National Institute for Health and Care Excellence

Draft for consultation

Type 2 diabetes in adults: management (medicines update)

[F2.7] Evidence reviews for subsequent pharmacological management of type 2 diabetes – Appendix D6

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

Disclaimer

The recommendations in this guideline represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, professionals are expected to take this guideline fully into account, alongside the individual needs, preferences and values of their patients or service users. The recommendations in this guideline are not mandatory and the guideline does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

Local commissioners and/or providers have a responsibility to enable the guideline to be applied when individual health professionals and their patients or service users wish to use it. They should do so in the context of local and national priorities for funding and developing services, and in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities. Nothing in this guideline should be interpreted in a way that would be inconsistent with compliance with those duties.

NICE guidelines cover health and care in England. Decisions on how they apply in other UK countries are made by ministers in the Welsh Government, Scottish Government, and Northern Ireland Executive. All NICE guidance is subject to regular review and may be updated or withdrawn.

Copyright

ISBN:

Appendices

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.

367. Pfeffer Marc, 2015

Bibliographic Reference	Pfeffer Marc, A; Claggett, Brian; Diaz, Rafael; Dickstein, Kenneth; Gerstein Hertzel, C; Kober Lars, V; Lawson Francesca, C; Ping, Lin; Wei, Xiaodan; Lewis Eldrin, F; Maggioni Aldo, P; McMurray John J, V; Probstfield Jeffrey, L; Riddle Matthew, C; Solomon Scott, D; Tardif, Jean-Claude; ELIXA, Investigators; Lixisenatide in Patients with Type 2 Diabetes and Acute Coronary Syndrome.; The New England journal of medicine; 2015; vol. 373 (no. 23); 2247-57

367.1. 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	ELIXA trial. Clinicaltrials.gov = NCT01147250
Study type	Randomised controlled trial (RCT)
Study location	49 countries (not specified)
Study setting	Not specified - study refers to 'multicentre'
Study dates	Enrolment occurred between July 9, 2010, and August 2, 2013; end-of-study visits initiated from November 11, 2014 with the last patient visit occurring on February 11, 2015.
Sources of funding	Funded by Sanofi
Inclusion criteria	People with type 2 diabetes and an acute coronary event within 180 days before screening.
Exclusion criteria	Age less than 30 years; percutaneous coronary intervention within the previous 15 days; coronary-artery bypass graft surgery for the qualifying event; planned coronary revascularisation procedure within 90 days after

	screening; an eGFR of less than 30mL/min/1.73m2; a Hba1c of <5.5% or >11.0%; an inability to provide written informed consent.
Recruitment / selection of participants	No additional information.
Intervention(s)	Lixisenatide N=3034 Lixisenatide 10 micrograms subcutaneously once a day for the first 2 weeks and then increased at the investigator's discretion to a maximum dose of 20 micrograms per day. Median follow up of 25 months. Concomitant therapy: Glycaemic control was managed by the investigators in accordance with local clinical practice guidance by the adjustment of concomitant glucose-lowering agents or the addition of new antidiabetic medications with the exception of other incretin therapies.
Strata 1: People with type 2 diabetes mellitus and heart failure	Mixed population 22% had heart failure
Strata 2: People with atherosclerotic cardiovascular disease	People with atherosclerotic cardiovascular diseases Majority had an NSTEMI, STEMI or unstable angina.
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	People without chronic kidney disease Mean eGFR was around 75 with no obvious reporting of CKD
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	eGFR ≥30mL/min/1.73m2
Subgroup 6: Albuminuria category at baseline	A1 (ACR <30mg/g or <3mg/mmol)
Population subgroups	No additional information.
Comparator	Placebo N=3034 Matching placebo subcutaneously once a day for the first 2 weeks and then increased at the investigator's discretion to a maximum equivalent dose. Median follow up of 25 months. Concomitant therapy: Glycaemic control was managed by the investigators in accordance with local clinical practice guidance by the adjustment of concomitant glucose-lowering agents or the addition of new antidiabetic medications with the exception of other incretin therapies.
Number of participants	6068
Duration of follow-up	Median 25 months.
Indirectness	No additional information.
Method of analysis	ITT

Additional comments	The primary analysis was conducted in the intention-to-treat population with the use of the Cox proportional-hazards model, with study group and geographic region as the covariates, to estimate the hazard ratio for the comparison of lixisenatide with placebo

367.2. Study arms

367.2.1. Lixisenatide (N = 3034)

Lixisenatide 10 micrograms subcutaneously once a day for the first 2 weeks and then increased at the investigator's discretion to a maximum dose of 20 micrograms per day. Median follow up of 25 months. Concomitant therapy: Glycaemic control was managed by the investigators in accordance with local clinical practice guidance by the adjustment of concomitant glucose-lowering agents or the addition of new antidiabetic medications with the exception of other incretin therapies.

367.2.2. Placebo (N = 3034)

Matching placebo subcutaneously once a day for the first 2 weeks and then increased at the investigator's discretion to a maximum equivalent dose. Median follow up of 25 months. Concomitant therapy: Glycaemic control was managed by the investigators in accordance with local clinical practice guidance by the adjustment of concomitant glucose-lowering agents or the addition of new antidiabetic medications with the exception of other incretin therapies.

367.3. Characteristics

367.3.1. Arm-level characteristics

Characteristic	Lixisenatide (N = 3034)	Placebo (N = 3034)
% Male Sample size	n = 2111 ; % = 70	n = 2096 ; % = 69
Mean age (SD) (years) Mean (SD)	59.9 (9.7)	60.6 (9.6)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA
Asian Sample size	n = 404 ; % = 13.3	n = 367 ; % = 12.1

Characteristic	Lixisenatide (N = 3034)	Placebo (N = 3034)
Black Sample size	n = 118 ; % = 3.9	n = 103 ; % = 3.4
Other Sample size	n = 254 ; % = 8.4	n = 246 ; % = 8.1
White Sample size	n = 2258 ; % = 74.4	n = 2318 ; % = 76.4
Hispanic ethnic group Sample size	n = 865 ; % = 28.5	n = 903 ; % = 29.8
Comorbidities Sample size	n = NA ; % = NA	n = NA ; % = NA
Hypertension Sample size	n = 2295 ; % = 75.6	n = 2340 ; % = 77.1
Percutaneous coronary intervention Sample size	n = 2052 ; % = 66.8	n = 2027 ; % = 66.8
Coronary artery bypass grafting Sample size	n = 258 ; % = 8.5	n = 249 ; % = 8.2
Heart failure Sample size	n = 682 ; % = 22.5	n = 676 ; % = 22.3
Stroke Sample size	n = 143 ; % = 4.7	n = 188 ; % = 6.2
Peripheral arterial disease Sample size	n = 237 ; % = 7.8	n = 229 ; % = 7.5
Atrial fibrillation Sample size	n = 176 ; % = 5.8	n = 190 ; % = 6.3
NSTEMI Sample size	n = 1165 ; % = 38.4	n = 1183 ; % = 39
STEMI Sample size	n = 1349 ; % = 44.5	n = 1317 ; % = 43.4

Characteristic	Lixisenatide (N = 3034)	Placebo (N = 3034)
Unstable angina Sample size	n = 514 ; % = 16.9	n = 528 ; % = 17.4
Unclassified qualifying acute coronary syndrome event Sample size	n = 6 ; % = 0.2	n = 6 ; % = 0.2
Presence of frailty Sample size	n = NR ; % = NR	n = NR ; % = NR
Time since type 2 diabetes diagnosed (years) Mean (SD)	9.2 (8.2)	9.4 (8.3)
HbA1c (%) Mean (SD)	7.6 (1.3)	7.7 (1.3)
Cardiovascular risk factors No of events	n = NA ; % = NA	n = NA ; % = NA
Blood pressure (mmHg) Mean (SD)	NA (NA)	NA (NA)
Systolic blood pressure Mean (SD)	130 (17)	129 (17)
Heart rate (/min) Mean (SD)	70.2 (9.9)	70.2 (10.1)
Smoking status Currently smoking Sample size	n = 354 ; % = 11.7	n = 355 ; % = 11.7
Alcohol consumption Sample size	n = NR ; % = NR	n = NR ; % = NR
Presence of severe mental illness Sample size	n = NA ; % = NA	n = NA ; % = NA
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

Characteristic	Lixisenatide (N = 3034)	Placebo (N = 3034)
Weight (kg) Mean (SD)	85.1 (19.6)	84.6 (19.2)
BMI (kg/m2) Mean (SD)	30.2 (5.8)	30.1 (5.6)
Number of people with obesity Sample size	n = NA ; % = NA	n = NA ; % = NA
Cholesterol and lipid levels (mg/dL) Mean (SD)	NA (NA)	NA (NA)
HDL cholesterol Mean (SD)	41.9 (10.9)	43 (10.8)
LDL cholesterol Mean (SD)	78.2 (35.2)	78.8 (35.4)
Albumin creatinine ratio (mg/grams) Median (IQR)	10.5 (6 to 33.6)	10.2 (6 to 29.6)
eGFR mL/min/1.73m2 Mean (SD)	75.2 (21.4)	76.7 (21.3)
Other antidiabetic medication used Sample size	n = NA ; % = NA	n = NA ; % = NA
Insulin Sample size	n = 1190 ; % = 39.2	n = 1184 ; % = 39
Metformin Sample size	n = 2038 ; % = 67.2	n = 1983 ; % = 65.4
Sulfonylureas Sample size	n = 988 ; % = 32.6	n = 1016 ; % = 33.5
Thiazolidinediones Sample size	n = 43 ; % = 1.4	n = 52 ; % = 1.7
Other diabetes medications Sample size	n = 177 ; % = 5.8	n = 144 ; % = 4.7

Characteristic	Lixisenatide (N = 3034)	Placebo (N = 3034)
ACEI or ARB Sample size	n = 2577 ; % = 84.9	n = 2579 ; % = 85
Statin Sample size	n = 2831 ; % = 93.3	n = 2796 ; % = 92.2
Anti-platelet Sample size	n = 2962 ; % = 97.6	n = 2955 ; % = 97.4
Beta-blocker Sample size	n = 2537 ; % = 83.6	n = 2587 ; % = 85.3
Blood pressure-lowering medication used See Other antidiabetic medication used Sample size	n = NA ; % = NA	n = NA ; % = NA
Statins/lipid-lowering medication used See Other antidiabetic medication used Sample size	n = NA ; % = NA	n = NA ; % = NA
Other treatment being received See Other antidiabetic medication used Sample size	n = NA ; % = NA	n = NA ; % = NA

1

2

368. Pfützner, 2005

Bibliographic Reference	Pfützner, A.; Marx, N.; Lübben, G.; Langenfeld, M.; Walcher, D.; Konrad, T.; Forst, T.; Improvement of cardiovascular risk markers by pioglitazone is independent from glycemic control: results from the pioneer study; J Am Coll Cardiol; 2005; vol. 45 (no. 12); 1925-31

368.1. Study details

Secondary publication of another included study- see primary study for details	
Trial name / registration number	PIONEER
Study type	Randomised controlled trial (RCT)
Study location	Clinical Department of the Institute for Clinical Research and Development, Mainz, Germany
Study setting	No information
Study dates	NR
Sources of funding	Takeda Pharma, Germany. A number of authors declare funding and honoraria from Takeda Pharma.
Inclusion criteria	Patients with T2DM aged 40 to 75 years, HbA1c: 6.6% to 9.9%, absence of significant hepatic or renal disease, absence of congestive heart failure (New York Heart Association functional class II to IV), no cigarette smoking, and no known carotid artery disease.
Exclusion criteria	NR
Recruitment / selection of participants	No additional information
Intervention(s)	Pioglitazone (n=89) Patients received a fixed dose of pioglitazone (45 mg/day) in the morning for 26 ± 2 weeks
Cointervention	Patients were permitted to take other additional oral antidiabetic except for metformin

Strata 1: People with type 2 diabetes mellitus and heart failure	People without heart failure "Absence of congestive heart failure (New York Heart Association functional class II to IV)" in the inclusion criteria.
Strata 2: People with atherosclerotic cardiovascular disease	Not stated/unclear People with known carotid artery disease were excluded. No information about other types of CVD. No information in baseline characteristics.
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear CKD not an inclusion/exclusion criteria. "Absence of significant renal disease" in the inclusion 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	Glimpiride (n=84) Patients received 1-6 mg per day Glimepiride titrated for optimal glycaemic control for 26 ± 2 weeks Additional oral antidiabetic medication were permitted except for thiazolidinediones
Number of participants	179
Duration of follow-up	26 weeks
Indirectness	No additional information
Method of analysis	ITT
Additional comments	The analysis of efficacy is based on the intention-to-treat population, which consists of all patients who were treated and provided assessment of the laboratory parameters at baseline and at end point of the study. All analyses were performed in an exploratory sense with appropriate parametrical and nonparametrical methods. Changes from baseline were evaluated by using analysis of covariance (ANCOVA) models with treatment groups as factor and baseline values as covariate.

