Brown, A. J. M.; Gandy, S.; McCrimmon, R.; Houston, J. G.; Struthers, A. D.; Lang, C. C.; A randomized controlled trial of dapagliflozin on left ventricular hypertrophy in people with type two diabetes: the DAPA-LVH trial; European Heart Journal; 2020; vol. 41 (no. 36); 3421-3432

54.1. Study details

Trial name / registration number	DAPA-LVH /NCT02956811
Study location	Tayside, Scotland
Study setting	NA
Study dates	February 2017 and May 2018
Sources of funding	Externally Sponsored Research grant from Astra Zeneca
Inclusion criteria	• aged 18–80 years and had been previously diagnosed with T2D based on the American Diabetes Association guidelines. • Presence of LVH was defined using echocardiography as either LV mass index of >115 g/m2 for men and >95 g/m2 for women indexed to body surface area (BSA) or >48 g/m2.7 or 44 g/m2.7 when indexed to height. • People with hypertension were not excluded from the study but their clinic BP had to be <145/90 mmHg (mean value of three measurements performed at 5-min intervals on the same arm). If any individual had borderline office measurements an ambulatory BP monitor was performed to ensure BP adequately controlled. • Participants had to have an HbA1c measurement within the last 6 months at screening between 48 and 85 mmol/mol
Exclusion criteria	• Any condition that in the opinion of the investigator may render the participant unable to complete the trial including non CV disease [e.g. active malignancy]. • Participants with type 1 diabetes mellitus • Participants who have previously had an episode of diabetic ketoacidosis. • Serum Potassium or Sodium results without the normal range • Diagnosis of clinical heart failure • History of human immunodeficiency virus • LV systolic dysfunction [LVEF < 45%] [last known result within in the previous 6 months]

	• eGFR < 60 ml/min/1.73m2 [last known result within in the previous month] assessed using an abbreviated Modification of Diet in Renal Disease (MDRD) equation and indexed to 1.73m2
Recruitment / selection of participants	NA
Intervention(s)	Dapagliflozin 10 mg administered orally.
Cointervention	Metformin +/- other antihyperglycemic drugs
Strata 1: People with type 2 diabetes mellitus and heart failure	People without heart failure Excluded diagnosis of clinical heart failure
Strata 2: People with atherosclerotic cardiovascular disease	Not stated/unclear Not an inclusion/exclusion criteria. Heart disease and stroke reported separately, unclear whether any overlap and therefore total proportions.
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear Excluded eGFR < 60 ml/min/1.73m2, CKD diagnosis unclear. No information in baseline characteristics.
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	Not stated/unclear
Subgroup 1: People with moderate or severe frailty	Not stated/unclear
Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear

Subgroup 3: People with non-alcoholic fatty liver disease	Not stated/unclear
Subgroup 4: People with obesity	Not stated/unclear
Subgroup 5: eGFR category at baseline	Mixed population
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Population subgroups	NA
Comparator	Matching placebo
Number of participants	66
Duration of follow-up	12 months
Indirectness	NA
Method of analysis	ITT

54.2. Study arms

54.2.1. Dapagliflozin (N = 32)

10 mg

54.2.2. Placebo (N = 34)

54.3. Characteristics

54.3.1. Arm-level characteristics

Characteristic	Dapagliflozin (N = 32)	Placebo (N = 34)
% Male Sample size	n = 20 ; % = 62.5	n = 18 ; % = 52.9
Mean age (SD) (years) Mean (SD)	64.25 (7.01)	66.74 (6.62)
Ischemic heart disease Sample size	n = 2 ; % = 6.3	n = 6 ; % = 17.6
Stroke Sample size	n = 1 ; % = 3.1	n = 6 ; % = 17.6
Hypercholesterolaemia Sample size	n = 17 ; % = 53.1	n = 21 ; % = 61.8
Hypertension Sample size	n = 26 ; % = 81.3	n = 25 ; % = 73.5
Time since type 2 diabetes diagnosed (years) Median (IQR)	8.5 (5.25 to 14.5)	10 (7.5 to 15)
Systolic blood pressue (24h) Mean (SD)	130.41 (9.62)	127.67 (10.65)
Diastolc blood pressure (24hr) Mean (SD)	74.41 (7.88)	72.46 (6.09)
Heart rate Mean (SD)	74.44 (13.9)	76.15 (14.08)
Never smoked Sample size	n = 14 ; % = 43.8	n = 17 ; % = 50
Current smoker Sample size	n = 3 ; % = 9.4	n = 1 ; % = 2.9
Ex-smoker Sample size	n = 15 ; % = 46.9	n = 16 ; % = 47.1
eGFR mL/min/1.73m2	107.53 (25.4)	96.56 (27.86)

Characteristic	Dapagliflozin (N = 32)	Placebo (N = 34)
Mean (SD)		
Metformin Sample size	n = 32 ; % = 100	n = 34 ; % = 100
Sulphonlylurea Sample size	n = 7 ; % = 21.9	n = 8 ; % = 23.5
DDP-IV inhibitor Sample size	n = 4 ; % = 12.5	n = 3 ; % = 8.8
GLP-1 agonist Sample size	n = 4 ; % = 12.5	n = 3 ; % = 8.8
Thiazolidinedione Sample size	n = 0 ; % = 0	n = 3 ; % = 8.8
Insulin Sample size	n = 7 ; % = 21.9	n = 7 ; % = 20.6
ACE-inhibitor Sample size	n = 17 ; % = 53.1	n = 18 ; % = 52.9
Angiotensin receptor blocker Sample size	n = 5 ; % = 15.6	n = 6 ; % = 17.6
Calcium channel blocker Sample size	n = 9 ; % = 28.1	n = 13 ; % = 38.2
Thiazide diuretic Sample size	n = 9 ; % = 28.1	n = 4 ; % = 11.8
Beta-blocker Sample size	n = 4 ; % = 12.5	n = 5 ; % = 14.7
Alpha-blocker Sample size	n = 4 ; % = 12.5	n = 3 ; % = 8.8
Statins/lipid-lowering medication used Sample size	n = 25 ; % = 78.1	n = 30 ; % = 88.2
Aspirin Sample size	n = 4 ; % = 12.5	n = 6 ; % = 17.6

Characteristic	Dapagliflozin (N = 32)	Placebo (N = 34)
Clopidogrel Sample size	n = 2 ; % = 6.3	n = 5 ; % = 14.7

55. Brown, 2017

Bibliographic Reference	Brown, Alexander J M; Lang, Chim; McCrimmon, Rory; Struthers, Allan; Does dapagliflozin regress left ventricular hypertrophy in patients with type 2 diabetes? A prospective, double-blind, randomised, placebo-controlled study.; BMC cardiovascular disorders; 2017; vol. 17 (no. 1); 229

55.1. Study details

Secondary publication of another included study- see primary study for details	Parent study is Brown 2020

55.2. Study arms

55.2.1. Dapagliflozin (N = 32)

10 mg

55.2.2. Placebo (N = 34)

56. Bunck, 2011

Bibliographic Reference	Bunck, M C; Eliasson, B; Corner, A; Heine, R J; Shaginian, R M; Taskinen, M-R; Yki-Jarvinen, H; Smith, U; Diamant, M; Exenatide treatment did not affect bone mineral density despite body weight reduction in patients with type 2 diabetes.; Diabetes, obesity & metabolism; 2011; vol. 13 (no. 4); 374-7

56.1. Study details

Secondary publication of another included study- see primary study for details	Bunck 2009 Bunck MC, Diamant M, Cornér A, Eliasson B, Malloy JL, Shaginian RM, Deng W, Kendall DM, Taskinen MR, Smith U, Yki-Järvinen H, Heine RJ. One-year treatment with exenatide improves beta-cell function, compared with insulin glargine, in metformin-treated type 2 diabetic patients: a randomized, controlled trial. Diabetes Care. 2009 May;32(5):762-8

57. Bunck, 2009

Bibliographic Reference	Bunck, M. C.; Diamant, M.; Cornér, A.; Eliasson, B.; Malloy, J. L.; Shaginian, R. M.; Deng, W.; Kendall, D. M.; Taskinen, M. R.; Smith, U.; Yki-Järvinen, H.; Heine, R. J.; One-year treatment with exenatide improves beta-cell function, compared with insulin glargine, in metformin-treated type 2 diabetic patients: a randomized, controlled trial; Diabetes Care; 2009; vol. 32 (no. 5); 762-8

57.1. Study details

Other publications associated with this study included in review	1. Mathijs C. Bunck, Michaela Diamant, Bjorn Eliasson, Anja Cornér, Rimma M. Shaginian, Robert J. Heine, Marja-Riitta Taskinen, Hannele Yki-Järvinen, Ulf Smith; Exenatide Affects Circulating Cardiovascular Risk Biomarkers Independently of Changes in Body Composition. Diabetes Care 1 August 2010; 33 (8): 1734–173 2. Bunck MC, Eliasson B, Cornér A, Heine RJ, Shaginian RM, Taskinen MR, Yki-Järvinen H, Smith U, Diamant M. Exenatide treatment did not affect bone mineral density despite body weight reduction in patients with type 2 diabetes. Diabetes Obes Metab. 2011 Apr;13(4):374-7. 3. van Raalte DH, Bunck MC, Smits MM, Hoekstra T, Cornér A, Diamant M, Eliasson B, Marja-RiittaTaskinen, Heine RJ, Smith U, HanneleYki-Järvinen, Mari A. Exenatide improves β-cell function up to 3 years of treatment in patients with type 2 diabetes: a randomised controlled trial. Eur J Endocrinol. 2016 Oct;175(4):345-52
Trial name / registration number	NCT00097500
Study location	Three study sites - Sweden, Finland, and the Netherlands
Study setting	NA
Study dates	27th September 2004 to 13th September 2007
Sources of funding	Amylin Pharmaceuticals and Eli Lilly and Company
Inclusion criteria	age 30–75 years, A1C 6.5–9.5%, BMI 25–40 kg/m2, and metformin treatment at a stable dose for at least 2 months. No other blood glucose–lowering agents were allowed within 3 months before screening. No changes in other agents known to affect beta-cell function (such as ACE inhibitors and angiotensin receptor blockers) were allowed during the study.
Exclusion criteria	NA

Recruitment / selection of participants	NA
Intervention(s)	Exenatide - initiated treatment at a dose of 5 micro gram twice daily, injected 15 min before breakfast and dinner, for a period of 4 weeks, followed by a dose increase to 10 micro grams twice daily. Exenatide was titrated to a maximum dose of 20 micro grams thrice daily, or the maximum tolerated dose.
Cointervention	Metformin
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear Not an inclusion/exclusion criteria. No information in baseline characteristics.
Strata 2: People with atherosclerotic cardiovascular disease	Not stated/unclear Not an inclusion/exclusion criteria. No information in baseline characteristics.
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear Not an inclusion/exclusion criteria. No information in baseline characteristics.
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	Not stated/unclear
Subgroup 1: People with moderate or severe frailty	Not stated/unclear
Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear

Subgroup 3: People with non-alcoholic fatty liver disease	Not stated/unclear
Subgroup 4: People with obesity	Not stated/unclear
Subgroup 5: eGFR category at baseline	Not stated/unclear
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Population subgroups	NA
Comparator	Insulin glargine. Participants were started at an initial dose of 10 IU once daily, injected at bedtime. Patients were instructed to increase the daily dose based on their fasting self monitored blood glucose (SMBG) levels, according to a prespecified algorithm.
Number of participants	69
Duration of follow-up	52 weeks
Indirectness	NA
Method of analysis	ITT

57.2. Study arms

57.2.1. Exenatide (N = 36)

57.2.2. Insulin glargine (N = 33)

57.3. Characteristics

57.3.1. Arm-level characteristics

Characteristic	Exenatide (N = 36)	Insulin glargine (N = 33)
% Male Sample size	n = 23 ; % = 63.9	n = 22 ; % = 66.7
Mean age (SD) (years) Mean (SD)	58.4 (1.4)	58.3 (1.3)
Time since type 2 diabetes diagnosed years Mean (SD)	5.7 (0.8)	4 (0.6)