368.2. Study arms

368.2.1. Pioglitazone (N = 89)

Patients received a fixed dose of 45 mg/ day pioglitazone in the morning for 26 +/- 2 weeks

368.2.2. Glimepiride (N = 84)

Patients received 1 - 6 mg/day glimepiride for 26 +/- 2 weeks

368.3. Characteristics

368.3.1. Arm-level characteristics

Characteristic	Pioglitazone (N = 89)	Glimepiride (N = 84)
% Male Sample size	n = 55 ; % = 61.8	n = 52 ; % = 61.9
Mean age (SD) (Years (mean, SD)) Mean (SD)	62.2 (8.4)	63 (7.4)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA
Caucasian Sample size	n = 88 ; % = 98.9	n = 81 ; % = 96.4
Other Sample size	n = 1 ; % = 1.1	n = 3 ; % = 3.6
Time since type 2 diabetes diagnosed (Years (mean, SD)) Mean (SD)	7.4 (7.9)	6.9 (6.5)
Smoking status Sample size	n = 0 ; % = 0	n = 0 ; % = 0
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
Blood pressure-lowering medication used Sample size	n = NA ; % = NA	n = NA ; % = NA
ACE inhibitor/ AT-1 antagonist	n = 52 ; % = 58	n = 41 ; % = 49

Characteristic	Pioglitazone (N = 89)	Glimepiride (N = 84)
Sample size		
Statins/lipid-lowering medication used Sample size	n = NA ; % = NA	n = NA ; % = NA
Statin treatment Sample size	n = 18 ; % = 20	n = 13 ; % = 15
Other treatment being received Sample size	n = NA ; % = NA	n = NA ; % = NA
Anit-platelet therapy Sample size	n = 25 ; % = 28	n = 26 ; % = 31

1

2

369. Pfützner, 2011

Bibliographic Reference	Pfützner, A.; Schöndorf, T.; Tschöpe, D.; Lobmann, R.; Merke, J.; Müller, J.; Lehmann, U.; Fuchs, W.; Forst, T.; PIOfix-study: effects of pioglitazone/metformin fixed combination in comparison with a combination of metformin with glimepiride on diabetic dyslipidemia; Diabetes Technol Ther; 2011; vol. 13 (no. 6); 637-43

369.1. Study details

Other publications associated with this study included in review	Forst T, Weber MM, Löbig M, Lehmann U, Müller J, Hohberg C, Friedrich C, Fuchs W, Pfützner A. Pioglitazone in addition to metformin improves erythrocyte deformability in patients with Type 2 diabetes mellitus. Clin Sci (Lond). 2010 Jul 9;119(8):345-51. doi: 10.1042/CS20100161. PMID: 20509857.
Trial name / registration number	PIOfix: NCT00770653
Study type	Randomised controlled trial (RCT)
Study location	Germany
Study setting	No additional information
Study dates	NR
Sources of funding	A number of authors are employees of Takeda Pharma and Acromion GmbH. Multiple authors declare funding from Takeda Pharma
Inclusion criteria	The trial population consisted of male and female individuals with type 2 diabetes, 18–75 years old, pretreated with metformin as monotherapy in an individually maximal tolerated dosage with baseline values for HbA1c of ≥6.5% and dyslipidemia defined as HDL cholesterol ≥1.03 mmol/L (40 mg/dL) and/or triglycerides ≥1.7 mmol/ L (150 mg/dL).
Exclusion criteria	After the usual clinical trial exclusion criteria (pregnancy, fatal disease, etc.), the most important exclusion reasons were type 1 diabetes mellitus, hypersensitivity to the study drugs or to drugs with similar chemical structures, history of severe or multiple allergies, a history of significant cardiovascular (greater than NY Heart Association stages II–IV), respiratory, gastrointestinal, hepatic (alanine aminotransferase >2.5 times the normal reference range), renal (creatinine >1.2/1.5 mg/dL for women/men), neurological, psychiatric, and/or hematological disease, and pretreatment with anti-diabetes therapy other than metformin within the last 3 months.

Recruitment / selection of participants	No additional information
Intervention(s)	Pioglitazone (n=146) Patients received a fixed dose combination of 15 mg of pioglitazone given twice daily for 6 months
Cointervention	Metformin: Patients receive 850 mg of metformin twice daily for 6 months
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear Excluded "a history of significant cardiovascular (greater than NY Heart Association stages II-IV)", otherwise unclear.
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	Not stated/unclear

non-alcoholic 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 + Metformin (n=142) Patients received a fixed dose combination of 2 mg of glimepiride in the morning with twice-daily 850 mg of metformin for 6 months
Number of participants	305
Duration of follow-up	5.5 months
Indirectness	No additional information
Method of analysis	ITT
Additional comments	All randomized patients who received at least one dose of study medication were included in the ‘‘all patients treated’’ analysis set. Thus, patients with HDL cholesterol values measured at baseline and at least once post-baseline were included into the full analysis set. All analyses of safety data were performed for the ‘‘all patients treated’’ analysis set; all analyses of efficacy were performed for the full analysis set. Missing data were accounted for by means of the last observation-carried-forward approach

369.2. Study arms

369.2.1. Pioglitazone + metformin (N = 146)

Patients received a fixed dose combination of 15 mg of pioglitazone with 850 mg of metformin given twice daily for 6 months

369.2.2. Glimepiride + metformin (N = 142)

Patients received a fixed dose combination of 2 mg of glimepiride in the morning with twice-daily 850 mg of metformin

369.3. Characteristics

369.3.1. Arm-level characteristics

Characteristic	Pioglitazone + metformin (N = 146)	Glimepiride + metformin (N = 142)
% Male Sample size	n = 96 ; % = 65.8	n = 91 ; % = 64.1
Mean age (SD) Mean (SD)	59 (10)	59 (10)
Ethnicity Sample size	n = NR ; % = NR	n = NR ; % = NR
Time since type 2 diabetes diagnosed (Years (mean, SD)) Mean (SD)	6.2 (5.4)	5.9 (4.8)
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
Blood pressure-lowering medication used Sample size	n = NA ; % = NA	n = NA ; % = NA

Characteristic	Pioglitazone + metformin (N = 146)	Glimepiride + metformin (N = 142)
RAS inhibition Sample size	n = 80 ; % = 54.8	n = 80 ; % = 56.3
Beta-blocker Sample size	n = 54 ; % = 37	n = 58 ; % = 40.8
Calcium channel blocker Sample size	n = 54 ; % = 37	n = 26 ; % = 18.3
Diuretics Sample size	n = 20 ; % = 13.7	n = 23 ; % = 16.2
Statins/lipid-lowering medication used Sample size	n = NA ; % = NA	n = NA ; % = NA
Statins Sample size	n = 45 ; % = 30.8	n = 46 ; % = 32.4
Ezitimibe Sample size	n = 1 ; % = 0.7	n = 2 ; % = 1.4
Fibrates Sample size	n = 1 ; % = 0.7	n = 1 ; % = 0.7
Other treatment being received Sample size	n = NR ; % = NR	n = NR ; % = NR

1

2

370. Philis-Tsimikas, 2019

Bibliographic Reference	Philis-Tsimikas, A.; Billings, L. K.; Busch, R.; Portillo, C. M.; Sahay, R.; Halladin, N.; Eggert, S.; Begtrup, K.; Harris, S.; Superior efficacy of insulin degludec/liraglutide versus insulin glargine U100 as add-on to sodium-glucose co-transporter-2 inhibitor therapy: a randomized clinical trial in people with uncontrolled type 2 diabetes; Diab Obes Metab; 2019; vol. 21 (no. 6); 1399-1408

370.1. 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	DUAL IX/NCT02773368
Study type	Randomised controlled trial (RCT) Open-label, parallel-group, treat-to-target RCT
Study location	International (74 sites in 11 countries: Argentina, Canada, Finland, Hungary, India, Russian Federation, Slovakia, Slovenia, Spain, Switzerland, USA)
Study setting	Outpatient
Study dates	05/2016 to 10/2017
Sources of funding	Sponsored by Novo Nordisk, A/D, Denmark.
Inclusion criteria	• Aged≥18 years • Type 2 diabetes diagnosis • HbA1c 7-11% inclusive • BMI ≥20 kg/m2 and <40 kg/m2 • Insulin-naive (short-term insulin treatment and prior insulin treatment for gestational diabetes were permitted) • Oral anti-diabetic treatment for at least 90 days prior to screening

	○ Stable dose of SGLT2 inhibitor ○ Stable dose of SGLT2 inhibitor in combination with metformin with or without DPP-4 inhibitor ○ Metformin (≥1500 mg or max tolerated) ○ DPP-4 inhibitor (≥half max approved dose) ○ Fixed dose combinations of: SGLT inhibitor + (metformin or DPP-4 inhibitor) ○ Stable dose of pioglitazone (≥half max approved dose) allowed if treated with SGLT2 inhibitor (except dapagliflozin)
Exclusion criteria	• Known or suspected hypersensitivity to trial product(s) or related products • Previous participation in this trial. • Female who is pregnant, breast-feeding, or intends to become pregnant, or of child-bearing potential and not using adequate contraception • Use of any oral anti-diabetic drug not listed in inclusion criteria • Use of GLP-1 RA within 90 days prior to screening • Acute decompensation of glycaemic control (e.g. diabetic ketoacidosis) • Family or personal history of multiple endocrine neoplasia type 2 or medullary thyroids carcinoma • Screening calcitonin ≥50 ng/L • History of pancreatitis (acute or chronic) • Any of the following: myocardial infarction, stroke or hospitalisation for unstable angina and/or transient ischaemic attack within the past 180 days prior to the day of screening • NYHA Class III or IV heart failure • Planned coronary, carotid or peripheral artery revascularization at the day of screening • Renal impairment eGFR <60 mL/min/1.73 m2 (CKD-EPI equation) • Impaired liver function, defined as ALT ≥2.5 times upper normal limit at screening • Inadequately treated blood pressure (Class 2 hypertension or higher (systolic ≥160 mmHg or diastolic ≥100 mmHg) at screening) • Anticipated initiation or change in concomitant medications for more than 14 consecutive days or on a frequent basis known to affect weight or glucose metabolism (e.g., orlistat, thyroid hormones, corticosteroids) • Proliferative retinopathy or maculopathy requiring acute treatment • History or presence of malignant neoplasms within the last 5 years (except basal and squamous cell skin cancer and in-situ carcinomas) • History of diabetic ketoacidosis • Any disorder, except for conditions associated with diabetes, which in the investigator's opinion might jeopardize subject's safety or compliance with the protocol.
Recruitment / selection of participants	After 2-week screening period, eligible participants randomised using interactive web-response system 1:1 to IDegLira or insulin glargine. Existing DPP-4 inhibitor treatment was discontinued at randomisation. After 26 week treatment, there were two safety FU assessment periods at 7 (+3) and 30 (+3) days after last dose of treatment drug.