58. Bunck, 2010

Bibliographic Reference	Bunck, Mathijs C; Diamant, Michaela; Eliasson, Bjorn; Corner, Anja; Shaginian, Rimma M; Heine, Robert J; Taskinen, Marja-Riitta; Yki-Jarvinen, Hannele; Smith, Ulf; Exenatide affects circulating cardiovascular risk biomarkers independently of changes in body composition.; Diabetes care; 2010; vol. 33 (no. 8); 1734-7

58.1. Study details

Secondary publication of another included study- see primary study for details	Bunck 2009 Bunck MC, Diamant M, Cornér A, Eliasson B, Malloy JL, Shaginian RM, Deng W, Kendall DM, Taskinen MR, Smith U, Yki-Järvinen H, Heine RJ. One-year treatment with exenatide improves beta-cell function, compared with insulin glargine, in metformin-treated type 2 diabetic patients: a randomized, controlled trial. Diabetes Care. 2009 May;32(5):762-8

59. Buse, 2011

Bibliographic Reference	Buse, J. B.; Bergenstal, R. M.; Glass, L. C.; Heilmann, C. R.; Lewis, M. S.; Kwan, A. Y.; Hoogwerf, B. J.; Rosenstock, J.; Use of twice-daily exenatide in Basal insulin-treated patients with type 2 diabetes: a randomized, controlled trial; Ann Intern Med; 2011; vol. 154 (no. 2); 103-12

59.1. Study details

Secondary publication of another included study- see primary study for details	No
Other publications associated with this study included in review	None
Trial name / registration number	NCT00765817
Study type	Randomised controlled trial (RCT) Double-blind parallel-group RCT
Study location	International (59 centres in 5 countries: Greece, Israel, Mexico, UK, USA)
Study setting	Outpatient (Diabetes centres)
Study dates	10/2008 to 01/2010
Sources of funding	Sponsored and funded by the Alliance of Eli Lilly and Company and Amylin Pharmaceuticals.
Inclusion criteria	• Aged ≥18 years • Diagnosis of type 2 diabetes • Receiving ≥20 U/d insulin glargine for at least 3 months with or without stable metformin dose or pioglitazone or metformin and pioglitazone • HbA1c level 7.1% to 10.5% inclusive • BMI≤45 kg/m2 • Stable body weight (<5% change over previous 3 months)

Exclusion criteria	• Clinically significant hematologic, oncologic, renal, cardiac, hepatic, or gastrointestinal disease • Participating in a weight-loss program in previous 3 months before the study • Received systemic glucocorticoid therapy in previous 8 weeks • >1 major hypoglycaemic episode in previous 6 months • Irregular sleep–wake cycle • History of pancreatitis
Recruitment / selection of participants	Participants recruited from 59 centres in 5 countries and randomised using computer-generated random sequence interactive voice response system in blocks of 4, stratified by HbA1c level (≤8%, >8%) to exenatide or placebo. Participants, investigators and other study personnel were blinded to treatment assignments for duration of trial. Participants with HbA1c level >8% maintained current insulin glargine dose, whilst those with HbA1c level≤8% decreased insulin dose by 20%. Insulin doses maintained for 5 weeks then began titration to achieve fasting plasma glucose level <5.6 mmol/L (treat-to-target algorithm). Medication adherence, study diaries and glycaemic control assessed at each visit. Participants also recorded self-monitored blood glucose and insulin dose adjustments made by investigator on basis of treat-to-target algorithm at least weekly from weeks 5-10 and subsequently every 2 weeks.
Intervention(s)	• Exenatide 10 mcg twice daily Subcutaneous injection of exenatide within 60 minutes before morning and evening meals for 30 weeks (5 mcg twice daily for 4 weeks then 10 mcg twice daily for 26 weeks) in addition to insulin glargine.
Cointervention	Insulin glargine with or without metformin or pioglitazone or both.
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear Not an inclusion/exclusion criteria. No information in baseline characteristics
Strata 2: People with atherosclerotic cardiovascular disease	Not stated/unclear Not an inclusion/exclusion criteria. No information in baseline characteristics
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	People without chronic kidney disease Excluded "clinically significant renal disease"

Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	Not stated/unclear
Subgroup 1: People with moderate or severe frailty	Not stated/unclear
Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear
Subgroup 3: People with non-alcoholic fatty liver disease	Not stated/unclear
Subgroup 4: People with obesity	Not stated/unclear
Subgroup 5: eGFR category at baseline	Not stated/unclear
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Comparator	• Placebo Matched placebo injection for 30 weeks.
Number of participants	N=261
Duration of follow-up	30 weeks
Indirectness	None
Method of analysis	Modified ITT

	mITT (appears to be LOCF) analysis (all randomised participants who received study drug and had post-baseline measurements) for efficacy (HbA1c, lipids, vital signs, weight) and mITT for safety outcomes.

59.2. Study arms

59.2.1. Exenatide 10 mcg twice daily (N = 138)

Subcutaneous injection of exenatide 10 mcg twice daily for 30 weeks, in addition to insulin glargine with or without metformin or pioglitazone or metformin and pioglitazone.

59.2.2. Placebo (N = 123)

Matching placebo injection for 30 weeks, in addition to insulin glargine with or without metformin or pioglitazone or metformin and pioglitazone.

59.3. Characteristics

59.3.1. Arm-level characteristics

Characteristic	Exenatide 10 mcg twice daily (N = 138)	Placebo (N = 123)
% Male Sample size	n = 70 ; % = 51	n = 78 ; % = 64
Mean age (SD) (years) Mean (SD)	59 (9)	59 (10)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA
American-Indian/Alaska Native Sample size	n = 13 ; % = 10	n = 13 ; % = 11
Asian Sample size	n = 5 ; % = 4	n = 2 ; % = 2
Black/African American Sample size	n = 14 ; % = 10	n = 9 ; % = 7
Hispanic Sample size	n = 44 ; % = 32	n = 43 ; % = 35

Characteristic	Exenatide 10 mcg twice daily (N = 138)	Placebo (N = 123)
Multiple Sample size	n = 2 ; % = 2	n = 0 ; % = 0
White Sample size	n = 103 ; % = 75	n = 98 ; % = 90
Comorbidities Nominal	NR	NR
Presence of frailty Nominal	NR	NR
Time since type 2 diabetes diagnosed Mean (SD)	12 (7)	12 (7)
Cardiovascular risk factors Nominal	NR	NR
Smoking status Nominal	NR	NR
Alcohol consumption Nominal	NR	NR
Presence of severe mental illness Nominal	NR	NR
People with significant cognitive impairment Nominal	NR	NR
People with a learning disability Nominal	NR	NR
Number of people with obesity Nominal	NR	NR
Other antidiabetic medication used Sample size	n = NA ; % = NA	n = NA ; % = NA
None Sample size	n = 21 ; % = 15	n = 17 ; % = 14

Characteristic	Exenatide 10 mcg twice daily (N = 138)	Placebo (N = 123)
Metformin only Sample size	n = 91 ; % = 66	n = 91 ; % = 75
Pioglitazone only Sample size	n = 2 ; % = 2	n = 6 ; % = 5
Metformin + Pioglitazone Sample size	n = 23 ; % = 17	n = 8 ; % = 7
Blood pressure-lowering medication used Nominal	NR	NR
Statins/lipid-lowering medication used Nominal	NR	NR
Other treatment being received Nominal	NR	NR

60. Buse, 2004

Bibliographic Reference	Buse, J. B.; Henry, R. R.; Han, J.; Kim, D. D.; Fineman, M. S.; Baron, A. D.; Effects of exenatide (Exendin-4) on glycemic control over 30 weeks in sulfonylurea-treated patients with type 2 diabetes; Diabetes Care; 2004; vol. 27 (no. 11); 2628-35

60.1. Study details

Secondary publication of another included study- see primary study for details	No
Other publications associated with this study included in review	None
Trial name / registration number	Exenatide-113/not reported
Study type	Randomised controlled trial (RCT) Triple-blind placebo-controlled parallel-group RCT
Study location	USA (101 sites)
Study setting	Outpatient (Diabetes centres)
Study dates	02/2002 to 08/2003
Sources of funding	Amylin Pharmaceuticals and Eli Lilly.
Inclusion criteria	• Fasting plasma glucose concentration <240 mg/dl at screening • BMI 27-45 kg/m2 inclusive • HbA1c 7.1-11% inclusive • Stable weight for previous 3 months (<10% change) • No clinically relevant (for T2 population) abnormal lab test values • If female, then postmenopausal, surgically sterile, or using contraceptives for at least 3 months before screening and during trial

Exclusion criteria	• Clinically significant comorbidity
	• Use of
	  ○ Metformin, thiazolidinediones, meglitinides, alpha-glucosidase inhibitors, exogenous insulin therapy or weigh-loss drugs within previous 3 months
	  ○ Corticosteroid therapy
	  ○ Drugs known to affect gastrointestinal motility
	  ○ Transplantation medications
	  ○ Any investigational drug

Recruitment / selection of participants	Participants recruited from 101 sites. After 4-week single-blind lead-in period with subcutaneous placebo injection twice daily, participants randomised to 1 of 4 arms (there were 2 placebo arms but only pooled baseline and outcome data reported). Sulphonylurea dose adjusted before single-blind lead-in period to maximally effective dose (4 mg/day glimepiride; 20 mg/day glipizide; 10 mg/day glipizide XL; 10 mg/day glyburide; 6 mg/day micronized glyburide; 350 mg/day chlorpropamide; 500 mg/day tolazamide). In event of hypoglycaemia (1 documented episode or 2 undocumented but suspected episodes), sulphonylurea dose progressively reduced by 50%. Participants could be withdrawn from trial if: HbA1c change ≥1.5% from baseline at any visit before end of trial or HbA1c level≥11.5% at weeks 18 or 24 were withdrawn from trial; or fasting plasma glucose>240 mg/dl on 2 consecutive visits or consistently recorded fingerstick fasting blood glucose>260 mg/dl for at least 2-wks not secondary to identified illness or pharmacological treatment.
Intervention(s)	• Exenatide 10 mcg twice daily • Exenatide 5 mcg twice daily Subcutaneous injection of exenatide 10 or 5 mcg twice daily 15 min before morning and evening meals for 30 weeks, in addition to sulphonylurea treatment. Participants in both exenatide arms began with 5 mcg twice daily for 4 weeks, with dose increasing to 10 mcg twice daily in 10 mcg arm for 26 weeks; those in 5 mcg arm remained on 5 mcg twice daily for 26 weeks.
Cointervention	Sulphonylurea treatment
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear Not an inclusion/exclusion criteria. No information in baseline characteristics
Strata 2: People with atherosclerotic cardiovascular disease	Not stated/unclear Not an inclusion/exclusion criteria. No information in baseline characteristics
Strata 3: People with type 2	Not stated/unclear

diabetes mellitus and chronic kidney disease	Not an inclusion/exclusion criteria. No information in baseline characteristics
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	Not stated/unclear
Subgroup 1: People with moderate or severe frailty	Not stated/unclear
Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear
Subgroup 3: People with non-alcoholic fatty liver disease	Not stated/unclear
Subgroup 4: People with obesity	Not stated/unclear
Subgroup 5: eGFR category at baseline	Not stated/unclear
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Comparator	• Placebo Matched placebo injection for each exenatide arm twice daily 15 min before morning and evening meals for 30 weeks, in addition to sulphonylurea treatment. Article pools baseline and outcome data.
Number of participants	N=377
Duration of follow-up	30 weeks

Indirectness	None
Method of analysis	ITT ITT analysis for safety outcomes. Modified ITT mITT LOCF analysis (all randomised participants who received at least one dose of study drug) on efficacy outcomes (HbA1c, weight, lipids).

60.2. Study arms

60.2.1. Exenatide 10 mcg twice daily (N = 129)

Subcutaneous injection of exenatide 10 mcg twice daily before morning and evening meals for 30 weeks, in addition to sulphonylurea treatment.

60.2.2. Exenatide 5 mcg twice daily (N = 125)

Subcutaneous injection of exenatide 5 mcg twice daily before morning and evening meals for 30 weeks, in addition to sulphonylurea treatment.

60.2.3. Placebo (N = 123)

Matching placebo injection twice daily 15 min before morning and evening meals for 30 weeks, in addition to sulphonylurea treatment. Note that trial had 2 placebo arms corresponding to exenatide arms but only reports pooled baseline and outcome data.

60.3. Characteristics

60.3.1. Study-level characteristics

Characteristic	**Study (N = 354)**
Other antidiabetic medication used Type of sulphonylurea Sample size	n = 354 ; % = 100
Chlorpropamide Sample size	n = 1 ; % = 0.3
Glimepiride Sample size	n = 71 ; % = 20

Characteristic	Study (N = 354)
Glipizide Sample size	n = 159 ; % = 45
Glyburide Sample size	n = 117 ; % = 33
Tolazamide Sample size	n = 4 ; % = 1
Blood pressure-lowering medication used Angiotensin-converting-enzyme (ACE) inhibitor Sample size	n = 138 ; % = 39
Statins/lipid-lowering medication used Serum lipid-reducing agent Sample size	n = 131 ; % = 37
Other treatment being received Anti-thrombotic agent Sample size	n = 120 ; % = 34

60.3.2. Arm-level characteristics

Characteristic	Exenatide 10 mcg twice daily (N = 129)	Exenatide 5 mcg twice daily (N = 125)	Placebo (N = 123)
% Male Sample size	n = 74 ; % = 57.4	n = 74 ; % = 59.2	n = 77 ; % = 62.6
Mean age (SD) Mean (SD)	56 (11)	55 (10)	55 (11)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
Asian Sample size	n = 2 ; % = 1.6	n = 2 ; % = 1.6	n = 2 ; % = 1.6
Black Sample size	n = 21 ; % = 16.3	n = 21 ; % = 16.8	n = 12 ; % = 9.8
Hispanic Sample size	n = 28 ; % = 21.7	n = 23 ; % = 18.4	n = 26 ; % = 21.1

Characteristic	Exenatide 10 mcg twice daily (N = 129)	Exenatide 5 mcg twice daily (N = 125)	Placebo (N = 123)
Native American Sample size	n = 0 ; % = 0	n = 1 ; % = 0.8	n = 0 ; % = 0
Other Sample size	n = 1 ; % = 0.8	n = 1 ; % = 0.8	n = 1 ; % = 0.8
White Sample size	n = 77 ; % = 59.7	n = 77 ; % = 61.6	n = 82 ; % = 66.7
Comorbidities Nominal	NR	NR	NR
Presence of frailty Nominal	NR	NR	NR
Time since type 2 diabetes diagnosed (years) Mean (SD)	6.6 (6.6)	6.3 (5.2)	5.7 (4.7)
Cardiovascular risk factors Nominal	NR	NR	NR
Smoking status Nominal	NR	NR	NR
Alcohol consumption Nominal	NR	NR	NR
Presence of severe mental illness Nominal	NR	NR	NR
People with significant cognitive impairment Nominal	NR	NR	NR
People with a learning disability Nominal	NR	NR	NR
Number of people with obesity Nominal	NR	NR	NR

61. Buse, 2020

Bibliographic Reference	Buse, John B; Bode, Bruce W; Mertens, Ann; Cho, Young Min; Christiansen, Erik; Hertz, Christin L; Nielsen, Morten A; Pieber, Thomas R; Long-term efficacy and safety of oral semaglutide and the effect of switching from sitagliptin to oral semaglutide in patients with type 2 diabetes: a 52-week, randomized, open-label extension of the PIONEER 7 trial.; BMJ open diabetes research & care; 2020; vol. 8 (no. 2)

61.1. Study details

Secondary publication of another included study- see primary study for details	This is a 52-week extension study of Pieber 2019 (comparing semaglutide to sitagliptin in addition to background oral antidiabetic drugs) but re-randomises participants in the original sitagliptin arm so has been treated as a separate trial.
Other publications associated with this study included in review	For original 52-week trial see: • Pieber, T. R., Bode, B., Mertens, A., Cho, Y. M., Christiansen, E., Hertz, C. L., ... & Yavuz, D. (2019). Efficacy and safety of oral semaglutide with flexible dose adjustment versus sitagliptin in type 2 diabetes (PIONEER 7): a multicentre, open-label, randomised, phase 3a trial. *The lancet Diabetes & endocrinology*, *7*(7), 528-539.
Trial name / registration number	PIONEER 7/NCT02849080.
Study type	Randomised controlled trial (RCT) Open-label, parallel-group, RCT extension study
Study location	International (71 sites in 9 countries: Argentina, Austria, Belgium, Egypt, Norway, South Korea, Switzerland, Turkey, USA)
Study setting	Outpatient (Diabetes centres)
Study dates	Original add-on trial: 09/2016 to 03/2018 Extension switching trial: 03/2018 to 03/2019
Sources of funding	Funded by Novo Nordisk A/S, Denmark.
Inclusion criteria	Original add-on trial (see Pieber 2019) • Aged≥18 years (≥19 years in South Korea) • Type 2 diabetes diagnosis≥90 days before screening • HbA1c 7.5-9.5% inclusive

	• Receiving stable dose of one or two of: metformin, sulphonylureas, SGLT2 inhibitor, thiazolidinediones ≥90 days before screening Switching extension trial • Participation in original add-on trial comparing semaglutide to sitagliptin as add-on to background oral anti-diabetic drugs and written consent to participate in extension trial • On randomised treatment from original trial
Exclusion criteria	• eGFR<60 mL/min/1.73 m2 • NYHA class IV heart failure • Proliferative retinopathy or maculopathy requiring acute treatment • History of pancreatitis • Family or personal history of multiple endocrine neoplasia type 2 or medullary thyroid carcinoma • History of malignant neoplasms within past 5 years.
Recruitment / selection of participants	Participants recruited from sitagliptin arm of original 52-week add-on study reported in Pieber 2019. After re-consenting to participation in this extension switching trial, participants were re-randomised 1:1 using interactive web-response system to either stay on sitagliptin or switch to semaglutide. Rescue therapy used at completion of main add-on trial was considered background therapy in this extension trial.
Intervention(s)	• Semaglutide 3-14 mg daily Switching from oral sitagliptin 100 mg daily to oral semaglutide 3-14 mg (flexible dose) daily in morning for 52 weeks, in addition to receiving stable dose of one or two of: metformin, sulphonylureas, SGLT2 inhibitor, thiazolidinediones. Semaglutide initiated at 3 mg until week 8; at week 8 and every 8 weeks, dose adjusted according to HbA1c level (measured by point of care device). Dose adjustments available at 3, 7 and 14 mg. If HbA1c level<7% then current dose maintained; if 7% or more, dose escalated to next dose level unless participant reported moderate-to-severe nausea or vomiting for 3 or more days in week before scheduled visit. If participant reported moderate-to-severe vomiting, dose maintained or decreased to minimum of 3 mg once daily irrespective of HbA1c level at investigator. discretion. Rescue therapy only permitted for participants in this arm after dose escalation.
Cointervention	• Background oral glucose-lowering drugs Participants continued receiving stable dose of background glucose-lowering drugs (one or two of metformin, sulphonylureas, SGLT2 inhibitor, thiazolidinediones) for duration of trial.
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear

Strata 2: People with atherosclerotic cardiovascular disease	Not stated/unclear
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	Not stated/unclear
Subgroup 1: People with moderate or severe frailty	Not stated/unclear
Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear
Subgroup 3: People with non-alcoholic fatty liver disease	Not stated/unclear
Subgroup 4: People with obesity	Not stated/unclear
Subgroup 5: eGFR category at baseline	eGFR ≥30mL/min/1.73m2 Exclusion criteria: eGFR<60 mL/min/1.73 m2
Subgroup 6: Albuminuria category at baseline	Not stated/unclear

Comparator	• Sitagliptin 100 mg daily Staying on oral sitagliptin 100 mg daily for an additional 52 weeks, in addition to receiving stable dose of one or two of: metformin, sulphonylureas, SGLT2 inhibitor, thiazolidinediones.
Number of participants	N=198 randomised (N=197 in safety analysis set as one participant did not receive treatment)
Duration of follow-up	52 weeks
Indirectness	None
Method of analysis	ITT ITT analysis (full analysis set, all randomised participants) for efficacy outcomes with multiple imputation for missing data Modified ITT mITT analysis (safety analysis set, all randomised participants who received at least one dose of study drug) for safety outcomes.

61.2. Study arms

61.2.1. Semaglutide 3-14 mg daily (N = 100)

Oral semaglutide 3-14 mg daily (flexible dose) for 52 weeks, switching from sitagliptin 100 mg daily, in addition to background oral antidiabetic drugs.

61.2.2. Sitagliptin 100 mg daily (N = 98)

Staying on oral sitagliptin 100 mg daily for an additional 52 weeks, in addition to background oral antidiabetic drugs.

61.3. Characteristics

61.3.1. Arm-level characteristics

Characteristic	Semaglutide 3-14 mg daily (N = 100)	Sitagliptin 100 mg daily (N = 98)
% Male Sample size	n = 57 ; % = 57	n = 55 ; % = 56.1

Characteristic	Semaglutide 3-14 mg daily (N = 100)	Sitagliptin 100 mg daily (N = 98)
Mean age (SD) (years) Mean (SD)	58 (10)	58 (10)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA
Asian Sample size	n = 17 ; % = 17	n = 17 ; % = 17.3
Black/African-American Sample size	n = 6 ; % = 6	n = 10 ; % = 10.2
Hispanic or Latino Sample size	n = 16 ; % = 16	n = 19 ; % = 19.4
Other American Indian, Alaska Native, Native Hawaiian, Pacific Islander, or other Sample size	n = 0 ; % = 0	n = 0 ; % = 0
White Sample size	n = 77 ; % = 77	n = 71 ; % = 72.4
Comorbidities Nominal	NR	NR
Presence of frailty Nominal	NR	NR
Time since type 2 diabetes diagnosed (years) Mean (SD)	8.1 (5.4)	9.6 (6.4)
Cardiovascular risk factors Nominal	NR	NR
Smoking status Nominal	NR	NR
Alcohol consumption Nominal	NR	NR
Presence of severe mental illness	NR	NR

Characteristic	Semaglutide 3-14 mg daily (N = 100)	Sitagliptin 100 mg daily (N = 98)
Nominal		
People with significant cognitive impairment Nominal	NR	NR
People with a learning disability Nominal	NR	NR
Number of people with obesity Nominal	NR	NR
Other antidiabetic medication used Sample size	n = NA ; % = NA	n = NA ; % = NA
Metformin only Sample size	n = 29 ; % = 29	n = 36 ; % = 36.7
Sulphonylurea only Sample size	n = 0 ; % = 0	n = 3 ; % = 3.1
SGLT-2 inhibitor only Sample size	n = 1 ; % = 1	n = 2 ; % = 2
Thiazolidinedione Sample size	n = 0 ; % = 0	n = 0 ; % = 0
Metformin + a sulphonylurea only Sample size	n = 45 ; % = 45	n = 40 ; % = 40.8
Metformin + SGLT inhibitor only Sample size	n = 15 ; % = 15	n = 9 ; % = 9.2
Metformin + a thiazolidinedione only Sample size	n = 1 ; % = 1	n = 1 ; % = 1
Metformin + insulin only Sample size	n = 0 ; % = 0	n = 2 ; % = 2
Metformin + other only Sample size	n = 0 ; % = 0	n = 0 ; % = 0
Sulphonylurea + SGLT2 inhibitor only Sample size	n = 0 ; % = 0	n = 0 ; % = 0

Characteristic	Semaglutide 3-14 mg daily (N = 100)	Sitagliptin 100 mg daily (N = 98)
Sulphonylurea + a thiazolidinedione only Sample size	n = 1 ; % = 1	n = 0 ; % = 0
Sulphonylurea + insulin only Sample size	n = 1 ; % = 1	n = 0 ; % = 0
Metformin + SGLT2 inhibitor + a sulphonylurea Sample size	n = 5 ; % = 5	n = 4 ; % = 4.1
Metformin + SGLT2 inhibitor + insulin Sample size	n = 0 ; % = 0	n = 1 ; % = 1
Metformin + a sulphonylurea + insulin Sample size	n = 1 ; % = 1	n = 0 ; % = 0
Metformin + a sulphonylurea + a thiazolidinedione Sample size	n = 1 ; % = 1	n = 0 ; % = 0
Blood pressure-lowering medication used Nominal	NR	NR
Statins/lipid-lowering medication used Nominal	NR	NR
Other treatment being received Nominal	NR	NR

Data for % Male, Mean Age, Ethnicity, and Duration of Diabetes were assessed at week 0 of original add-on study (see Pieber 2019); all other data from week 52 of original study (baseline of this extension study).