Intervention(s)	• IDegLira daily titrated Subcutaneous injection of IDegLira once daily for 26 weeks, administered using 3mL FlexTouch pen (fixed ratio insulin degludec/liraglutide 100 U/3.6 mg per mL solution) as add-on to existing therapy. Initiated at dose of 10 U and titrated twice-weekly to FPG target of 4-5 mmol/L according to titration algorithm. Max dose of IDegLira was 50 U.
Cointervention	• Background anti-diabetic drug therapy All participants continued their existing diabetes treatment for duration of trial with exception of DPP-4 inhibitors.
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear People "presently classified as being in NYHA Class III or IV" were excluded (see supplementary information). No information in baseline characteristics, so unclear about people with Class II.
Strata 2: People with atherosclerotic cardiovascular disease	Not stated/unclear Exclusion criteria state: "Any of the following: myocardial infarction, stroke or hospitalisation for unstable angina and/or transient ischaemic attack within the past 180 days prior to the day of screening" (see supplementary information). No information in baseline characteristics.
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear CKD not an inclusion/exclusion criteria. Exclusion criteria state: "Renal impairment eGFR <60 mL/min/1.73 m2 as per CKD-EPI" (see supplementary information). 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	eGFR ≥30mL/min/1.73m2 Exclusion criteria: eGFR<60 mL/min/1.73 m2
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Population subgroups	
Comparator	• Insulin glargine U100 daily titrated Subcutaneous insulin glargine U100 once daily titrated for 26 weeks, using 3mL pre-filled Solostar pen, as add-on to existing therapy. Initiated at dose of 10 U and titrated twice-weekly to FPG target of 4-5 mmol/L according to titration algorithm with no max dose.
Number of participants	N=420 randomised (N=419 in safety analysis set)
Duration of follow-up	26 weeks + 7 and 30 days safety FU
Indirectness	None
Method of analysis	ITT Treatment policy estimand, assuming all randomised participants regardless of whether they remained on assigned treatment with multiple imputation for missing data) conducted for all efficacy outcomes with multiple imputation for missing data Modified ITT mITT analysis (all randomised participants who received at least one study drug dose) conducted for safety outcomes

1

370.2. Study arms

370.2.1. IDegLira daily titrated (N = 210)

Subcutaneous injection of IDegLira once daily (via 3 mL FlexTouch pen) titrated twice-weekly, for 26 weeks, in addition to stable dose of SGLT2 inhibitor and another oral antidiabetic drug.

370.2.2. Insulin glargine U100 daily titrated (N = 210)

Subcutaneous injection of insulin glargine U100 once daily (via 3 mL Solostar pen) titrated twice-weekly, for 26 weeks, in addition to stable dose of SGLT2 inhibitor and another oral antidiabetic drug.

370.3. Characteristics

370.3.1. Arm-level characteristics

Characteristic	IDegLira daily titrated (N = 210)	Insulin glargine U100 daily titrated (N = 210)
% Male Sample size	n = 121 ; % = 57.6	n = 126 ; % = 60
Mean age (SD) (years) Mean (SD)	56.1 (10.4)	57.2 (10.2)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA
Asian Sample size	n = 31 ; % = 14.8	n = 35 ; % = 16.7
Black Sample size	n = 3 ; % = 1.4	n = 2 ; % = 1
Other Sample size	n = 1 ; % = 0.5	n = 2 ; % = 1
White Sample size	n = 187 ; % = 83.3	n = 181 ; % = 81.4
Comorbidities Nominal	NR	NR

Characteristic	IDegLira daily titrated (N = 210)	Insulin glargine U100 daily titrated (N = 210)
Presence of frailty Nominal	NR	NR
Time since type 2 diabetes diagnosed (years) Mean (SD)	9.8 (6.2)	9.3 (6.3)
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 Use of OAD at screening Sample size	n = NA ; % = NA	n = NA ; % = NA
SGLT2 inhibitor +/- Pioglitazone Sample size	n = 4 ; % = 1.9	n = 7 ; % = 3.3
SGLT2 inhibitor + Metformin +/- Pioglitazone Sample size	n = 141 ; % = 67.1	n = 132 ; % = 62.9
SGLT2 inhibitor + DPP-4 inhibiotr +/- Pioglitazone Sample size	n = 1 ; % = 0.5	n = 7 ; % = 3.3

Characteristic	IDegLira daily titrated (N = 210)	Insulin glargine U100 daily titrated (N = 210)
SGLT2 inhibitor + Metformin + DPP inhibitor +/- Pioglitazone Sample size	n = 64 ; % = 30.5	n = 64 ; % = 30.5
Blood pressure-lowering medication used Nominal	NR	NR
Statins/lipid-lowering medication used Nominal	NR	NR
Other treatment being received Nominal	NR	NR

1

2

371. Philis-Tsimikas, 2013

Bibliographic Reference	Philis-Tsimikas, A.; Del Prato, S.; Satman, I.; Bhargava, A.; Dharmalingam, M.; Skjoth, T. V.; Rasmussen, S.; Garber, A. J.; Effect of insulin degludec versus sitagliptin in patients with type 2 diabetes uncontrolled on oral antidiabetic agents; Diabetes Obes Metab; 2013; vol. 15 (no. 8); 760-766

371.1. 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	BEGIN/NCT01046110
Study type	Randomised controlled trial (RCT) Open-label, parallel-group, RCT
Study location	International (78 sites in 7 countries: Argentina, Canada, India, Mexico, South Africa, Turkey, USA)
Study setting	Outpatient
Study dates	01/2010 to 11/2010
Sources of funding	Funded by Novo Nordisk, A/S, Denmark.
Inclusion criteria	• Type 2 diabetes diagnosis≥6 months • BMI≤40 kg/m2 • HbA1c 7.5-11% inclusive (7.5-10% in Argentina) • Treated with stable dose ≥3 months of one or two oral anti-diabetic drugs (including any combination of metformin, sulphonylureas, glinides or pioglitazone) • Insulin-naive

Exclusion criteria	• Using GLP-1 RA, another DPP-4 inhibitor or rosiglitazone within 3-mo of screening
Recruitment / selection of participants	Eligible participants randomised using central interactive voice/web-response system 1:1 to insulin degludec or sitagliptin as add-on to background oral anti-diabetic treatment (OAD). Participants stratified by pioglitazone use at screening to ensure balanced use in treatment arms.
Intervention(s)	• Sitagliptin 100 mg daily Oral sitagliptin 100 mg tablet once daily for 26 weeks, in addition to background OAD.
Cointervention	• Background oral antidiabetic drug therapy All participants continued their existing oral anti-diabetic drug treatment for duration of trial.
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
Comparator	• Insulin degludec 100 U/ml Subcutaneous injection of insulin degludec 100 U/ml once daily at any time of day for 26 weeks, in addition to background OAD. Insulin titrated using treat-to-target approach to achieve pre-breakfast self-measured plasma glucose <5.0 mmol/L. New dose recommended by titration algorithm actioned at discretion of investigator.
Number of participants	N=458 randomised
Duration of follow-up	26 weeks
Indirectness	None
Method of analysis	ITT ITT LOCF analysis (all randomised participants allocated to treatment) for all efficacy outcomes; full analysis set). Note that one participating site was closed down and participants from this site (n=11) were excluded from full analysis set. Modified ITT mITT analysis (all randomised participants who received at least one study drug dose) for all safety outcomes.

1

371.2. Study arms

371.2.1. Sitagliptin 100 mg daily (N = 229)

Oral sitagliptin 100 mg daily for 26 weeks, in addition to 1 or 2 background oral anti-diabetic drugs.

371.2.2. Insulin degludec 100 U/mL daily (N = 229)

Subcutaneous injection of insulin degludec 100 U/mL (using 3 ml Flexpen) for 26 weeks, in addition to 1 or 2 background oral anti-diabetic drugs.

371.3. Characteristics

371.3.1. Arm-level characteristics

Characteristic	Sitagliptin 100 mg daily (N = 229)	Insulin degludec 100 U/mL daily (N = 229)
% Male Sample size	n = 121 ; % = 54.5	n = 141 ; % = 62.7
Mean age (SD) (years) Mean (SD)	54.9 (11.4)	56.4 (10.2)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA
Asian Sample size	n = 57 ; % = 25.3	n = 55 ; % = 24.8
Black Sample size	n = 17 ; % = 7.6	n = 17 ; % = 7.7
Hispanic or Latin American Sample size	n = 45 ; % = 20	n = 49 ; % = 22.1
Other Sample size	n = 16 ; % = 7.1	n = 11 ; % = 5
White Sample size	n = 135 ; % = 60	n = 139 ; % = 62.6
Comorbidities Nominal	NR	NR

Characteristic	Sitagliptin 100 mg daily (N = 229)	Insulin degludec 100 U/mL daily (N = 229)
Presence of frailty Nominal	NR	NR
Time since type 2 diabetes diagnosed (years) Mean (SD)	7.7 (5.9)	7.8 (6.2)
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
Metformin only Sample size	n = 55 ; % = 24.4	n = 57 ; % = 25.7
Pioglitazone +/- (sulphonylurea or glinide) or metformin Sample size	n = 9 ; % = 4	n = 15 ; % = 6.8
Sulphonylurea or glinide +/- metformin Sample size	n = 161 ; % = 71.6	n = 150 ; % = 67.6
Blood pressure-lowering medication used Nominal	NR	NR

Characteristic	Sitagliptin 100 mg daily (N = 229)	Insulin degludec 100 U/mL daily (N = 229)
Statins/lipid-lowering medication used Nominal	NR	NR
Other treatment being received Nominal	NR	NR

Data for baseline characteristics is for N=222 for sitagliptin arm and N=225 for insulin degludec arm.

372. Phrommintikul, 2019

Bibliographic Reference	Phrommintikul, A.; Wongcharoen, W.; Kumfu, S.; Jaiwongkam, T.; Gunaparn, S.; Chattipakorn, S.; Chattipakorn, N.; Effects of dapagliflozin vs vildagliptin on cardiometabolic parameters in diabetic patients with coronary artery disease: a randomised study; Br J Clin Pharmacol; 2019; vol. 85 (no. 6); 1337-1347

372.1. 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	NCT03178591
Study type	Randomised controlled trial (RCT)
Study location	Thailand
Study setting	Clinic
Study dates	No additional information.
Sources of funding	Thailand research fund
Inclusion criteria	Adult patients (age ≥ 18 years old), male or non-child bearing potential female with type 2 diabetes who had HbA1c level within 6.5% - 9% and established coronary artery disease.
Exclusion criteria	Significant renal function (estimated glomerular filtration rate <30 mL/min); significant hepatic impairment or ALT/AST elevations beyond 2 times of upper normal limit or known hepatic failure; planned coronary intervention or planed surgical intervention (percutaneous coronary intervention or coronary artery bypass grafting); recent (<30 d) ACS; hypersensitivity to either of the study drug components; history of lactic acidosis or diabetic ketoacidosis; current treatment with insulin or GLP-1 agonist, DPP-4

	inhibitors or SGLT2 inhibitors; inability to comply with study protocol; active malignancy other than basal cell carcinoma; clinically advanced congestive HF (New York Heart Association class III-IV); recent HF decompensation (<3 months); chronic inflammation (i.e. inflammatory bowel disease, lupus, inflammatory arthritis, rheumatoid arthritis) or chronic infection (i.e. chronic diabetic foot infection); and pregnancy, lactation or child-bearing potential.
Recruitment / selection of participants	Eligible patients were randomised 1:1 to receive either 10 mg dapagliflozin or 50 - 100 mg vildagliptin (according to glomerular filtration rate)
Intervention(s)	Dapagliflozin 10 mg daily, administered orally
Cointervention	Background therapy of coronary artery disease and diabetes remained unchanged during follow-up period unless there were adverse effects related to medications.
Strata 1: People with type 2 diabetes mellitus and heart failure	Mixed population
Strata 2: People with atherosclerotic cardiovascular disease	People with atherosclerotic cardiovascular diseases The study recruited people with type 2 diabetes and established coronary artery disease (CAD). CAD was defined as "stable angina with >70% stenosis of at least 1 major epicardial artery from coronary angiogram or coronary computed tomography angiography, or post myocardial infarction (>30 days) with at least one non–infarct-related artery stenosis (>70% stenosis) from coronary angiogram."
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	People without chronic kidney disease CKD not an inclusion/exclusion criteria. The study excluded "people with significant renal function (estimated glomerular filtration rate<30mL/min)" Baseline characteristics reports 12.2% had chronic kidney disease.
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	eGFR ≥30mL/min/1.73m2
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Population subgroups	No information available.
Comparator	Vildagliptin 50 - 100 mg daily, orally administered
Number of participants	N= 49
Duration of follow-up	6-month follow-up
Indirectness	
Method of analysis	Modified ITT
Additional comments	