62. Buse, 2013

Bibliographic Reference	Buse, John B; Nauck, Michael; Forst, Thomas; Sheu, Wayne H-H; Shenouda, Sylvia K; Heilmann, Cory R; Hoogwerf, Byron J; Gao, Aijun; Boardman, Marilyn K; Fineman, Mark; Porter, Lisa; Schernthaner, Guntram; Exenatide once weekly versus liraglutide once daily in patients with type 2 diabetes (DURATION-6): a randomised, open-label study.; Lancet (London, England); 2013; vol. 381 (no. 9861); 117-24

62.1. Study details

Secondary publication of another included study- see primary study for details	NA
Other publications associated with this study included in review	NA
Trial name / registration number	DURATION-6 / NCT01029886
Study location	105 sites in 19 countries (Argentina, Australia, Austria, Belgium, Canada, Czech Republic, France, Germany, Hungary, Israel, Italy, Mexico, Poland, Romania, Slovakia, South Africa, South Korea, Spain, and Taiwan)
Study setting	NA
Study dates	11/01/2010 to 17/01/2011
Sources of funding	Eli Lilly and Company and Amylin Pharmaceuticals LLC
Inclusion criteria	HbA1c concentration between 7·1% and 11·0% (54 mmol/mol to 97 mmol/mol), inclusive; a body-mass index of 45 kg/m² and less; and a stable bodyweight for at least 3 months
Exclusion criteria	active cardiac disease within 3 months of screening; inflammatory bowel disease or other severe gastrointestinal diseases; medullary carcinoma; a family history of medullary carcinoma or multiple endocrine neoplasm type-2 syndrome; liver or renal disease; creatinine clearance less than 60 mL/min; active or untreated

	malignancy; acute or chronic pancreatitis; haemoglobinopathy; hemolytic or chronic anemia; two or more episodes of major hypoglycemia within 6 months; and use of excluded drugs (insulin, α-glucosidase inhibitors, meglitinides, DPP-4 inhibitors, GLP-1 receptor agonists, or rosiglitazone)
Recruitment / selection of participants	NA
Intervention(s)	Intervention arm - Exenatide 2mg administered subcutaneously once weekly.
Cointervention	NA
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear Not an inclusion/exclusion criteria. No information in baseline characteristics.
Strata 2: People with atherosclerotic cardiovascular disease	Not stated/unclear Excluded "active cardiac disease within 3 months of screening", unclear prior to this. No information in baseline characteristics.
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	People without chronic kidney disease Excluded "renal disease". No information in baseline characteristics.
Subgroup 4: People with obesity	People with obesity Includes a subgroup on obese and non-obese participants
Population subgroups	Obese and non-obese subgroups
Comparator	Comparison arm - Liraglutide 1.8 mg administered subcutaneously once daily; Liraglutide was up titrated from 0·6 mg per day, to 1·2 mg per day, then to 1·8 mg per day. Each titration was to be completed after at least 1 week but could be delayed if the patient had severe nausea or vomiting as established by the investigators.

Number of participants	791
Duration of follow-up	26 weeks
Indirectness	NA
Method of analysis	ITT
Additional comments	NA

62.2. Study arms

62.2.1. Exenatide (N = 461)

Administered 2 mg subcutaneously, once weekly

62.2.2. Liraglutide (N = 450)

Given subcutaneously 1.8 mg once daily

62.3. Characteristics

62.3.1. Arm-level characteristics

Characteristic	Exenatide (N = 461)	Liraglutide (N = 450)
% Male Sample size	n = 254 ; % = 55	n = 245 ; % = 54
Mean age (SD) Mean (SD)	57 (9.4)	57 (9.6)
Hispanic Sample size	n = 98 ; % = 21	n = 99 ; % = 22
Non-Hispanic Sample size	n = 363 ; % = 79	n = 348 ; % = 78
Time since type 2 diabetes diagnosed (years) Mean (SD)	8 (6)	9 (6)

Characteristic	Exenatide (N = 461)	Liraglutide (N = 450)
HbA1c (%) Mean (SD)	8.5 (1)	8.4 (1)
Systolic blood pressure Mean (SD)	132 (14)	134 (14)
Diastolic blood pressure Mean (SD)	79 (9)	80 (9)
Cholesterol (mmol/l) Mean (SD)	4.5 (1)	4.6 (1.1)
HDL (mmol/l) Mean (SD)	1.1 (0.3)	1.2 (0.3)
Non-HDL (mmol/L) Mean (SD)	3.4 (1)	3.5 (1.1)
LDL (mmol/l) Mean (SD)	2.5 (0.9)	2.5 (0.9)
Metformin plus sulfonylurea Sample size	n = 275 ; % = 60	n = 277 ; % = 62
Metformin alone Sample size	n = 150 ; % = 33	n = 136 ; % = 30
Sulfonylurea alone Sample size	n = 18 ; % = 4	n = 18 ; % = 4
Metformin plus pioglitazone Sample size	n = 16 ; % = 4	n = 18 ; % = 4
Metformin plus sulfonylurea plus pioglitazone Sample size	n = 1 ; % = 0.2	n = 1 ; % = 0.2
Pioglitazone alone Sample size	n = 1 ; % = 0.2	n = 0 ; % = 0

63. Buse, 2009

Bibliographic Reference	Buse, John B; Rosenstock, Julio; Sesti, Giorgio; Schmidt, Wolfgang E; Montanya, Eduard; Brett, Jason H; Zychma, Marcin; Blonde, Lawrence; Liraglutide once a day versus exenatide twice a day for type 2 diabetes: a 26-week randomised, parallel-group, multinational, open-label trial (LEAD-6).; Lancet (London, England); 2009; vol. 374 (no. 9683); 39-47

63.1. Study details

Secondary publication of another included study- see primary study for details	NA
Other publications associated with this study included in review	
Trial name / registration number	LEAD 6 / NCT00518882
Study location	multinational (132 office-based sites across 15 countries)
Study setting	NA
Study dates	Aug 24, 2007 to April 9, 2008
Sources of funding	Novo Nordisk A/S
Inclusion criteria	Aged 18–80 years with type 2 diabetes; HbA1c value was 7–11%; body-mass index (BMI) of 45·0 kg/m² or less on stable treatment with maximally tolerated doses of metformin, sulphonylurea, or both, for 3 months or more
Exclusion criteria	previous insulin treatment (except short term treatment for intercurrent illness); previous exposure to exenatide or liraglutide; impaired liver or renal function; clinically significant cardiovascular disease; retinopathy or maculopathy requiring acute treatment; uncontrolled hypertension (≥180/100 mm Hg); cancer
Recruitment / selection of participants	NA

Intervention(s)	Subcutaneous liraglutide 1·8 mg once a day. Post randomization, participants underwent a 2-week liraglutide dose-escalation period (during which the initial dose of 0·6 mg was increased by 0·6 mg a week to a maximum dose of 1·8 mg once a day). This was followed by a 22–24-week maintenance period when no dose reduction of liraglutide or exenatide was allowed.
Cointervention	Metformin and sulfonylureas
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear Not an inclusion/exclusion criteria. No information in baseline characteristics.
Strata 2: People with atherosclerotic cardiovascular disease	Not stated/unclear Excluded "clinically significant cardiovascular disease", otherwise unclear. No information in baseline characteristics.
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear Excluded "impaired renal function", otherwise unclear. No information in baseline characteristics.
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	Not stated/unclear
Subgroup 1: People with moderate or severe frailty	Not stated/unclear
Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear
Subgroup 3: People with non-alcoholic	Not stated/unclear

fatty liver disease	
Subgroup 4: People with obesity	Not stated/unclear
Subgroup 5: eGFR category at baseline	Not stated/unclear
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Population subgroups	NA
Comparator	Subcutaneous 10 micrograms of Exenatide administered twice daily. After randomization, participants underwent 4-week exenatide dose-escalation period (during which 5 µg twice a day was increased to 10 µg twice a day after 4 weeks).6 This was followed by a 22–24-week maintenance period when no dose reduction of liraglutide or exenatide was allowed.
Number of participants	464
Duration of follow-up	24 weeks. Participants completing this study could enrol in a 52-week liraglutide 1·8-mg extension phase.
Indirectness	NA
Method of analysis	ITT
Additional comments	NA

63.2. Study arms

63.2.1. Liraglutide (N = 233)

1.8 mg once daily

63.2.2. Exenatide (N = 231)

10 micrograms twice daily

63.3. Characteristics

63.3.1. Arm-level characteristics

Characteristic	Liraglutide (N = 233)	Exenatide (N = 231)
% Male Sample size	n = 114 ; % = 49	n = 127 ; % = 55
Mean age (SD) (years) Mean (SD)	56.3 (9.8)	57.1 (10.8)
Hispanic or Latin American ethnic origin Sample size	n = 32 ; % = 14	n = 25 ; % = 11
Time since type 2 diabetes diagnosed (years) Mean (SD)	8.5 (6.2)	7.9 (5.9)
Systolic blood pressure Mean (SD)	132 (16.2)	134 (17)
Diastolic blood pressure Mean (SD)	79.6 (8.4)	78.9 (8.9)
Metformin and Sulfonylureas combination Sample size	n = 145 ; % = 62	n = 147 ; % = 64
Sulfonylureas alone Sample size	n = 24 ; % = 10	n = 21 ; % = 9
Metformin alone Sample size	n = 64 ; % = 27	n = 63 ; % = 27

64. Buse, 2014

Bibliographic Reference	Buse, John B; Vilsboll, Tina; Thurman, Jerry; Blevins, Thomas C; Langbakke, Irene H; Bottcher, Susanne G; Rodbard, Helena W; Contribution of liraglutide in the fixed-ratio combination of insulin degludec and liraglutide (IDegLira).; Diabetes care; 2014; vol. 37 (no. 11); 2926-33

64.1. Study details

Secondary publication of another included study- see primary study for details	NA
Other publications associated with this study included in review	NA
Trial name / registration number	DUAL II [NCT01392573,]
Study type	Randomised controlled trial (RCT)
Study location	75 trial sites across Bulgaria, Switzerland, Denmark, Hungary, India, Slovenia, United States
Study setting	NR
Study dates	Randomisation and treatment between 28 November 2011 and 4 October 2012
Sources of funding	Novo Nordisk
Inclusion criteria	• ≥18 years of age • Inadequately controlled type 2 diabetes (A1C of 7.5 to10.0% [58 to 86 mmol/mol], inclusive) • BMI ≥27 kg/m2 • Treated for ≥ 90 days with basal insulin at a stable dose (20 to 40 units/day [±10%]) in combination with metformin with or without sulfonylurea or glinides