1

372.2. Study arms

372.2.1. Dapagliflozin 10 mg (N = 25)

Administered orally, once daily

372.2.2. Vildagliptin 50 - 100 mg (N = 24)

Administered orally, once daily

372.3. Characteristics

372.3.1. Arm-level characteristics

Characteristic	Dapagliflozin 10 mg (N = 25)	Vildagliptin 50 - 100 mg (N = 24)
% Male No of events	n = 14 ; % = 56	n = 12 ; % = 50
Ethnicity Nominal	NR	NR
Hypertension No of events	n = 18 ; % = 72	n = 20 ; % = 83.3
Dyslipidaemia No of events	n = 21 ; % = 84	n = 23 ; % = 95.8
Chronic renal disease No of events	n = 2 ; % = 8	n = 4 ; % = 16.7
Heart failure No of events	n = 5 ; % = 20	n = 7 ; % = 29.2
Prior myocardial infarction No of events	n = 15 ; % = 60	n = 18 ; % = 75
Coronary revascularisation No of events	n = 17 ; % = 68	n = 18 ; % = 75
Presence of frailty Nominal	NR	NR
Alcohol consumption	NR	NR

Characteristic	Dapagliflozin 10 mg (N = 25)	Vildagliptin 50 - 100 mg (N = 24)
Nominal		
Presence of severe mental illness Nominal	NR	NR
People with significant cognitive impairment Nominal	NR	NR
Number of people with obesity Nominal	NR	NR
Sulfonylurea No of events	n = 20 ; % = 80	n = 17 ; % = 70.8
Metformin No of events	n = 23 ; % = 92	n = 21 ; % = 87.5
Thiazolidinedione No of events	n = 2 ; % = 8	n = 3 ; % = 12.5
Beta-blocker No of events	n = 23 ; % = 92	n = 22 ; % = 91.7
ACE inhibitor No of events	n = 12 ; % = 48	n = 14 ; % = 58.3
ARB No of events	n = 7 ; % = 28	n = 7 ; % = 29.2
CCB No of events	n = 6 ; % = 24	n = 5 ; % = 20.8
Diuretic No of events	n = 12 ; % = 48	n = 12 ; % = 50
Statin No of events	n = 24 ; % = 96	n = 24 ; % = 100
Clopidogrel No of events	n = 11 ; % = 44	n = 10 ; % = 41.7
Nitrate No of events	n = 5 ; % = 20	n = 6 ; % = 25

Characteristic	Dapagliflozin 10 mg (N = 25)	Vildagliptin 50 - 100 mg (N = 24)
Aspirin No of events	n = 23 ; % = 92	n = 23 ; % = 95.8

1

2

373. Pieber, 2019

Bibliographic Reference	Pieber, T. R.; Bode, B.; Mertens, A.; Cho, Y. M.; Christiansen, E.; Hertz, C. L.; Wallenstein, S. O. R.; Buse, J. B.; Akin, S.; Aladag, N.; et, al; 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; Lancet Diabetes Endocrinol; 2019; vol. 7 (no. 7); 528-539

373.1. Study details

Secondary publication of another included study- see primary study for details	No
Other publications associated with this study included in review	For 52-week extension (re-randomised) study comparing switching to semaglutide from sitagliptin or staying on sitagliptin, see: • Buse, J. B., Bode, B. W., Mertens, A., Cho, Y. M., Christiansen, E., Hertz, C. L., ... & Pieber, T. R. (2020). 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 and Care*, *8*(2), e001649.
Trial name / registration number	PIONEER 7/NCT02849080
Study type	Randomised controlled trial (RCT) Open-label, parallel-group, RCT
Study location	International (81 sites in 10 countries: Argentina, Austria, Belgium, Brazil, Egypt, Norway, South Korea, Switzerland, Turkey, USA)
Study setting	Outpatient
Study dates	09/2016 to 02/2017
Sources of funding	Funded by Novo Nordisk A/S, Denmark.
Inclusion criteria	• Aged≥18 years (≥19 years in South Korea) • Type 2 diabetes diagnosis • HbA1c level 7.5-9.5% inclusive

	• Receiving stable dose (for≥90 days before screening) of one or two of: metformin, sulphonylureas, SGLT2 inhibitor, thiazolidinediones.
Exclusion criteria	• eGFR<60 mL/min/1.73m2 • 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	After 2-wk screening period, eligible participants randomised 1:1, using interactive web-response system, stratified by glucose-lowering drug use at screening. Study visits were at weeks 4, 8, 16, 24, 32, 40, 48 and 52 weeks. After 52-wk treatment, participants underwent 5-week FU period and completed trial or re-consented and were re-randomised to a 52-week extension switching study (see Buse 2020).
Intervention(s)	• Semaglutide 3-14 mg daily Oral semaglutide 3-14 mg daily (flexible dose) in morning fasting state, for 52 weeks, in addition to background glucose-lowering drugs (one or two of: metformin, sulphonylureas, SGLT2 inhibitors, or 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.
Cointervention	• Background oral glucose-lowering drugs All participants continued background oral glucose-lowering drugs (one or two of: metformin, sulphonylureas, SGLT2 inhibitors, or thiazolidinediones).
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear Excluded "New York Heart Association class IV heart failure", otherwise unclear. 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	Excluded "renal impairment (estimated glomerular filtration rate [eGFR] of <60 mL/min per 1·73 m²)", but 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	eGFR ≥30mL/min/1.73m2 Exclusion criteria: eGFR<60 mL/min/1.73m2
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Comparator	• Sitagliptin 100 mg daily Oral sitagliptin 100 mg daily for 52 weeks, in addition to background glucose-lowering drugs (one or two of: metformin, sulphonylureas, SGLT2 inhibitors, or thiazolidinediones).
Number of participants	N=504 (N=503 in full analysis set due to one participant not receiving treatment)
Duration of follow-up	52 weeks

Indirectness	None
Method of analysis	ITT Treatment policy estimand using all randomised participants regardless of treatment discontinuation or rescue medication use, for all efficacy outcomes with multiple imputation for missing data; also reports trial product estimand using data collected before premature discontinuation or rescue medication use. Modified ITT mITT analysis (all randomised participants who received at least one study drug dose) for safety analysis.

373.2. Study arms

373.2.1. Semaglutide 3-14 mg daily (N = 253)

Oral semaglutide 3-14 mg daily for 52 weeks, in addition to background glucose-lowering drugs (one or two of: metformin, sulphonylureas, SGLT2 inhibitors, or thiazolidinediones).

373.2.2. Sitagliptin 100 mg daily (N = 251)

Oral sitagliptin 100 mg daily for 52 weeks, in addition to background glucose-lowering drugs (one or two of: metformin, sulphonylureas, SGLT2 inhibitors, or thiazolidinediones).

373.3. Characteristics

373.3.1. Arm-level characteristics

Characteristic	Semaglutide 3-14 mg daily (N = 253)	Sitagliptin 100 mg daily (N = 251)
% Male Sample size	n = 145 ; % = 57	n = 140 ; % = 56
Mean age (SD) (years) Mean (SD)	56.9 (9.7)	57.9 (10.1)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA

Characteristic	Semaglutide 3-14 mg daily (N = 253)	Sitagliptin 100 mg daily (N = 251)
Asian Sample size	n = 34 ; % = 13	n = 38 ; % = 15
Black/African-American Sample size	n = 22 ; % = 9	n = 25 ; % = 10
Hispanic or Latino Sample size	n = 48 ; % = 19	n = 57 ; % = 23
Other Sample size	n = 2 ; % = 1	n = 2 ; % = 1
White Sample size	n = 195 ; % = 77	n = 186 ; % = 74
Comorbidities Nominal	NR	NR
Presence of frailty Nominal	NR	NR
Time since type 2 diabetes diagnosed (years) Mean (SD)	8.6 (6.3)	9 (6.2)
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

Characteristic	Semaglutide 3-14 mg daily (N = 253)	Sitagliptin 100 mg daily (N = 251)
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 = 102 ; % = 40	n = 87 ; % = 35
Sulphonylurea only Sample size	n = 3 ; % = 1	n = 6 ; % = 2
SGLT-2 inhibitor only Sample size	n = 1 ; % = 0.4	n = 3 ; % = 1
Thiazolidinedione only Sample size	n = 0 ; % = 0	n = 1 ; % = 0.4
Metformin + a sulphonylurea only Sample size	n = 119 ; % = 47	n = 116 ; % = 46
Metformin + SGLT2 inhibitor only Sample size	n = 16 ; % = 6	n = 31 ; % = 12
Metformin + a thiazolizinedione only Sample size	n = 9 ; % = 4	n = 3 ; % = 1
Metformin + other only Sample size	n = 1 ; % = 0.4	n = 0 ; % = 0
Sulphonylurea + other only Sample size	n = 1 ; % = 0.4	n = 3 ; % = 1
Metformin + SGLT2 inhibitor + a sulphonylurea Sample size	n = 1 ; % = 0.4	n = 1 ; % = 0.4
Blood pressure-lowering medication used Nominal	NR	NR

Characteristic	Semaglutide 3-14 mg daily (N = 253)	Sitagliptin 100 mg daily (N = 251)
Statins/lipid-lowering medication used Nominal	NR	NR
Other treatment being received Nominal	NR	NR

1

2

374. Pinget, 2013

Bibliographic Reference	Pinget, M.; Goldenberg, R.; Niemoeller, E.; Muehlen-Bartmer, I.; Guo, H.; Aronson, R.; Efficacy and safety of lixisenatide once daily versus placebo in type 2 diabetes insufficiently controlled on pioglitazone (GetGoal-P); Diabetes Obes Metab; 2013; vol. 15 (no. 11); 1000-1007

374.1. 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	GetGoal-P/NCT00763815
Study type	Randomised controlled trial (RCT) Double-blind, parallel-group, RCT
Study location	International (150 centres in 13 countries: Austria, Canada, France, Germany, Greece, Guatemala, India, Mexico, Peru, Puerto Rico, Romania, Turkey, USA)
Study setting	Outpatient
Study dates	09/2008 to 06/2011
Sources of funding	Sanofi
Inclusion criteria	• Adults with type 2 diabetes diagnosis for at least 1 year • Stable dose of pioglitazone≥30 mg/day with or without metformin (≥1500 mg/day) for at least 3 months • HbA1c 7-10% inclusive
Exclusion criteria	• Use of oral or injectable glucose-lowering agents other than metformin or pioglitazone for 3-mo prior to screening • FPG at screening>13.9 mmol/L