Exclusion criteria	• Known or suspected hypersensitivity to trial products or related products • Previous participation in this trial. Participation is defined as randomized (screening failures are allowed to be re-screened once during the recruitment period) • Females of childbearing potential who are pregnant, breast-feeding or intend to become pregnant or are not using adequate contraceptive methods (adequate contraceptive measures as required by local law or practice). US: acceptable forms of birth control include sexual abstinence; sterilization of either partner; oral, injectable, implant or transdermal hormonal methods; intrauterine or vaginal device or consistent use of proven barrier methods with spermicide use as indicated • Use of any drug (except for basal insulin, metformin, sulfonylurea and glinides), which in the investigator's opinion could interfere with glucose level (e.g. systemic corticosteroids) • Treatment with GLP-1 receptor agonists (e.g. exenatide, liraglutide), dipeptidyl peptidase-4 (DPP-4) inhibitors and/or thiazolidinediones within 90 days prior to screening • Subject with a clinically significant, active (during the past 12 months) disease of the gastrointestinal, pulmonary, endocrinological (except for type 2 diabetes), neurological, genitourinary or hematological system (except for conditions associated with type 2 diabetes), that in the opinion of the investigator may confound the results of the trial or pose additional risk in administering trial drug • The receipt of any investigational product within 30 days prior to screening • Impaired liver function, defined as alanine aminotransferase (ALAT) ≥2.5 times upper normal range (UNR) (one retest analysed at the central laboratory within a week from first sample taken is permitted with the result of the last sample being the conclusive) • Impaired renal function defined as serum-creatinine ≥133 µmol/L (≥1.5 mg/dL) for males and ≥125 µmol/L (≥1.4 mg/dL) for females, or as allowed according to local contraindications for metformin (one retest analyzed at the central laboratory within a week from first sample taken is permitted with the result of the last sample being the conclusive) • Screening calcitonin ≥50 ng/L • Subjects with personal or family history of medullary thyroid carcinoma (MTC) or multiple endocrine neoplasia type 2 (MEN 2) • Cardiac disorder defined as: congestive heart failure (NYHA class III-IV), diagnosis of unstable angina pectoris, cerebral stroke and/or myocardial infarction within the last 52 weeks prior to screening and/or planned coronary, carotid or peripheral artery revascularization procedures • Severe uncontrolled treated or untreated hypertension (systolic blood pressure ≥180 mm Hg or diastolic blood pressure ≥100 mm Hg) • Proliferative retinopathy requiring acute treatment or maculopathy (macular oedema) according to investigator's opinion • Mental incapacity, unwillingness or language barrier precluding adequate understanding of the trial procedure or cooperation with trial site personnel

	• Known or suspected abuse of alcohol or narcotics • History of chronic pancreatitis or idiopathic acute pancreatitis • Cancer (except basal cell skin cancer or squamous cell skin cancer), which in the investigator's opinion could interfere with the results of the trial, or cancer during the 5 past years
Recruitment / selection of participants	831 participants were enrolled, and 413 participants were randomised
Intervention(s)	IDegLira was titrated (provided as 100 units/mL IDeg and 3.6 mg liraglutide in a 3 mL prefilled FlexPen). Initial dose was 16 dose steps IDegLira (16 units IDeg plus 0.6 mg liraglutide). Maximum dose was 50 dose steps (50 units IDeg plus 1.8 mg liraglutide). Dosed once daily, independent of meals, but preferably at the same time every day.
Cointervention	Participants discontinued all glucose-lowering drugs except metformin (kept at pretrial dose and frequency) and transferred from current basal insulin to IDegLira or insulin degludec. Doses of IDegLira or insulin degldec were adjusted biweekly according to a predetermined titration algorithm, based on self-measured breakfast FPG (mean prebreakfast glucose concentration of 4.0 to 5.0 mmol/L).
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear Exclusion criteria state: "Cardiac disorder defined as: congestive heart failure (NYHA class III-IV), diagnosis of unstable angina pectoris, cerebral stroke and/or myocardial infarction within the last 52 weeks prior to screening and/or planned coronary, carotid or peripheral artery revascularization procedures"
Strata 2: People with atherosclerotic cardiovascular disease	Not stated/unclear
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	Not stated/unclear

Subgroup 1: People with moderate or severe frailty	Not stated/unclear
Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear
Subgroup 3: People with non-alcoholic fatty liver disease	Not stated/unclear
Subgroup 4: People with obesity	Not stated/unclear Inclusion criteria: "BMI≥27 kg/m2"
Subgroup 5: eGFR category at baseline	Not stated/unclear
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Population subgroups	NR
Comparator	IDeg was titrated (provided as 100 units/mL in a 3 mL prefilled FlexPen). Initial dose of IDeg was 16 units. Maximum dose was 50 units IDeg. Dosed once daily, independent of meals, but preferably at the same time every day.
Number of participants	207 participants were allocated to IDegLira; 32 (16%) of participants withdrew, and 175 participants (85%) completed. 206 participants were allocated to IDeg; 35 (17%) of participants withdrew, and 171 (83%) of participants completed treatment.
Duration of follow-up	26 weeks
Indirectness	Directly applicable
Method of analysis	ITT The full analysis set as randomised. The primary endpoint was analysed using an ANCOVA model.
Additional comments	Sensitivity analyses were also reported for a completer analysis

64.2. Study arms

64.2.1. IDegLira (N = 207)

64.2.2. Insulin degludec (N = 206)

64.3. Characteristics

64.3.1. Arm-level characteristics

Characteristic	IDegLira (N = 207)	Insulin degludec (N = 206)
% Male For FAS only (IDegLira: n=199; IDeg: n=199) Sample size	n = 56 ; % = 28.1	n = 53 ; % = 26.7
Mean age (SD) For FAS only (IDegLira: n=199; IDeg: n=199) Mean (SD)	57 (9)	58 (11)
White Sample size	n = 79 ; % = 39.7	n = 76 ; % = 38.2
Black Sample size	n = 5 ; % = 2.5	n = 5 ; % = 2.5
Asian Sample size	n = 17 ; % = 8.5	n = 18 ; % = 9
Other Sample size	n = 0 ; % = 0	n = 1 ; % = 0.5
Hispanic or Latino Sample size	n = 8 ; % = 4	n = 12 ; % = 6
Non-hispanic or Latino Sample size	n = 92 ; % = 46.2	n = 88 ; % = 44.2
Comorbidities Nominal	NR	NR

Characteristic	IDegLira (N = 207)	Insulin degludec (N = 206)
Presence of frailty Nominal	NR	NR
Time since type 2 diabetes diagnosed For FAS only (IDegLira: n=199; IDeg: n=199) Mean (SD)	10 (6)	11 (7)
Cardiovascular risk factors Nominal	NR	NR
Smoking status Nominal	NR	NR
Alcohol consumption Nominal	NR	NR
Presence of severe mental illness Nominal	NR	NR
People with significant cognitive impairment Nominal	NR	NR
People with a learning disability Nominal	NR	NR
Number of people with obesity Nominal	NR	NR
Other antidiabetic medication used Sample size	n = NA ; % = NA	n = NA ; % = NA
Basal insulin + metformin Sample size	n = 95 ; % = 48	n = 98 ; % = 49
Basal insulin + metformin + SU/glinides Sample size	n = 104 ; % = 52	n = 101 ; % = 51
Blood pressure-lowering medication used Nominal	NR	NR
Statins/lipid-lowering medication used Nominal	NR	NR

Characteristic	IDegLira (N = 207)	Insulin degludec (N = 206)
Other treatment being received Nominal	NR	NR

65. Butler, 2019

Bibliographic Reference	Butler, Javed; Zannad, Faiez; Fitchett, David; Zinman, Bernard; Koitka-Weber, Audrey; von Eynatten, Maximilian; Zwiener, Isabella; George, Jyothis; Brueckmann, Martina; Cheung, Alfred K; Wanner, Christoph; Empagliflozin Improves Kidney Outcomes in Patients With or Without Heart Failure.; Circulation. Heart failure; 2019; vol. 12 (no. 6); e005875

65.1. Study details

Secondary publication of another included study- see primary study for details	EMPA-REG OUTCOME trial. Zinman, Bernard, Wanner, Christoph, Lachin John, M et al. (2015) Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. The New England journal of medicine 373(22): 2117-28
Other publications associated with this study included in review	Wanner, Christoph, Lachin John, M, Inzucchi Silvio, E et al. (2018) Empagliflozin and Clinical Outcomes in Patients With Type 2 Diabetes Mellitus, Established Cardiovascular Disease, and Chronic Kidney Disease. Circulation 137(2): 119-129 Zinman, Bernard, Inzucchi, Silvio E, Lachin, John M et al. (2014) Rationale, design, and baseline characteristics of a randomized, placebo-controlled cardiovascular outcome trial of empagliflozin (EMPA-REG OUTCOME TM). Cardiovascular diabetology 13: 102
Trial name / registration number	EMPA-REG OUTCOME. ClinicalTrials.gov number, NCT01131676

66. Cahn, 2021

Bibliographic Reference	Cahn, Avivit; Raz, Itamar; Leiter, Lawrence A; Mosenzon, Ofri; Murphy, Sabina A; Goodrich, Erica L; Yanuv, Ilan; Rozenberg, Aliza; Bhatt, Deepak L; McGuire, Darren K; Wilding, John P H; Gause-Nilsson, Ingrid A M; Langkilde, Anna Maria; Sabatine, Marc S; Wiviott, Stephen D; Cardiovascular, Renal, and Metabolic Outcomes of Dapagliflozin Versus Placebo in a Primary Cardiovascular Prevention Cohort: Analyses From DECLARE-TIMI 58.; Diabetes care; 2021; vol. 44 (no. 5); 1159-1167

66.1. Study details

Secondary publication of another included study- see primary study for details	DECLARE-TIMI 58 trial. Wiviott Stephen, D, Raz, Itamar, Bonaca Marc, P et al. (2019) Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes. The New England journal of medicine 380(4): 347-357
Other publications associated with this study included in review	Wiviott et al. (2018) The design and rationale for the Dapagliflozin Effect on Cardiovascular Events (DECLARE)-TIMI 58 Trial. American heart journal; 2018; vol. 200; 83-89 Mosenzon, Ofri, Wiviott Stephen, D, Cahn, Avivit et al. (2019) Effects of dapagliflozin on development and progression of kidney disease in patients with type 2 diabetes: an analysis from the DECLARE-TIMI 58 randomised trial. The lancet. Diabetes & endocrinology 7(8): 606-617 Zelniker T, A, Bonaca M, P, Furtado R, H.M et al. (2020) Effect of dapagliflozin on atrial fibrillation in patients with type 2 diabetes mellitus: Insights from the DECLARE-TIMI 58 Trial. Circulation: 1227-1234 Zelniker, Thomas A, Raz, Itamar, Mosenzon, Ofri et al. (2021) Effect of Dapagliflozin on Cardiovascular Outcomes According to Baseline Kidney Function and Albuminuria Status in Patients With Type 2 Diabetes: A Prespecified Secondary Analysis of a Randomized Clinical Trial. JAMA cardiology 6(7): 801-810
Trial name / registration number	DECLARE-TIMI 58 trial. ClinicalTrials.gov number, NCT01730534

67. Camerini-Davalos, 1994

Bibliographic Reference	Camerini-Davalos, R. A.; Velasco, C. A.; Reddi, A. S.; Effect of insulin-glipizide combination on skeletal muscle capillary basement membrane width in diabetic patients; Clin Ther; 1994; vol. 16 (no. 6); 952-61

67.1. Study details

Secondary publication of another included study- see primary study for details	No
Other publications associated with this study included in review	None
Trial name / registration number	Not reported
Study type	Randomised controlled trial (RCT) Double-blind parallel-group RCT
Study location	Metropolitan Hospital Center Diabetes Clinic, New York, NY, USA
Study setting	Outpatient (Diabetes centres)
Study dates	Not reported
Sources of funding	Supported in part by Diabetes Research Fund, New York, NY; the Michael J. Bilotto Research Fund of HOPE for Diabetes Foundation, New York, NY; the Veterans Administration Research Fund, Washington, DC; Roerig-Pfizer Pharmaceuticals, New York, NY.
Inclusion criteria	• Glucose levels inadequately controlled using oral antihyperglycaemic agents • Required insulin to control glucose levels • At least 3 consecutive FPG levels>140 mg/dL and C-peptide 0.83 ng/dL
Exclusion criteria	• Women who were pregnant, who were of childbearing potential, or who were known to use unreliable contraceptive methods