	• History of unexplained pancreatitis, chronic pancreatitis, pancreatectomy, stomach/gastric surgery or inflammatory bowel disease • End-stage renal disease and/or dialysis for patients treated only with pioglitazone • For patients treated with metformin in addition to pioglitazone, creatinine>1.4 mg/dl in women or>1.5 mg/dl in men • History of allergic reaction to any GLP-1RAs • Clinically-relevant history of gastrointestinal disease, with prolonged nausea and vomiting during the previous 6 months
Recruitment / selection of participants	After 2-wk screening period, eligible participants entered 1-wk single-blind placebo run-in period, and were then randomised 2:1 to lixisenatide or placebo using interactive voice-response system and predefined randomisation list. Participants continued on existing pioglitazone and/or metformin dose and were stratified by HbA1c baseline values (<8%; ≥8%) and metformin use (yes; no). Rescue therapy permitted from baseline to week 7 if FPG >15 mmol/l at least 3 times; >13.3 mmol/l from weeks 8-12; >11.1 mmol/l from week 12 to 24; after wk 24, >10 mmol/l or HbA1c>8%. After 24 weeks, there was variable extension period (data not extracted) that ended after last participant completed 72-wks treatment.
Intervention(s)	• Lixisenatide 20 mcg daily Subcutaneous injection of lixisenatide 20 mcg daily, within 1 hour before breakfast, for 24 weeks, in addition to stable dose of pioglitazone (with or without metformin). Initial dose 10 mcg four times daily for 1 week, 15 mcg four times daily for 1 week and then maintenance dose of 20 mcg four times daily if tolerated. If not tolerated, dose could be reduced to 15 or 10 mcg daily. Drug and placebo were double-blind but not volume.
Cointervention	• Pioglitazone≥30 mg daily All participants continued receiving existing pioglitazone dose for duration of trial.
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	Not stated/unclear CKD not an inclusion /exclusion criteria. Exclusion criteria state: "end-stage renal disease and/or dialysis for patients treated only with pioglitazone and for patients treated with

chronic kidney disease	metformin in addition to pioglitazone, creatinine >1.4 mg/dl in women or >1.5 mg/dl in men." 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 Volume-matched placebo for 24 weeks, within 1 hour before breakfast, for 24 weeks, in addition to existing pioglitazone dose.

Number of participants	N=484 randomised
Duration of follow-up	24 weeks
Indirectness	None
Method of analysis	Modified ITT mITT observed cases analysis (all randomised participants who received at least one dose of study drug and had baseline and at least one post-baseline measurement of any primary or secondary efficacy parameter) for all efficacy outcomes; safety set was all randomised participants who received at least one dose of study drug.
Additional comments	Trial continued after week 24 onto variable extension period that ended when last participant completed 72 weeks treatment. Data for this extension period has not been extracted.

374.2. Study arms

374.2.1. Lixisenatide 80 mcg daily (N = 323)

Subcutaneous injection of lixisenatide 20 mcg daily for 24 weeks, in addition to stable dose of pioglitazone.

374.2.2. Placebo (N = 161)

Volume matched placebo for 24 weeks, in addition to stable dose of pioglitazone.

374.3. Characteristics

374.3.1. Arm-level characteristics

Characteristic	Lixisenatide 80 mcg daily (N = 323)	Placebo (N = 161)
% Male Sample size	n = 171 ; % = 53	n = 82 ; % = 51
Mean age (SD) (years) Mean (SD)	56 (9.5)	55.3 (9.5)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA

Characteristic	Lixisenatide 80 mcg daily (N = 323)	Placebo (N = 161)
Asian Sample size	n = 13 ; % = 4	n = 10 ; % = 6
Black Sample size	n = 13 ; % = 4	n = 8 ; % = 5
Other Sample size	n = 23 ; % = 7	n = 13 ; % = 8
Caucasian Sample size	n = 275 ; % = 85	n = 132 ; % = 82
Comorbidities Nominal	NR	NR
Presence of frailty Nominal	NR	NR
Time since type 2 diabetes diagnosed Mean (SD)	8.1 (5.4)	8.1 (5.6)
Cardiovascular risk factors Nominal	NR	NR
Smoking status Sample size	n = NR ; % = NR	n = 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

Characteristic	Lixisenatide 80 mcg daily (N = 323)	Placebo (N = 161)
Other antidiabetic medication used Sample size	n = NA ; % = NA	n = NA ; % = NA
Metformin Sample size	n = 262 ; % = 81	n = 130 ; % = 81
Blood pressure-lowering medication used Nominal	NR	NR
Statins/lipid-lowering medication used Nominal	NR	NR
Other treatment being received Nominal	NR	NR

1

2

375. Pollock, 2019

Bibliographic Reference	Pollock, C.; Stefansson, B.; Reyner, D.; Rossing, P.; Sjostrom, C. D.; Wheeler, D. C.; Langkilde, A. M.; Heerspink, H. J. L.; Albuminuria-lowering effect of dapagliflozin alone and in combination with saxagliptin and effect of dapagliflozin and saxagliptin on glycaemic control in patients with type 2 diabetes and chronic kidney disease (DELIGHT): a randomised, double-blind, placebo-controlled trial; Lancet Diabetes Endocrinol; 2019; vol. 7 (no. 6); 429-441

375.1. 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	NCT02547935
Study type	Randomised controlled trial (RCT)
Study location	Multi-centre, multi-national study conducted at 116 research centres in Australia, Canada, Japan, South Korea, Mexico, South Africa, Spain, Taiwan and the USA.
Study setting	No additional information.
Study dates	14 July 2015 to 18 May 2018.
Sources of funding	Astra Zeneca
Inclusion criteria	Adults aged 18 years and older with type 2 diabetes and moderate-to-severe chronic kidney disease. • Type 2 diabetes for > 12 months • increased albuminuria, defined as UACR 30-3500mg/g)

	• renal impairment, defined as eGFR of 20-80 mL/min per 1.73m² to enter the lead-in period (25-75mL/min per 1.73m² to enter randomisation) • inadequate glycaemic control , defined as HbA_{1c} of 7.0-11.0% (53-97mmol/mol) at screening • receiving stable glucose-lowering and anti-hypertensive treatments, including angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers, at clinically appropriate dose for at least 12 weeks before randomisation • BMI between 20 and 45 kg/m² at screening
Exclusion criteria	• Type 1 diabetes • known non-diabetic kidney disease • severe cardiovascular disease • 2 or more major hypoglycaemia events within 12 weeks before screening • haemoglobin less than 9g/dL (or 5.6 mmol/L) • evidence of hepatic disease • poorly controlled blood pressure (systolic blood pressure ≥180 mm Hg or diastolic blood pressure ≥110 mm Hg) • current use of SGLT2 inhibitors, GLP-1 receptor agonists or DPP-4 inhibitors • long-term treatment with glucocorticoids • cardiovascular events within 3 months of screening: myocardial infarction, cardiac surgery or revascularisation, unstable angina, unstable heart failure, heart failure New York Heart Association class III-IV, transient ischaemic attack or significant cerebrovascular disease, unstable or previously undiagnosed arrhythmia • simultaneous treatment with ACE inhibitor and ARB
Recruitment / selection of participants	No additional information
Intervention(s)	1) Dapagliflozin (10mg), oral, once daily 2) Dapagliflozin (10mg,) + Saxagliptin (2.5mg,) oral, once daily
Cointervention	Glucose-lowering therapy Antihypertensive therapy Dietary advice
Strata 1: People with type 2 diabetes	Not stated/unclear Exclusion criteria state: " Any of the following cardiovascular/vascular diseases within 3 months prior to signing the consent at Visit 1: a) Myocardial infarction b) Cardiac surgery or revascularisation c) Unstable

mellitus and heart failure	angina d) Unstable heart failure e) HF New York Heart Association Class III-IV f) Transient ischemic attack or significant cerebrovascular disease g) Unstable or previously undiagnosed arrhythmia" (see supplement). No information in baseline characteristics. Unclear about NYHA Class II.
Strata 2: People with atherosclerotic cardiovascular disease	Not stated/unclear Exclusion criteria state: " Any of the following cardiovascular/vascular diseases within 3 months prior to signing the consent at Visit 1: a) Myocardial infarction b) Cardiac surgery or revascularisation c) Unstable angina d) Unstable heart failure e) HF New York Heart Association Class III-IV f) Transient ischemic attack or significant cerebrovascular disease g) Unstable or previously undiagnosed arrhythmia" (see supplement). No information in baseline characteristics. Unclear regarding events preceding the 3 months.
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	People with chronic kidney disease Study population was people with type 2 diabetes and moderate to severe chronic kidney disease. "Participants were required to have increased albuminuria (urine albumin to creatinine ratio [UACR] 30–3500 mg/g), an estimated glomerular filtration rate (eGFR) of 20–80 mL/min per 1·73 m² to enter the lead in period (25–75 mL/min per 1·73 m² for randomisation)."
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 Not an inclusion/exclusion criteria. No information reported in baseline characteristics.
Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear Type 2 diabetes for at least 12 months in the inclusion criteria. Known duration of diabetes (mean) reported in baseline characteristics table.
Subgroup 3: People with non-alcoholic fatty liver disease	People without non-alcoholic fatty liver disease People with significant hepatic disease were excluded

Subgroup 4: People with obesity	Not stated/unclear Mean BMI at baseline reported. No additional information.
Subgroup 5: eGFR category at baseline	Not stated/unclear Baseline eGFR reported as a mean and categories: ≤45 and > 45
Subgroup 6: Albuminuria category at baseline	Mixed population Albuminuria subgroup categories align with UACR categories in the baseline characteristics table. Baseline table reports: A1 = 7% overall A2 = 45% overall A3 = 48% overall
Comparator	Placebo (matched)
Number of participants	N= 448
Duration of follow-up	24 weeks
Indirectness	
Method of analysis	Modified ITT
Additional comments	"All randomly allocated patients with non-missing baseline data and at least one assessment during the double-blind treatment period were included in the analysis (full analysis set), resulting in only small losses from the intention-to-treat population."

375.2. Study arms

375.2.1. Dapagliflozin + Saxagliptin (N = 155)

375.2.2. Dapagliflozin (N = 145)

375.2.3. Placebo (N = 148)

375.3. Characteristics

375.3.1. Arm-level characteristics

Characteristic	Dapagliflozin + Saxagliptin (N = 155)	Dapagliflozin (N = 145)	Placebo (N = 148)
% Male Sample size	n = 110 ; % = 71	n = 102 ; % = 70	n = 105 ; % = 71
Mean age (SD) Mean (SD)	64 (9.2)	64.7 (8.6)	64.7 (8.5)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
White Sample size	n = 77 ; % = 50	n = 55 ; % = 38	n = 64 ; % = 43
Black Sample size	n = 8 ; % = 5	n = 7 ; % = 5	n = 11 ; % = 7
Asian Sample size	n = 57 ; % = 37	n = 67 ; % = 46	n = 53 ; % = 36
Other Sample size	n = 13 ; % = 8	n = 16 ; % = 11	n = 13 ; % = 8
Comorbidities Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
Diabetic retinopathy Sample size	n = 62 ; % = 42	n = 56 ; % = 39	n = 64 ; % = 41
Cardiac disorders Sample size	n = 53 ; % = 34	n = 58 ; % = 40	n = 41 ; % = 28
Vascular disorders Sample size	n = 23 ; % = 16	n = 20 ; % = 14	n = 26 ; % = 17

Characteristic	Dapagliflozin + Saxagliptin (N = 155)	Dapagliflozin (N = 145)	Placebo (N = 148)
Presence of frailty Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Time since type 2 diabetes diagnosed Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
HbA1c (%) Mean (SD)	8.2 (1)	8.44 (1)	8.57 (1.2)
Blood pressure Mean (SD)	NA (NA)	NA (NA)	NA (NA)
Systolic blood pressure Mean (SD)	139.6 (18.1)	138 (16.5)	140.2 (18.6)
Diastolic blood pressure Mean (SD)	77.3 (10.7)	76.9 (9.5)	75.7 (11.5)
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 Mean (SD)	NR (NR)	NR (NR)	NR (NR)
BMI (kg/m2)	30.81 (5.4)	30.19 (5.3)	30.34 (5.6)