	• Patients requiring long-term therapy with drugs known to affect glucose metabolism or sulphonylurea kinetics (sulphonamides, phenylbutazone, oxyphenbutazone, probenecid, coumarines, monoamine oxidase inhibitors, corticotropin, adrenal steroids, epinephrine, nicotinic acid, and salicylates) • Any clinical or laboratory abnormalities.
Recruitment / selection of participants	Recruited from diabetes clinic in New York. Participants taking oral antihyperglycaemic drug at screening discontinued medication 3 months before enrolment in trial. All participants asked to adhere to American Diabetes Association diet calculated to maintain body weight with 45% carbohydrates, 18% proteins and 37% fats, divided into 3 meals with bedtime snack. Randomisation was computer-generated. Half dose of treatment given at breakfast and half at dinner, in addition to intermediate-acting human insulin (once or twice daily injection).
Intervention(s)	• Glipizide 5 mg daily Oral glipizide 5 mg daily for 36 months, in addition to intermediate-acting insulin.
Cointervention	• Insulin (intermediate-acting) once or twice daily Intermediate-acting human insulin, once or twice daily, for 36 months
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear Not an inclusion/exclusion criteria. No information in baseline characteristics
Strata 2: People with atherosclerotic cardiovascular disease	People without atherosclerotic cardiovascular diseases "No patient had evidence of vascular complications"
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	People without chronic kidney disease No patient had evidence of renal disease based on history, a physical examination , and routine laboratory determinations
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	Not stated/unclear

Subgroup 1: People with moderate or severe frailty	Not stated/unclear
Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear
Subgroup 3: People with non-alcoholic fatty liver disease	Not stated/unclear
Subgroup 4: People with obesity	Not stated/unclear
Subgroup 5: eGFR category at baseline	Not stated/unclear
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Population subgroups	
Comparator	• Placebo Matching placebo for 36 months, in addition to intermediate-acting human insulin (once or twice daily).
Number of participants	N=70
Duration of follow-up	36 months
Indirectness	None
Method of analysis	ITT ITT completer analysis for all outcomes

67.2. Study arms

67.2.1. Glipizide 5 mg daily (N = 40)

Oral glipizide 5 mg daily for 36 months, in addition to intermediate-acting human-type insulin.

67.2.2. Placebo (N = 30)

Matching pllacebo for 36 months, in addition to intermediate-acting human-type insulin.

67.3. Characteristics

67.3.1. Arm-level characteristics

Characteristic	Glipizide 5 mg daily (N = 40)	Placebo (N = 30)
% Male Sample size	n = 15 ; % = 44.1	n = 10 ; % = 37
Mean age (SD) (years) Custom value	Mean 46, range 22-59	Mean 47.4, range 20-61
Ethnicity Nominal	NR	NR
Comorbidities Nominal	NR	NR
Presence of frailty Nominal	NR	NR
Time since type 2 diabetes diagnosed (years) Custom value	Mean 10.5, range 1-25	Mean 14.1, range 2-25
Cardiovascular risk factors Nominal	NR	NR
Smoking status Nominal	NR	NR
Alcohol consumption	NR	NR

Characteristic	Glipizide 5 mg daily (N = 40)	Placebo (N = 30)
Nominal		
Presence of severe mental illness Nominal	NR	NR
People with significant cognitive impairment Nominal	NR	NR
People with a learning disability Nominal	NR	NR
Number of people with obesity Nominal	NR	NR
Other antidiabetic medication used Prior treatment Sample size	n = NA ; % = NA	n = NA ; % = NA
None Sample size	n = 1 ; % = 2.9	n = 2 ; % = 7.4
Diet only Sample size	n = 3 ; % = 8.8	n = 3 ; % = 11.1
Oral drugs Sample size	n = 2 ; % = 5.9	n = 3 ; % = 11.1
Diet + oral drugs Sample size	n = 4 ; % = 11.8	n = 5 ; % = 18.5
Insulin (conventional treatment) Sample size	n = 24 ; % = 70.6	n = 14 ; % = 51.9
Blood pressure-lowering medication used Nominal	NR	NR
Statins/lipid-lowering medication used Nominal	NR	NR
Other treatment being received Nominal	NR	NR

68. Cannon Christopher, 2018

Bibliographic Reference	Cannon Christopher, P; McGuire Darren, K; Pratley, Richard; Dagogo-Jack, Sam; Mancuso, James; Huyck, Susan; Charbonnel, Bernard; Shih Weichung, J; Gallo, Silvina; Masiukiewicz, Urszula; Golm, Gregory; Cosentino, Francesco; Lauring, Brett; Terra Steven, G; VERTIS-CV, Investigators; Design and baseline characteristics of the eValuation of ERTugliflozin effIcacy and Safety CardioVascular outcomes trial (VERTIS-CV).; American heart journal; 2018; vol. 206; 11-23

68.1. Study details

Secondary publication of another included study- see primary study for details	VERTIS CV trial. Cannon Christopher, P, Pratley, Richard, Dagogo-Jack, Samuel et al. (2020) Cardiovascular Outcomes with Ertugliflozin in Type 2 Diabetes. The New England journal of medicine 383(15): 1425-1435
Trial name / registration number	VERTIS CV/NCT01986881

69. Cannon Christopher, 2020

Bibliographic Reference	Cannon Christopher, P; Pratley, Richard; Dagogo-Jack, Samuel; Mancuso, James; Huyck, Susan; Masiukiewicz, Urszula; Charbonnel, Bernard; Frederich, Robert; Gallo, Silvina; Cosentino, Francesco; Shih Weichung, J; Gantz, Ira; Terra Steven, G; Cherney David Z, I; McGuire Darren, K; VERTIS, CV; Investigators; Cardiovascular Outcomes with Ertugliflozin in Type 2 Diabetes.; The New England journal of medicine; 2020; vol. 383 (no. 15); 1425-1435

69.1. Study details

Secondary publication of another included study- see primary study for details	Parent study for the VERTIS CV trial
Other publications associated with this study included in review	Cannon Christopher, P, McGuire Darren, K, Pratley, Richard et al. (2018) Design and baseline characteristics of the eValuation of ERTugliflozin efFIcacy and Safety CardioVascular outcomes trial (VERTIS-CV). American heart journal 206: 11-23 Cherney, David Z I, Cosentino, Francesco, Pratley, Richard E et al. (2022) The differential effects of ertugliflozin on glucosuria and natriuresis biomarkers: Prespecified analyses from VERTIS CV. Diabetes, obesity & metabolism 24(6): 1114-1122 Cosentino, F, Cannon C, P, Cherney D, Z.I et al. (2020) Efficacy of Ertugliflozin on Heart Failure-Related Events in Patients with Type 2 Diabetes Mellitus and Established Atherosclerotic Cardiovascular Disease: Results of the VERTIS CV Trial. Circulation
Trial name / registration number	VERTIS CV/NCT01986881
Study type	Randomised controlled trial (RCT)
Study location	34 countries
Study setting	Primary care: 567 centres

Study dates	Recruited: December 2013 through July 2015 and from June 2016 through April 2017 Follow-up: mean 3.5 years, median 3.0 years
Sources of funding	Merck Sharp & Dohme and Pfizer
Inclusion criteria	1. Subjects greater than or equal to 40 years of age at the time of the initial Screening visit (V1) with a diagnosis of T2DM in accordance with American Diabetes Association (ADA) guidelines 2. HbA1c at the Screening visit 1 (V1) of 7.0-10.5% (53-91 mmol/mol) on stable allowable AHA(s) or on no background AHA for at least 8 weeks prior to the Screening visit V1. 3. Body Mass Index (BMI) equal to or greater than 18.0 kg/m2 4. There is adequate documentation of the objective evidence that the subject has established vascular disease such as investigational site's medical records, copies of such records from other institutions, or a letter from a referring physician that specifically states the diagnosis and date of the most recent occurrence of the qualifying event(s) or procedure(s) 5. Male and female (not of reproductive potential; or of reproductive potential and agrees to remain abstinent from heterosexual activity or agrees to use acceptable contraception to prevent pregnancy) 6. Evidence of a personally signed and dated informed consent document (ICD) indicating that the subject (or a legal representative) has been informed of all pertinent aspects of the trial. 7. In the investigator’s opinion subjects are willing and likely able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures whether or not they receive investigational product for the duration of the trial 8. Subjects must have evidence or a history of atherosclerosis involving the coronary, cerebral or peripheral vascular systems as follows (must have at least one of the following a-d) a) Coronary artery disease as indicated by a history of presumed spontaneous myocardial infarction (hospitalized with final diagnosis of myocardial infarction, excluding peri-procedural or definite secondary myocardial infarction [eg, due to profound anemia or hypertensive emergency, troponin increase in sepsis] in which the most recent event occurred at least 3 months (90 days) prior to the Screening visit V1; OR b) Coronary artery disease as indicated by a history of coronary revascularization through either a Percutaneous Coronary Intervention (PCI) at least 3 months (90 days) prior to the Screening visit V1 or Coronary Artery Bypass Graft (CABG) at least 3 months (90 days) prior to the Screening visit V1; OR c) Ischemic (presumed thrombotic) cerebrovascular disease as indicated by a history of ischemic stroke (hospitalized with a final diagnosis of non-hemorrhagic stroke [includes completion of a standard evaluation for stroke in an acute care facility or stroke clinic without hospital admission] with the most recent event occurring at least 3 months (90 days) prior to

	the Screening visit V1 or a history of carotid revascularization at least 3 months (90 days) prior to the Screening visit V1; OR d) Peripheral arterial disease as indicated by: 1. Angiographically-documented peripheral vascular disease; or 2. Resting ankle/brachial index (ABI) of <0.85 (measured by a certified vascular laboratory) plus symptoms of claudication; or 3. Amputation, peripheral bypass, or peripheral angioplasty of the extremities secondary to ischemia occurring at least 3 months (90 days) prior to the Screening visit V1.
Exclusion criteria	(1) Subjects who had been previously randomized into this trial. (2) Subjects experiencing a cardiovascular event (eg, myocardial infarction or stroke) or undergoing coronary angioplasty or peripheral intervention procedure between the Screening visit V1 and randomisation. (3) Subjects undergoing any cardiovascular surgery (eg, valvular surgery) within 3 months (90 days) of the Screening visit V1. (4) Subjects with any planned coronary revascularization or peripheral intervention procedure or other cardiovascular surgery. (5) Subjects with New York Heart Association (NYHA) Class IV heart failure at the Screening visit V1. (6) Mean value for triplicate screening sitting systolic blood pressure >160 mm Hg and/or diastolic blood pressure >90 mm Hg after at least a 5-minute seated rest at the Screening visit V), confirmed via 1 repeat triplicate set at the Screening visit V1 if deemed necessary. For subjects with a mean triplicate value of sitting systolic blood pressure >160 mm Hg and/or diastolic blood pressure >90 mm Hg after at least a 5-minute seated rest at the Screening visit V1 the investigator or the treating physician is allowed to adjust background blood pressure medication(s) to lower blood pressure values in order for the subject to be re-assessed for enrolment eligibility. (7) Subject has a clinically significant electrocardiogram (ECG) abnormality at Screening visit V) that requires further diagnostic evaluation or intervention (eg, new, clinically significant arrhythmia or a conduction disturbance). (8) History of type 1 diabetes mellitus or a history of ketoacidosis. (9) History of other specific types of diabetes (e.g., genetic syndromes, secondary pancreatic diabetes, diabetes due to endocrinopathies, drug- or chemical-induced, and post-organ transplant). (10) Subject has active, obstructive uropathy or indwelling urinary catheter. (11) Subject has a history of malignancy less than or equal to 5 years prior to signing informed consent, except for adequately treated basal cell or squamous cell skin cancer or in situ cervical cancer. Note (1) A subject with a history of malignancy >5 years prior to signing informed consent should have no evidence of residual or recurrent disease. Note (2) A subject with any history of melanoma, leukemia, lymphoma, or renal cell carcinoma is excluded. (12) Subject routinely consumes >2 alcoholic drinks per day or >14 alcoholic drinks per week or engages in binge drinking. Note (1): One alcoholic drink is defined as 5 oz (150 mL) of wine, or 12 oz (350 mL) of beer, or 1.5 oz (50 mL) of 80-proof liquor. Note (2): Binge drinking is defined as a pattern of 5 or more alcoholic drinks (male), or 4 or more alcoholic drinks (female) in about 2 hours. (13) Any clinically significant malabsorption condition. (14) Subjects with a known hypersensitivity or intolerance to any SGLT2 inhibitor. (15) Screening fasting plasma or finger-stick glucose >270 mg/dL (15 mmol/L), confirmed by a single repeat following counseling on exercise and diet. (16) History of one or more severe hypoglycemic episodes within 6 months of Screening V) or a severe hypoglycemic episode occurring

	during the interval between the Screening visit V1 and randomisation. (17) Fasting triglycerides >600 mg/dL (6.78 mmol/L) at Screening (V1), confirmed by a single repeat if deemed necessary. For subjects with fasting triglycerides >600 mg/dL the investigator or treating physician is allowed to adjust background lipid altering medication(s) to lower fasting triglycerides in order for the subject to be re-assessed for enrolment eligibility. (18) Subjects currently taking blood pressure or lipid altering medications that have not been on a stable dose for at least 4 weeks prior to randomisation. Subjects who require a change in blood pressure and/or lipid altering medications to meet the entry criteria related to blood pressure and/or triglycerides must be on a stable dose of such therapy for at least 4 weeks prior to randomisation. (19) Subjects who meet any of the following categories: • Subject is on a weight-loss program and is not weight-stable. • Subject is on a weight-loss medication (e.g., orlistat, phentermine/topiramate, lorcaserin) and is not weight-stable. • Subject is on other medications associated with weight changes (e.g., anti-psychotic agents) and is not weight-stable. • Subject has undergone bariatric surgery >12 months prior to Visit 1/Screening and is not weight-stable. • Subject has undergone bariatric surgery within 12 months of Screening visit V1. Note: Weight-stable is defined as <5% change in body weight in the last 6 months. (20) Subjects currently being treated for hyperthyroidism, subjects on thyroid replacement therapy that have not been on a stable dose for at least 6 weeks prior to the Screening visit V1 and/or subjects who have a thyroid stimulating hormone (TSH) outside of the laboratory reference range at the Screening visit V). Subjects excluded due to TSH criterion may be re-tested after being on a stable thyroid replacement regimen for at least 6 weeks. (21). eGFR <30 mL/min/1.73 m2 as determined by the 4-variable Modification of Diet in Renal Disease (MDRD) equation, confirmed via a single repeat if deemed necessary. (22). Subjects with a haemoglobin <10 g/dL (100 g/L). Confirmed via a single repeat if deemed necessary. (23) Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >2 X the upper limit of normal (ULN) at the Screening visit V1, or a total bilirubin >1.5 X the ULN unless the subject has a history of Gilbert's. (24) Subject has a medical history of active liver disease (other than non-alcoholic hepatic steatosis), including chronic active hepatitis B or C (assessed by medical history), primary biliary cirrhosis, or symptomatic gallbladder disease. (25) Subject is on or likely to require treatment for greater than or equal to 14 consecutive days or repeated courses of pharmacologic doses of corticosteroids. These medications are not to be used from the time of the start of the Day 1 Visit (Visit 2) to the completion of the trial. Note: Inhaled, nasal, and topical corticosteroids and physiological replacement doses of adrenal steroids are permitted. (26) The following therapeutic agents are prohibited for the duration of the trial. These medications are not to be used from 8 weeks before the Screening visit V1) until the completion of the trial. • Treatment with another SGLT2 inhibitor; • Treatment with rosiglitazone; • Treatment with chlorpropamide. (27) Subjects who have donated blood or blood products within six weeks of Screening V1 or who plan to donate blood or blood products at any time during the trial. (28) Subjects who have undergone a surgical procedure within 4 weeks prior to signing informed consent or have planned major surgery during the trial. Note: A subject who has undergone minor surgery within the 4 weeks prior to Screening Visit V1 and is fully recovered or a subject who has planned minor surgery may participate. Minor surgery is defined as a surgical procedure involving

	local anaesthesia. For exclusion regarding cardiovascular surgery, see exclusion criterion (3). (29). Subjects with: • Known history of Human Immunodeficiency Virus (HIV); • Blood dyscrasias or any disorders causing haemolysis or unstable red blood cells. 30. At randomization, subject has developed a new medical condition, suffered a change in status of an established medical condition, developed a laboratory or ECG abnormality, or required a new treatment or medication during the pre-randomization period which meets any previously described trial exclusion criterion or which, in the opinion of the investigator, exposes the subject to risk by enrolling in the trial. (31) Other severe acute or chronic medical or psychiatric condition or laboratory abnormality at the Screening visit V1 that may increase the risk associated with trial participation or investigational product administration or may interfere with the interpretation of trial results and, in the judgment of the investigator, would make the subject inappropriate for entry into this trial. (32) Subjects who have previously been randomised in a trial with ertugliflozin. (33) Participation in other studies involving investigational drug (s) (Phases 1-4) within 30 days before the Screening visit V1) and/or during trial participation. (34) Subject is pregnant or breast-feeding, or is expecting to conceive during the trial, including 14 days following the last dose of blinded investigational product. (35) Subject is expecting to undergo hormonal therapy in preparation to donate eggs during the period of the trial, including 14 days following the last dose of blinded investigational product. (36) Subjects who are investigational site staff members directly involved in the conduct of the trial and their family members, site staff members otherwise supervised by the investigator, or subjects who are Pfizer/Merck employees directly involved in the conduct of the trial.
Recruitment / selection of participants	Recruitment advertisements
Intervention(s)	Ertugliflozin 5 mg or 5 mg Concomitant therapy: Subjects who are treated with oral anti-hyperglycemic agents (AHA), insulin or GLP-1 agonists, either alone or in combination, stable for at least 8 weeks prior to the Screening visit (V1) or subjects who are on only diet and exercise for T2DM are eligible to be enrolled (<2% were on no AHA). Background AHA treatment must continue to remain stable throughout the length of the Screening period. The only prohibited concomitant AHA therapy is the use of any other SGLT2 therapy (eg, dapagliflozin, canagliflozin, empagliflozin, etc.), rosiglitazone or chlorpropamide within 8 weeks of the Screening visit (V1), between the screening period and randomization or during the trial. Doses of background anti-hyperglycemic medication were held constant for the initial 18 weeks of the study except for those patients meeting the glycemic rescue criteria or with clinically significant hypoglycemia. After week 18, changes in anti-hyperglycemic medication were permitted except for prohibited agents (i.e., other SGLT2 inhibitors, chlorpropamide, or rosiglitazone). The investigator or the treating provider were encouraged to make any changes in the background cardiovascular treatment regimen to

	achieve appropriate targets for secondary disease prevention per treatment guidelines at any time during the study. Subjects will be counselled on appropriate dietary and lifestyle guidelines for T2DM at Day 1 visit (V2) and asked to follow the advice throughout participation in the trial. Counselling on dietary guidelines should be in accordance with local medical standards of care for subjects with T2DM
Strata 1: People with type 2 diabetes mellitus and heart failure	Mixed population Excluded "Subjects with New York Heart Association (NYHA) Class III or IV heart failure at the Screening visit", other HF not exclusion criteria. 23.5% of people in the Ertugliflozin and 24.5% of people in the placebo arm had heart failure
Strata 2: People with atherosclerotic cardiovascular disease	People with atherosclerotic cardiovascular diseases Inclusion criteria "established atherosclerotic cardiovascular disease involving the coronary, cerebrovascular, or peripheral arterial systems"
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Mixed population Cherney 2022 paper gives KDIGO CKD low-, moderate- and high-/very-high-risk categories at baseline were 3916 (48.8%), 2568 (32.0%) and 1548 (19.3%), respectively. NICE CKD guideline indicates that KDIGO low risk is 'no CKD' and other risk categories are 'with CKD'. Therefore 48.8% have no CKD. Using these subgroups for analysis.
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	People at higher risk of developing cardiovascular disease Majority will be at higher risk of developing cardiovascular disease (due to mean higher BMI, mean higher blood pressure and history of cardiovascular disease)
Subgroup 1: People with moderate or severe frailty	Not stated/unclear
Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear
Subgroup 3: People with non-alcoholic fatty liver disease	Not stated/unclear

Subgroup 4: People with obesity	Not stated/unclear
Subgroup 5: eGFR category at baseline	eGFR ≥30mL/min/1.73m2
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Population subgroups	No additional information
Comparator	placebo Concomitant therapy: Subjects who are treated with oral anti-hyperglycemic agents (AHA), insulin or GLP-1 agonists, either alone or in combination, stable for at least 8 weeks prior to the Screening visit (V1) or subjects who are on only diet and exercise for T2DM are eligible to be enrolled (<2% were on no AHA). Background AHA treatment must continue to remain stable throughout the length of the Screening period. The only prohibited concomitant AHA therapy is the use of any other SGLT2 therapy (e.g., dapagliflozin, canagliflozin, empagliflozin, etc.), rosiglitazone or chlorpropamide within 8 weeks of the Screening visit (V1), between the screening period and randomization or during the trial. Doses of background anti-hyperglycemic medication were held constant for the initial 18 weeks of the study except for those patients meeting the glycemic rescue criteria or with clinically significant hypoglycemia. After week 18, changes in anti-hyperglycemic medication were permitted except for prohibited agents (i.e., other SGLT2 inhibitors, chlorpropamide, or rosiglitazone). The investigator or the treating provider were encouraged to make any changes in the background cardiovascular treatment regimen to achieve appropriate targets for secondary disease prevention per treatment guidelines at any time during the study. Subjects will be counselled on appropriate dietary and lifestyle guidelines for T2DM at Day 1 visit (V2) and asked to follow the advice throughout participation in the trial. Counselling on dietary guidelines should be in accordance with local medical standards of care for subjects with T2DM
Number of participants	Ertugliflozin: n=5499 Placebo: n=2747
Duration of follow-up	Mean duration: 3.5 years Median duration: 3.0 years

Indirectness	No indirectness
Method of analysis	ITT
Additional comments	Primary and secondary time-to-first-event outcomes analysed using a stratified Cox proportional hazards model including treatment group as a covariate and study as the stratification factor. Subjects without endpoints will be censored at the study cut-off date or last contact date, if earlier. The primary analysis set for the non-inferiority analysis of the primary outcome of MACE will be the full analysis set, which will include all patients who were randomized and who received at least 1 dose of investigational product and will include confirmed events occurring up to 365 days after the last dose of investigational product for those with premature discontinuation. 8246 randomized patients 8238 patients received at least 1 dose of investigational product and constitute the full analysis set for the non-inferiority analysis for MACE

69.2. Study arms

69.2.1. Ertugliflozin (N = 5499)

5 mg or 15 mg; immediate release tablets for oral administration; subjects randomized to ertugliflozin 5 mg will be instructed to take 1 ertugliflozin 5 mg tablet and 1 placebo tablet matching the ertugliflozin 10 mg tablet per day. Subjects randomized to ertugliflozin 15 mg will be instructed to take 1 ertugliflozin 5 mg tablet and 1 ertugliflozin 10 mg tablet per day.