Characteristic	Dapagliflozin + Saxagliptin (N = 155)	Dapagliflozin (N = 145)	Placebo (N = 148)
Mean (SD)			
Number of people with obesity Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Cholesterol and lipid levels (mmol/L) Mean (SD)	NA (NA)	NA (NA)	NA (NA)
Total cholesterol Mean (SD)	4.5 (1.1)	4.6 (1.2)	4.5 (1.1)
LDL cholesterol Mean (SD)	2.3 (0.9)	2.4 (1)	2.3 (0.9)
HDL cholesterol Mean (SD)	1.2 (0.4)	1.2 (0.3)	1.2 (0.4)
Albumin creatinine ratio (mg/g creatinine) Median (IQR)	218.4 (74 to 936)	270 (69 to 751)	257.5 (80 to 949)
eGFR mL/min/1.73m2 (ml/min/1.73 m2) Mean (SD)	49 (13)	50.2 (13)	47.7 (13.5)
Other antidiabetic medication used Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
Insulin Sample size	n = 107 ; % = 70	n = 104 ; % = 72	n = 107 ; % = 72
Metformin Sample size	n = 92 ; % = 61	n = 86 ; % = 59	n = 92 ; % = 61
Sulfonylureas Sample size	n = 48 ; % = 32	n = 39 ; % = 27	n = 58 ; % = 39
Blood pressure-lowering medication used Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA

Characteristic	Dapagliflozin + Saxagliptin (N = 155)	Dapagliflozin (N = 145)	Placebo (N = 148)
Renin-angiotensin system inhibitors Sample size	n = 152 ; % = 100	n = 143 ; % = 99	n = 147 ; % = 99
Loop diuretics Sample size	n = 36 ; % = 24	n = 26 ; % = 18	n = 36 ; % = 24
Thiazides Sample size	n = 40 ; % = 26	n = 38 ; % = 26	n = 30 ; % = 20
Statins/lipid-lowering medication used Sample size	n = 106 ; % = 70	n = 105 ; % = 72	n = 111 ; % = 75
Other treatment being received Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Albumin creatinine ratio (categories) (mg/g creatinine) Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
Normoalbuminuria UACR <30mg/g Sample size	n = 12 ; % = 8	n = 10 ; % = 7	n = 11 ; % = 7
Microalbuminuria UACR 30-300mg/g Sample size	n = 73 ; % = 47	n = 64 ; % = 44	n = 65 ; % = 44
Macroalbuminuria UACR 300-3500mg/g Sample size	n = 70 ; % = 45	n = 71 ; % = 49	n = 72 ; % = 49
eGFR categories (ml/min/1.73 m2) Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
Mean eGFR≤45 Sample size	n = 65 ; % = 42	n = 53 ; % = 37	n = 70 ; % = 47
Mean eGFR >45 Sample size	n = 90 ; % = 58	n = 92 ; % = 63	n = 78 ; % = 53

1

1

376. Pozzilli, 2017

Bibliographic Reference	Pozzilli, P.; Norwood, P.; Jodar, E.; Davies, M. J.; Ivanyi, T.; Jiang, H.; Woodward, D. B.; Milicevic, Z.; Placebo-controlled, randomized trial of the addition of once-weekly glucagon-like peptide-1 receptor agonist dulaglutide to titrated daily insulin glargine in patients with type 2 diabetes (AWARD-9); Diabetes Obes Metab; 2017; vol. 19 (no. 7); 1024-1031

376.1. Study details

Secondary publication of another included study- see primary study for details	No
Other publications associated with this study included in review	Health-related quality of life 28-wk data reported in: • Yu, M., Van Brunt, K., Milicevic, Z., Varnado, O., & Boye, K. S. (2017). Patient-reported outcomes in patients with type 2 diabetes treated with dulaglutide added to titrated insulin glargine (AWARD-9). *Clinical Therapeutics*, *39*(11), 2284-2295.
Trial name / registration number	Assessment of Weekly AdministRation of LY2189265 [dulaglutide] in Diabetes (AWARD-9)/NCT02152371
Study type	Randomised controlled trial (RCT) Double-blind, parallel-group, treat-to-target RCT
Study location	International (Czech Republic, Hungary, Italy, Puerto Rico, UK, USA
Study setting	Outpatient
Study dates	05/2014 to 10/2015
Sources of funding	Sponsored by Eli Lilly and Co., Indianapolis, IN, USA.
Inclusion criteria	• Type 2 diabetes diagnosis (WHO definition) • Treated with basal insulin glargine once daily with or without metformin for at least 3 months prior to screening • Stable doses of once daily insulin glargine and metformin (if taken) during the 3-month period prior to screening • HbA1c 7.0-10.5%

	• Require further insulin glargine dose increase at week 3 (end of lead-in period) per the treat-to-target (TTT) algorithm based on self-monitored plasma glucose data collected during prior week
	• Stable weight (±5%) ≥3 months prior to screening
	• BMI≤45 kg/m2 at screening
	• Able and willing to administer once weekly randomized therapy
	• If female, then of childbearing potential who must:
	  ○ Test negative for pregnancy at screening, based on a serum pregnancy test
	  ○ Agree to use a reliable method of birth control
	  ○ Not be breastfeeding

Exclusion criteria	• Type 1 diabetes diagnosis
	• Use of any:
	  ○ other glucose-lowering medications within 3 months prior to Visit 1
	  ○ weight loss promoting drugs in past 3 months or between screening and visit 3
	  ○ chronic systemic glucocorticoid therapy (>14 days), or past use of such 4-wks prior to screening or between screening and visit 3
	• eGFR<30 mL/min/1.73 m2; if on metformin, then serum calcitonin ≥20 pg/mL, serum creatinine ≥1·5 mg/dL (male) or ≥1.4 mg/dL (female) or a creatinine clearance <60 mL/min/1.73 m2
	• Acute myocardial infarction, NYHA class III or IV heart failure, or cerebrovascular accident (stroke)
	• Acute or chronic hepatitis, signs and symptoms of any other liver disease, or alanine aminotransferase (ALT) level >2.5 times the upper limit of the reference range
	• History of: pancreatitis; ≥1 episode of diabetic ketoacidosis or hyperosmolar state/coma; hypoglycaemia unawareness in past 6 months; transplanted organ; active or untreated malignancy in prior 5 years; any other condition may interfere with protocol
	• Known clinically significant gastric emptying abnormality or have undergone gastric bypass surgery or restrictive bariatric surgery
	• Self or family history of: type 2A or type 2B multiple endocrine neoplasia (MEN 2A or 2B) in the absence of known C-cell hyperplasia; medullary C-cell hyperplasia, focal hyperplasia, or carcinoma (including sporadic, familial, or part of MEN 2A or 2B syndrome)
	• Recent cardiovascular event

Recruitment / selection of participants	Following 3-wk screening/lead-in period in which participants self-monitored plasma glucose, eligible participants - those who required increase in glargine dose as result of above target FPG as per treat-to-target algorithm - randomised 1:1 using computer-generated random sequence and interactive voice response system. Treatment phase began with 4-wk stabilization phase then 24-wk titration phase. Office visits during treatment weekly or every 2 weeks for first 2 months, then every 4-6 weeks. Participants experiencing hyperglycaemia stopped study drug and discontinued study, as did any other participant who discontinued study drug for any reason.

Intervention(s)	• Dulaglutide 1.5 mg weekly Subcutaneous injection of dulaglutide 1.5 mg weekly for 28 weeks, in addition to titrated daily insulin glargine.
Cointervention	• Insulin glargine titrated daily All participants received titrated daily insulin glargine for duration of trial. In lead-in period, dose assessments were once weekly and were adjusted according to titration algorithm only to prevent hypoglycaemia or severe hyperglycaemia. After randomisation, during initial 4-wk stabilization phase insulin dose adjusted twice weekly. Glargine dose remained unchanged if baseline HbA1c >8% or was decreased 20% if HbA1c≤8% immediately after randomisation. Additional adjustments only if hypo- or severe hyper-glycaemia. After 4 weeks, insulin dose adjusted without limitation until trial end.
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	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	eGFR ≥30mL/min/1.73m2 Exclusion criteria: eGFR<30 mL/min/1.73 m2
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Comparator	• Placebo Matching subcutaneous placebo for 28 weeks, in addition to titrated daily insulin glargine.
Number of participants	N=300 randomised (272 completers)
Duration of follow-up	28 weeks
Indirectness	None
Method of analysis	Modified ITT mITT LOCF analysis (all randomised participants who received at least 1 dose study drug) for all efficacy and safety outcomes

376.2. Study arms

376.2.1. Dulaglutide 1.5 mg weekly (N = 150)

Subcutaneous injection of dulaglutide 1.5 mg weekly for 28 weeks, in addition to titrated daily insulin glargine with or without metformin.

376.2.2. Placebo (N = 150)

Matched placebo for 28 weeks, in addition to titrated daily insulin glargine with or without metformin.

376.3. Characteristics

376.3.1. Arm-level characteristics

Characteristic	Dulaglutide 1.5 mg weekly (N = 150)	Placebo (N = 150)
% Male Sample size	n = 85 ; % = 56.7	n = 88 ; % = 58.7
Mean age (SD) (years) Mean (SD)	60.2 (9.5)	60.6 (10.1)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA
Asian Sample size	n = 0 ; % = 0	n = 1 ; % = 0.7
Black/African-American Sample size	n = 5 ; % = 3.3	n = 6 ; % = 4
Hispanic or Latino Sample size	n = 26 ; % = 17.3	n = 25 ; % = 16.7
Multiple Sample size	n = 1 ; % = 0.7	n = 3 ; % = 2
White Sample size	n = 143 ; % = 95.3	n = 138 ; % = 92
Comorbidities Nominal	NR	NR
Presence of frailty Nominal	NR	NR
Time since type 2 diabetes diagnosed Mean (SD)	13 (7.5)	13.3 (7.7)
Cardiovascular risk factors Nominal	NR	NR

Characteristic	Dulaglutide 1.5 mg weekly (N = 150)	Placebo (N = 150)
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
Metformin Sample size	n = 134 ; % = 89.3	n = 131 ; % = 87.3
Blood pressure-lowering medication used Nominal	NR	NR
Statins/lipid-lowering medication used Nominal	NR	NR
Other treatment being received Nominal	NR	NR

1

2

377. Pratley, 2018

Bibliographic Reference	Pratley, R. E.; Eldor, R.; Raji, A.; Golm, G.; Huyck, S. B.; Qiu, Y.; Sunga, S.; Johnson, J.; Terra, S. G.; Mancuso, J. P.; et, al.; Ertugliflozin plus sitagliptin versus either individual agent over 52 weeks in patients with type 2 diabetes mellitus inadequately controlled with metformin: the VERTIS FACTORIAL randomized trial; Diabetes Obes Metab; 2018; vol. 20 (no. 5); 1111-1120

377.1. 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	VERTIS FACTORIAL [NCT02099110]
Study type	Randomised controlled trial (RCT)
Study location	Multicentre trial in 21 countries across 242 trial centres [USA; Canada; Argentina; Colombia; Mexico; Czech Republic; Hungary; Israel; Poland; Romania; Russian Federation; Slovakia; Ukraine; Malaysia; Philippines; New Zealand; Bulgaria; Italy; Finland; Thailand; Chile]
Study setting	NR
Study dates	April 29, 2014 to May 26, 2016
Sources of funding	Merck Sharp & Dohme Corp., a subsidiary of Merck & Co. Inc and Pfizer Inc.
Inclusion criteria	• Aged ≥18 years with type 2 diabetes and HbA1c ≥7.5 and ≤11.0% with stable (≥8 weeks) metformin monotherapy ≥1500 mg/d • Participants receiving ≥1500 mg/d metformin for <8 weeks or receiving <1500 mg/d at screening entered a titration/stabilization period and were eligible after completing 8 weeks of metformin monotherapy ≥1500 mg/d

Exclusion criteria	• Type 1 diabetes • History of ketoacidosis • An estimated eGFR <60 mL/min/1.73 m2 • Serum creatinine ≥1.3 mg/dL (men) of ≥1.2 mg/dL (women) • History of a cardiovascular event within 3 months of screening • Patients treated with any AHA other than protocol-approved agents within 12 weeks of screening
Recruitment / selection of participants	NR
Intervention(s)	• Ertugliflozin 5 mg (E5) • Ertugliflozin 15 mg (E15) • Sitagliptin 100 mg (S100) • Ertugliflozin 5 mg + Sitagliptin 100 mg (E5/S100) • Ertugliflozin 15 mg + Sitagliptin 100 mg (E15/S100) [Oral sitagliptin and ertugliflozin were administered as separate tablets once daily, at approximately the same time each morning, without regard to food intake.]
Cointervention	• Metformin • Patients received glycaemic rescue therapy with open-label glimepiride (or insulin glargine if glimepiride was not considered appropriate by the investigator) if they met rescue criteria
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear Exclusion criteria state: "history of NYHA functional class III-IV heart failure within 3 months of Visit 1/Screening" (see protocol). No information in baseline characteristics.
Strata 2: People with atherosclerotic cardiovascular disease	Not stated/unclear Exclusion criteria state: "History of myocardial infarction, unstable angina, arterial revascularization, stroke, or transient ischemic attack within 3 months of Visit 1/Screening" (see protocol). No information in baseline characteristics.
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear CKD not an inclusion/exclusion criteria. People with "an estimated glomerular filtration rate (eGFR) 60mL/min/1.73m2, serum creatinine ≥1.3mg/dL (men) or ≥1.2mg/dL (women) within 3 months of screening" were excluded.
Strata 4: People with type 2	Not stated/unclear

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	Not stated/unclear
Population subgroups	NR
Comparator	NA
Number of participants	2,582 patients were screened and 1,233 patients were randomised. Of 250 participants allocated to E5, 218 (87.2%) completed week 52 on study medication, and 18.4% had received rescue medication. Of 248 patients allocated to E15, 208 (83.9%) completed week 52 on study medication, and 21.0% had received rescue medication. Of 247 participants allocated to S100, 207 (83.6%) completed on study medication and 27.9% received rescue medication. Of 243 participants allocated to E5/S100, 213 (87.7%) completed on study medication and 11.1% received rescue therapy. Of 245 participants allocated to E15/S100, 207 (84.5%) completed on study medication and 10.7% received rescue medication.
Duration of follow-up	Week 26 and 52.

Indirectness	Directly applicable
Method of analysis	Not stated/unclear Defined as all randomised, treated patients who had ≥1 measurement of the efficacy outcome. Observations obtained after initiation of glycaemic rescue therapy were treated as missing and imputed via multiple imputation in a longitudinal data analysis model.
Additional comments	NA

377.2. Study arms

377.2.1. Ertugliflozin 5 mg (N = 250)

377.2.2. Ertugliflozin 15 mg (N = 248)

377.2.3. Sitagliptin 100 mg (N = 247)

377.2.4. Ertugliflozin 5 mg + Sitagliptin 100 mg (N = 243)

377.2.5. Ertugliflozin 15 mg + Sitagliptin 100 mg (N = 245)

377.3. Characteristics

377.3.1. Arm-level characteristics

Characteristic	Ertugliflozin 5 mg (N = 250)	Ertugliflozin 15 mg (N = 248)	Sitagliptin 100 mg (N = 247)	Ertugliflozin 5 mg + Sitagliptin 100 mg (N = 243)	Ertugliflozin 15 mg + Sitagliptin 100 mg (N = 245)
% Male Sample size	n = 127 ; % = 50.8	n = 134 ; % = 54	n = 154 ; % = 62.3	n = 123 ; % = 50.6	n = 126 ; % = 51.6

Characteristic	Ertugliflozin 5 mg (N = 250)	Ertugliflozin 15 mg (N = 248)	Sitagliptin 100 mg (N = 247)	Ertugliflozin 5 mg + Sitagliptin 100 mg (N = 243)	Ertugliflozin 15 mg + Sitagliptin 100 mg (N = 245)
Mean age (SD) Mean (SD)	55.1 (10.1)	55.3 (9.5)	54.8 (10.7)	55.2 (10.4)	55.1 (9.8)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
American Indian or Alaska Native Sample size	n = 7 ; % = 2.8	n = 4 ; % = 1.6	n = 4 ; % = 1.6	n = 2 ; % = 0.8	n = 4 ; % = 1.6
Asian Sample size	n = 22 ; % = 8.8	n = 22 ; % = 8.9	n = 29 ; % = 11.7	n = 22 ; % = 9.1	n = 36 ; % = 14.8
Black or African American Sample size	n = 7 ; % = 2.8	n = 6 ; % = 2.4	n = 11 ; % = 4.5	n = 12 ; % = 4.9	n = 10 ; % = 4.1
Multiple Sample size	n = 8 ; % = 3.2	n = 11 ; % = 4.4	n = 9 ; % = 3.6	n = 10 ; % = 4.1	n = 6 ; % = 2.5
Native Hawaiian or other Pacific Islander Sample size	n = 0 ; % = 0	n = 0 ; % = 0	n = 1 ; % = 0.4	n = 0 ; % = 0	n = 0 ; % = 0
White Sample size	n = 206 ; % = 82.4	n = 205 ; % = 82.7	n = 193 ; % = 78.1	n = 197 ; % = 81.1	n = 188 ; % = 77
Comorbidities Nominal	NR	NR	NR	NR	NR
Presence of frailty Nominal	NR	NR	NR	NR	NR
Time since type 2 diabetes diagnosed Sample size	n = 7.1 ; % = 5.4	n = 7.3 ; % = 5.4	n = 6.2 ; % = 5.2	n = 7 ; % = 5.6	n = 6.9 ; % = 5.2

Characteristic	Ertugliflozin 5 mg (N = 250)	Ertugliflozin 15 mg (N = 248)	Sitagliptin 100 mg (N = 247)	Ertugliflozin 5 mg + Sitagliptin 100 mg (N = 243)	Ertugliflozin 15 mg + Sitagliptin 100 mg (N = 245)
Cardiovascular risk factors Nominal	NR	NR	NR	NR	NR
Smoking status Nominal	NR	NR	NR	NR	NR
Alcohol consumption Nominal	NR	NR	NR	NR	NR
Presence of severe mental illness Nominal	NR	NR	NR	NR	NR
People with significant cognitive impairment Nominal	NR	NR	NR	NR	NR
People with a learning disability Nominal	NR	NR	NR	NR	NR
BMI Mean (SD)	31.8 (6.2)	31.5 (5.8)	31.7 (6.5)	32.5 (6.7)	31.8 (6.5)
Number of people with obesity Nominal	NR	NR	NR	NR	NR
Other antidiabetic medication used Nominal	NR	NR	NR	NR	NR

Characteristic	Ertugliflozin 5 mg (N = 250)	Ertugliflozin 15 mg (N = 248)	Sitagliptin 100 mg (N = 247)	Ertugliflozin 5 mg + Sitagliptin 100 mg (N = 243)	Ertugliflozin 15 mg + Sitagliptin 100 mg (N = 245)
Blood pressure-lowering medication used Nominal	NR	NR	NR	NR	NR
Statins/lipid-lowering medication used Nominal	NR	NR	NR	NR	NR
Other treatment being received Nominal	NR	NR	NR	NR	NR

1

2

378. Pratley, 2009

Bibliographic Reference	Pratley, R. E.; Kipnes, M. S.; Fleck, P. R.; Wilson, C.; Mekki, Q.; Efficacy and safety of the dipeptidyl peptidase-4 inhibitor alogliptin in patients with type 2 diabetes inadequately controlled by glyburide monotherapy; Diabetes Obes Metab; 2009; vol. 11 (no. 2); 167-76

378.1. Study details

Secondary publication of another included study- see primary study for details	Trial: Alogliptin Study 007
Other publications associated with this study included in review	NA
Trial name / registration number	NCT00286468
Study type	Randomised controlled trial (RCT)
Study location	Argentina, Australia, Brazil, Chile, Dominican Republic, Guatemala, India, Mexico, Netherlands, New Zealand, Peru, Poland, South Africa, United Kingdom, United States
Study setting	Unspecified clinical setting
Study dates	April 2006 to June 2007
Sources of funding	Takeda
Inclusion criteria	• Diagnosis of type 2 diabetes mellitus , currently treated with a sulfonylurea alone but experiencing inadequate glycemic control. Should have received the sulfonylurea monotherapy for at least the 3 months prior to Screening; has been on a stable sulfonylurea dose equivalent to at least 10 mg of glyburide (Exception: documented maximum tolerated dose equivalent to less than 10 mg but at least 5 mg glyburide) for at least 8 weeks. • No treatment with antidiabetic agents other than a sulfonylurea within the 3 months prior to Screening. (Exception: if a subject has

	received other antidiabetic therapy for less than 7 days within the 3 months prior to Screening.) • Body mass index greater than or equal to 23 kg/m2 and less than or equal to 45 kg/m2. • Fasting C-peptide concentration greater than or equal to 0.8 ng/mL. (If this screening criterion is not met, the subject still qualifies if C-peptide is greater than or equal to 1.5 ng/mL after a challenge test.). • Glycosylated hemoglobin concentration between 7.0% and 10.0%, inclusive. • If regular use of other, non-excluded medications, must be on a stable dose for at least the 4 weeks prior to Screening. However, as needed use of prescription or over-the-counter medications is allowed at the discretion of the investigator. • Systolic blood pressure less than or equal to180 mm Hg and diastolic pressure less than or equal to 110 mm Hg • Hemoglobin greater than or equal to 12 g per dL for males and greater than or equal to 10 g per dL for females • Alanine aminotransferase less than or equal to 3 time the upper limit of normal. • Serum creatinine ≤2.0 mg/dL (≤17 micromol/L) • Thyroid-stimulating hormone level less than or equal to the upper limit of the normal range and the subject is clinically euthyroid. • Neither pregnant nor lactating • Female subjects of childbearing potential must be practicing adequate contraception. Adequate contraception must be practiced for the duration of participation in the study. • Able and willing to monitor their own blood glucose concentrations with a home glucose monitor. • No major illness or debility that in the investigator's opinion prohibits the subject from completing the study. • Able and willing to provide written informed consent
Exclusion criteria	• Urine albumin to creatinine ratio of greater than 1000 µg per mg at Screening. If elevated, the subject may be rescreened within 1 week. • History of cancer, other than squamous cell or basal cell carcinoma of the skin, that has not been in full remission for at least 5 years prior to Screening. (A history of treated cervical intraepithelial neoplasia I or cervical intraepithelial neoplasia II is allowed.) • History of laser treatment for proliferative diabetic retinopathy within the 6 months prior to Screening. • History of treated diabetic gastric paresis. • New York Heart Association Class III or IV heart failure regardless of therapy. Currently treated subjects who are stable at Class I or II are candidates for the study. • History of coronary angioplasty, coronary stent placement, coronary bypass surgery, or myocardial infarction within the 6 months prior to Screening. • History of any hemoglobinopathy that may affect determination of glycosylated hemoglobin. • History of infection with hepatitis B, hepatitis C, or human immunodeficiency virus.