69.2.2. Placebo (N = 2747)

Matching placebo; immediate release tablets for oral administration. Subjects randomized to placebo will take 1 placebo tablet matching the ertugliflozin 5 mg tablet and 1 placebo tablet matching the ertugliflozin 10 mg tablet per day. Thus, all subjects will take two tablets each day of ertugliflozin/placebo

69.3. Characteristics

69.3.1. Arm-level characteristics

Characteristic	Ertugliflozin (N = 5499)	Placebo (N = 2747)
% Male Sample size	n = 3866 ; % = 70.3	n = 1903 ; % = 69.3
Mean age (SD) Mean (SD)	64.4 (8.1)	64.4 (8)
White Sample size	n = 4826 ; % = 87.8	n = 2414 ; % = 87.9
Black Sample size	n = 166 ; % = 3	n = 69 ; % = 2.9
Asian Sample size	n = 336 ; % = 6.1	n = 162 ; % = 5.9
Other Sample size	n = 171 ; % = 3.1	n = 102 ; % = 3.7
Coronary artery disease Sample size	n = 4144 ; % = 75.4	n = 2112 ; % = 76.9
Cerebrovascular disease Sample size	n = 1276 ; % = 23.2	n = 613 ; % = 22.3
Peripheral arterial disease Sample size	n = 1029 ; % = 18.7	n = 512 ; % = 18.6
Heart failure Sample size	n = 1286 ; % = 23.4	n = 672 ; % = 24.5
Myocardial infarction Sample size	n = 2625 ; % = 47.7	n = 2625 ; % = 48.4
Stroke Sample size	n = 1181 ; % = 21.5	n = 558 ; % = 20.3
Presence of frailty Sample size	n = NA ; % = NA	n = NA ; % = NA

Characteristic	Ertugliflozin (N = 5499)	Placebo (N = 2747)
Time since type 2 diabetes diagnosed (years) Mean (SD)	12.9 (8.3)	13.1 (8.4)
Cardiovascular risk factors Sample size	n = NA ; % = NA	n = NA ; % = NA
Smoking status Sample size	n = NA ; % = NA	n = NA ; % = NA
Alcohol consumption Mean (SD)	NA (NA)	NA (NA)
Presence of severe mental illness Sample size	n = NA ; % = NA	n = NA ; % = NA
BMI (kg/m2) Mean (SD)	31.9 (5.4)	32 (5.5)
Number of people with obesity Sample size	n = NA ; % = NA	n = NA ; % = NA
Albumin creatinine ratio Mean (SD)	NA (NA)	NA (NA)
eGFR mL/min/1.73m2 Mean (SD)	76.1 (20.9)	75.7 (20.8)
<60mL/min/1.73m2 - no. % Mean (SD)	1199 (21.8)	608 (22.1)
Other antidiabetic medication used Sample size	n = NA ; % = NA	n = NA ; % = NA
None Sample size	n = 77 ; % = 1.4	n = 29 ; % = 1.1
Metformin Sample size	n = 4168 ; % = 75.8	n = 2124 ; % = 77.3
Insulin Sample size	n = 2556 ; % = 46.5	n = 1344 ; % = 48.9

Characteristic	Ertugliflozin (N = 5499)	Placebo (N = 2747)
Sulfonylurea Sample size	n = 2268 ; % = 41.2	n = 1122 ; % = 40.8
Dipeptidyl peptidase 4 inhibitor Sample size	n = 619 ; % = 11.3	n = 292 ; % = 10.6
Glucagon-like peptide-1 receptor agonist Sample size	n = 192 ; % = 3.5	n = 86 ; % = 3.1
Blood pressure-lowering medication used Sample size	n = 5221 ; % = 94.9	n = 2632 ; % = 95.8
Renin-angiotensin-aldosterone system blocker Sample size	n = 4447 ; % = 80.9	n = 2239 ; % = 81.5
Beta-blocker Sample size	n = 3789 ; % = 68.9	n = 1903 ; % = 69.3
Calcium channel blocker Sample size	n = 1847 ; % = 33.6	n = 950 ; % = 34.6
Diuretic (any) Sample size	n = 2346 ; % = 42.7	n = 1196 ; % = 43.5
Diuretic (loop) Sample size	n = 826 ; % = 15	n = 426 ; % = 15.5
Mineralocorticoids receptor antagonists Sample size	n = 450 ; % = 8.2	n = 224 ; % = 8.2
Statins/lipid-lowering medication used Sample size	n = 4655 ; % = 84.7	n = 2313 ; % = 84.2
Statin Sample size	n = 4505 ; % = 81.9	n = 2242 ; % = 81.6
Ezetimibe Sample size	n = 178 ; % = 3.2	n = 115 ; % = 4.2
Glycated hemoglobin (%) Mean (SD)	8.2 (1)	8.2 (0.9)

Characteristic	Ertugliflozin (N = 5499)	Placebo (N = 2747)
Total cholesterol (mg/dL) Mean (SD)	168.9 (46.9)	168.3 (45.5)
Low-density lipoprotein cholesterol (mg/dL) Mean (SD)	89.3 (38.5)	88.8 (37.7)
High-density lipoprotein cholesterol (mg/dL) Mean (SD)	43.7 (12)	43.9 (12.3)
Triglycerides (mg/dL) Mean (SD)	181.4 (119.2)	178.9 (104.7)
Systolic blood pressure (mmHg) Mean (SD)	133.5 (13.7)	133.1 (13.9)
Diastolic blood pressure (mmHg) Mean (SD)	76.8 (8.3)	76.4 (8.7)

70. Capehorn, 2020

Bibliographic Reference	Capehorn, M S; Catarig, A-M; Furberg, J K; Janez, A; Price, H C; Tadayon, S; Verges, B; Marre, M; Efficacy and safety of once-weekly semaglutide 1.0mg vs once-daily liraglutide 1.2mg as add-on to 1-3 oral antidiabetic drugs in subjects with type 2 diabetes (SUSTAIN 10).; Diabetes & metabolism; 2020; vol. 46 (no. 2); 100-109

70.1. Study details

Secondary publication of another included study- see primary study for details	No
Other publications associated with this study included in review	None
Trial name / registration number	SUSTAIN 10/NCT03191396
Study type	Randomised controlled trial (RCT) Open-label parallel-group RCT
Study location	International (11 European countries: Bulgaria, Czech Republic, Finland, France, Hungary, Italy, Poland, Slovenia, Spain, Sweden, UK)
Study setting	Outpatient (Diabetes centres)
Study dates	06/2017 to 11/2017
Sources of funding	Funded by Novo Nordisk
Inclusion criteria	• Aged 18 years • Type 2 diabetes • HbA1c 7.0–11.0% inclusive • Stable daily doses of any of the following antidiabetic drug(s) or combination regimens 90 days prior to screening: biguanides (metformin≥1500 mg or maximum tolerated dose [MTD]), sulfonylurea or SGLT-2i (for both SU and SGLT-2i, 0.5 maximum

	approved dose according to local label or MTD as documented in subject medical record).
Exclusion criteria	• Renal impairment (eGFR) < 30 mL/min/1.73 m2 • Presence of New York Heart Association Class IV heart failure • Proliferative retinopathy or maculopathy requiring acute treatment, verified by fundus photography or dilated fundoscopy within the 90 days prior to randomization • Impaired liver function (alanine aminotransferase≥2.5 times upper limit of normal at screening) • Presence or history of malignant neoplasms within the past 5 years prior to screening
Recruitment / selection of participants	After 2-wk screening period, participants were randomised 1:1 to semaglutide or liraglutide for 30 weeks (stratified by background sulphonylurea and SGLT2-inhibitor use: SU±MET; SGLT2±MET; SU and SGLT2±MET; MET monotherapy), followed by 5-wk safety period. Participants continued on stable, pre-trial background drug treatment (unless rescue criteria met or safety concerns). Rescue medication (intensification of antidiabetic background medication and/or initiation of new antidiabetic medication) offered if subjects experienced persistent and unacceptable hyperglycaemia (fasting plasma glucose [FPG] levels≥13.3 mmol/L from week 8 to the end of week 15, or ≥11.1 mmol/L from week 16 to the end of treatment). Rescue medication prescribed at investigators' discretion according to ADA/EASD 2012 and 2015 guidelines. GLP-1RAs, DPP-4 inhibitors, and amylin analogues were not permitted.
Intervention(s)	• Semaglutide 1.0 mg weekly Subcutaneous injection of semaglutide 1.0 mg weekly for 30 weeks, administered to thigh, abdomen or upper arm, preferably on same day every week though at any time of day irrespective of meals. Dose escalation period was 8 weeks with starting dose of 0.25 mg weekly increased every week by 0.25 mg weekly for another 3 weeks then 0.5 mg weekly for 4 weeks.
Cointervention	Stable background antihyperglycaemic drug therapy
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear Exclusion criteria for NYHA class IV heart failure, unclear about others
Strata 2: People with atherosclerotic cardiovascular disease	Not stated/unclear

Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	People without chronic kidney disease exclusion criteria: renal impairment
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	Not stated/unclear
Subgroup 1: People with moderate or severe frailty	Not stated/unclear
Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear
Subgroup 3: People with non-alcoholic fatty liver disease	Not stated/unclear
Subgroup 4: People with obesity	Not stated/unclear
Subgroup 5: eGFR category at baseline	eGFR ≥30mL/min/1.73m2 Exclusion criteria: eGFR<30 mL.min/1.73 m2
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Population subgroups	
Comparator	• Liraglutide 1.2 mg daily Subcutaneous injection of liraglutide 1.2 mg daily for 30 weeks, administered to thigh, abdomen or upper arm, preferably on same day

	every week though at any time of day irrespective of meals. Liraglutide maintenance dose reached after 1 week of 0.6 mg daily. IN event of unacceptable gastrointestinal adverse events, escalation of liraglutide could be extended to 2 weeks at investigator discretion.
Number of participants	N=577
Duration of follow-up	30 weeks + 5-wk safety period
Indirectness	None
Method of analysis	Per protocol Sensitivity analysis conducted for HbA1c level using per protocol analysis (non-inferiority testing only) ITT Primary estimand was trial policy, assuming all randomised participants completed treatment and didn't use rescue medication. ITT analysis (full analysis set, all randomised participants) from 'on-treatment without rescue medication' period for all efficacy outcomes with multiple imputation for missing data (assumed to be missing at random) Modified ITT mITT analysis conducted for safety outcomes (all randomised participants who received at least one dose of trial product)

70.2. Study arms

70.2.1. Semaglutide 1.0 mg weekly (N = 290)

Subcutaneous semaglutide injection 1.00 mg weekly for 30 weeks, in addition to background diabetes drug treatment.

70.2.2. Liraglutide 1.2 mg daily (N = 287)

Subcutaneous liraglutide injection 1.00 mg weekly for 30 weeks, in addition to background diabetes drug treatment.

70.3. Characteristics

70.3.1. Arm-level characteristics

Characteristic	Semaglutide 1.0 mg weekly (N = 290)	Liraglutide 1.2 mg daily (N = 287)
% Male Sample size	n = 160 ; % = 55.2	n = 167 ; % = 58.2
Mean age (SD) (years) Mean (SD)	60.1 (10.5)	58.9 (10)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA
White Sample size	n = 264 ; % = 91	n = 268 ; % = 93.4
Comorbidities Sample size	n = NA ; % = NA	n = NA ; % = NA
Diabetic nephropathy Sample size	n = 20 ; % = 6.9	n = 25 ; % = 8.7
Diabetic neuropathy Sample size	n = 55 ; % = 19	n = 40 ; % = 13.9
Diabetic retinopathy Sample size	n = 43 ; % = 14.8	n = 39 ; % = 13.6
Macroangiopathy Sample size	n = 27 ; % = 9.3	n = 19 ; % = 6.6
Presence of frailty Nominal	NR	NR
Time since type 2 diabetes diagnosed (years) Mean (SD)	9.6 (6.1)	8.9 (5.7)
Smoking status Nominal	NR	NR
Alcohol consumption Nominal	NR	NR

Characteristic	Semaglutide 1.0 mg weekly (N = 290)	Liraglutide 1.2 mg daily (N = 287)
Presence of severe mental illness Nominal	NR	NR
People with significant cognitive impairment Nominal	NR	NR
People with a learning disability Nominal	NR	NR
Number of people with obesity Nominal	NR	NR
Other antidiabetic medication used Sample size	n = NA ; % = NA	n = NA ; % = NA
Biguanides Sample size	n = 279 ; % = 96.2	n = 268 ; % = 93.4
DPP4 inhibitors Sample size	n = 0 ; % = 0	n = 1 ; % = 0.3
Other blood glucose-lowering drugs (excluding insulin) Sample size	n = 1 ; % = 0.3	n = 0 ; % = 0
SGLT2 inhibitors Sample size	n = 73 ; % = 25.2	n = 69 ; % = 24
Sulphonylureas Sample size	n = 136 ; % = 46.9	n = 134 ; % = 46.7