	• History of a psychiatric disorder that will affect the subject's ability to participate in the study. • History of angioedema in association with use of angiotensin-converting enzyme inhibitors or angiotensin-II receptor inhibitors. • History of alcohol or substance abuse within the 2 years prior to Screening. • Receipt of any investigational drug within the 30 days prior to Screening or a history of receipt of an investigational antidiabetic drug within the 3 months prior to Screening. • Prior treatment in an investigational study of alogliptin. Excluded Medications and Treatments: • Treatment with antidiabetic agents other than study drug or glyburide is not allowed within the 3 months prior to Screening and through the completion of the end-of-treatment/early termination procedures. • Treatment with weight-loss drugs, any investigational antidiabetics, Bosentan (used for the treatment of pulmonary hypertension), or oral or systemically injected glucocorticoids is not allowed from 3 months prior to randomization through the completion of the end-of- treatment/early termination procedures. Inhaled corticosteroids are allowed. • Subjects must not take any medications, including over-the-counter products, without first consulting with the investigator.
Recruitment / selection of participants	After completing the run-in period, patients with HbA1c values of 7.0–10.0%, fasting plasma glucose (FPG) <275 mg/dl, and ——————— 75% compliance with the single-blind placebo regimen (based on tablet count) were eligible to enter the double-blind treatment period if their sulphonylurea dose had been stable for the past 8 weeks. Randomisation was in accordance with a permuted block schedule that was stratified for HbA1c at week 1 (HbA1c <8.0 vs. 8.0%) and for geographic region.
Intervention(s)	Alogliptin 12.5 mg and 25 mg
Cointervention	Glyburide
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear "New York Heart Association classes III or IV heart failure" an exclusion criterion. No information in baseline characteristics.
Strata 2: People with atherosclerotic cardiovascular disease	Not stated/unclear People with "a history of coronary angioplasty, coronary stent placement, coronary bypass surgery, or myocardial infarction within 6 months" were excluded. No information in baseline characteristics.
Strata 3: People with	Not stated/unclear

type 2 diabetes mellitus and chronic kidney disease	CKD not an inclusion /exclusion criteria. The following were excluded: "a serum creatinine >2.0mg/dl; a urine albumin/creatinine ratio>1000ug/ mg." 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 Patient were excluded if they had a body mass index (BMI) <23 or >45 kg/m2
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	500 patients were randomly assigned to double-blind treatment (placebo, n = 99; alogliptin 12.5 mg, n = 203; alogliptin 25 mg, n = 198). Eighty-nine patients (17.8%) discontinued treatment because of the need for

	hyperglycaemic rescue, and 48 patients (9.6%) did not complete the study for other reasons.
Duration of follow-up	26 weeks
Indirectness	None
Method of analysis	Modified ITT
Additional comments	The efficacy dataset included all patients who were randomized to double-blind treatment and received at least one dose of study drug; analysis of efficacy variables included data from patients with a baseline assessment and at least one post-baseline assessment (26 week primary analysis used LOCF). The safety dataset included all patients who received at least one dose of double-blind study drug

378.2. Study arms

378.2.1. Alogliptin 12.5 mg (N = 203)

Alogliptin and glyburide: Alogliptin 12.5 mg, tablets, orally, once daily and glyburide for up to 26 weeks

378.2.2. Alogliptin 25 mg (N = 198)

Alogliptin and glyburide: Alogliptin 25 mg, tablets, orally, once daily and glyburide for up to 26 weeks

378.2.3. Placebo (N = 99)

Placebo and glyburide: Alogliptin placebo-matching tablets, orally, once daily and glyburide for up to 26 weeks.

378.3. Characteristics

378.3.1. Arm-level characteristics

Characteristic	Alogliptin 12.5 mg (N = 203)	Alogliptin 25 mg (N = 198)	Placebo (N = 99)
% Male	54.7	50	51.5

Characteristic	Alogliptin 12.5 mg (N = 203)	Alogliptin 25 mg (N = 198)	Placebo (N = 99)
Nominal			
Mean age (SD) Mean (SD)	56.5 (11.1)	56.5 (11.7)	57.1 (10)
White Nominal	69.5	71.2	72.7
Asian Nominal	10.3	12.1	13.1
Black Nominal	3.9	5.6	3
Native Hawaiian/ other pacific islander Nominal	0	0	0
Native American/Alaskan Nominal	0	0	0
Other Nominal	16.3	11.1	11.1
Comorbidities Nominal	NR	NR	NR
Presence of frailty Nominal	NR	NR	NR
Time since type 2 diabetes diagnosed Mean (SD)	7.8 (6.1)	7.6 (6)	7.7 (5.3)
less than 8 percent Nominal	44.3	43.9	44.4
greater than 8 percent Nominal	55.7	56.1	55.6
Cardiovascular risk factors Nominal	NR	NR	NR
Smoking status	NR	NR	NR

Characteristic	Alogliptin 12.5 mg (N = 203)	Alogliptin 25 mg (N = 198)	Placebo (N = 99)
Nominal			
Alcohol consumption Mean (SD)	NR (NR)	NR (NR)	NR (NR)
Presence of severe mental illness Nominal	NR	NR	NR
People with significant cognitive impairment Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
People with a learning disability Nominal	NR	NR	NR
BMI Mean (SD)	30.2 (4.8)	30 (4.8)	30 (5.3)
Number of people with obesity Nominal	NR	NR	NR
Other antidiabetic medication used (mg) Glyburide dose during the study (mg) Mean (SD)	12.3 (4.5)	12.4 (4.5)	11.2 (4.1)
Blood pressure-lowering medication used Nominal	NR	NR	NR
Statins/lipid-lowering medication used Nominal	NR	NR	NR
Other treatment being received Nominal	NR	NR	NR

1

2

379. Pratley, 2010

Bibliographic Reference	Pratley, R. E.; Nauck, M.; Bailey, T.; Montanya, E.; Cuddihy, R.; Filetti, S.; Thomsen, A. B.; Søndergaard, R. E.; Davies, M.; Liraglutide versus sitagliptin for patients with type 2 diabetes who did not have adequate glycaemic control with metformin: a 26-week, randomised, parallel-group, open-label trial; Lancet; 2010; vol. 375 (no. 9724); 1447-56

379.1. Study details

Other publications associated with this study included in review	Pratley 2011 Pratley R, Nauck M, Bailey T, Montanya E, Cuddihy R, Filetti S, Garber A, Thomsen AB, Hartvig H, Davies M; 1860-LIRA-DPP-4 Study Group. One year of liraglutide treatment offers sustained and more effective glycaemic control and weight reduction compared with sitagliptin, both in combination with metformin, in patients with type 2 diabetes: a randomised, parallel-group, open-label trial. Int J Clin Pract. 2011 Apr;65(4):397-407. doi: 10.1111/j.1742-1241.2011.02656.x. Epub 2011 Mar 1. PMID: 21355967; PMCID: PMC3085127. Davies 2011 Davies M, Pratley R, Hammer M, Thomsen AB, Cuddihy R. Liraglutide improves treatment satisfaction in people with Type 2 diabetes compared with sitagliptin, each as an add on to metformin. Diabet Med. 2011 Mar;28(3):333-7. doi: 10.1111/j.1464-5491.2010.03074.x. PMID: 21309842.
Trial name / registration number	1860-LIRA-DPP-4 / NCT00700817
Study type	Randomised controlled trial (RCT)
Study location	158 sites in 11 European countries (Croatia, Germany, Ireland, Italy, Netherlands, Romania, Serbia, Slovakia, Slovenia, Spain, and UK), the USA, and Canada
Study setting	Office-based sites
Study dates	June 16 2008 and June 11 2009
Sources of funding	Funded by Novo Nordisk, Denmark. Numerous authors declare funding and honoraria from numerous pharmaceutical companies
Inclusion criteria	ged 18–80 years, had type 2 diabetes mellitus, had glycosylated haemoglobin (HbA1c) of 7·5–10·0%, had a body-mass index of 45·0 kg/m²

	or lower, and had been treated with metformin (≥1500 mg daily) for 3 months or longer.
Exclusion criteria	1. treatment with insulin, glucagon-like peptide (GLP)-1 receptor agonists (including liraglutide or exenatide) or dipeptidyl peptidase (DPP)-4 inhibitors (except for short-term treatment with insulin in connection with intercurrent illness at the discretion of the investigator). 2. Treatment with anti-diabetic drugs other than metformin within the last three months prior to the trial. 3. Impaired liver function, defined as alanine transaminase (ALAT) ≥2·5 times upper normal limit (one retest analysed at the central laboratory within a week is permitted with the result of the last sample being the conclusive). 4. Impaired renal function defined as creatinine clearance (CrCl) <50mL/min (calculated by the Cockcroft-Gault formula), or as allowed according to local contraindications for metformin use (one retest analysed at the central laboratory within a week permitted with the result of the last sample being the conclusive). 5. Known clinically significant active cardiovascular disease, including history of unstable angina, acute coronary event, other significant cardiac events (including history of arrhythmias or conduction delays on electrocardiogram (ECG), or cerebral stroke within the past 6 months, and/or heart failure (New York Association (NYHA) Class IV, at the discretion of the Investigator. 6. Known proliferative retinopathy or maculopathy requiring acute treatment, as judged by the Investigator. 7. Uncontrolled treated or untreated hypertension (systolic blood pressure ≥180 mmHg and/or diastolic blood pressure ≥100 mmHg) (see also Section 1.3 below regarding measurement of blood pressure). 8. Cancer (except basal cell skin cancer or squamous cell skin cancer) or any other clinically significant disorder, except for conditions associated with type 2 diabetes history, which in the Investigator’s opinion could interfere with the results of the trial. 9. Recurrent major hypoglycaemia or hypoglycaemic unawareness, as judged by the Investigator. 10. Known or suspected allergy to trial product(s) or related products. 11. Use of any drug (except for metformin), which in the Investigator’s opinion could interfere with the glucose level (e.g. systemic corticosteroids).

	12. Receipt of any other anti-diabetic investigational drug within 3 months or receipt of any investigational drug not affecting blood glucose within 1 month prior to screening into this trial. 13. Any contraindications or other restrictions to metformin (including known acute or chronic acidosis or planned use of radio-contrast agents containing iodine) or sitagliptin according to the local labelling. 14. Surgery scheduled for the trial duration period (excluding minor surgical procedures performed in local anaesthesia, as judged by the Investigator). 15. Previous participation in the randomised phase of this trial. Re-screening is allowed once within the limits of the recruitment period. 16. Known or suspected abuse of alcohol or narcotics. 17. 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. 18. Mental incapacity, unwillingness or language barrier precluding adequate understanding or cooperation.
Recruitment / selection of participants	No additional information
Intervention(s)	1.2 mg liraglutide (n=225) Liraglutide was started at 0·6 mg/day and escalated by 0·6 mg/week to the allocated dose of 1.2 mg; injection was performed once daily subcutaneously with a pen device. 1.8 mg liraglutide (n=221) Liraglutide was started at 0·6 mg/day and escalated by 0·6 mg/week to the allocated dose of 1.8 mg; injection was performed once daily subcutaneously with a pen device. All participants received treatment for an initial 26 weeks and continued for another 26 weeks in the originally assigned treatment groups.
Cointervention	Metformin Patients received stable background treatment of metformin throughout the trial
Strata 1: People with type 2	Not stated/unclear

diabetes mellitus and heart failure	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 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	NA
Comparator	Sitagliptin (n=219) Patients received 100 mg oral sitagliptin once daily for initial 26 weeks and a further 26 week extension period
Number of participants	665
Duration of follow-up	52 weeks
Indirectness	NA
Method of analysis	ITT
Additional comments	Primary efficacy analyses were done on the full analysis set (randomised participants who were exposed to at least one dose of trial drug and with at least one HbA1c measurement taken after baseline) with missing values imputed by last observation carried forward, and on the per-protocol set. For non-inferiority, we expected similar outcomes to be recorded with the full analysis and per-protocol sets, but for superiority, we judged the full analysis set to be primary. We present data for the full analysis set.

379.2. Study arms

379.2.1. Liraglutide 1.2 mg (N = 225)

Patients received 1.2 mg liraglutide subcutaneously daily for 52 weeks.

379.2.2. Liraglutide 1.8 mg (N = 221)

Patients received 1.8 mg liraglutide subcutaneously daily for 52 weeks.

379.2.3. Sitagliptin (N = 219)

Patients received 100 mg oral sitagliptin once daily for 52 weeks.

379.3. Characteristics

379.3.1. Arm-level characteristics

Characteristic	Liraglutide 1.2 mg (N = 225)	Liraglutide 1.8 mg (N = 221)	Sitagliptin (N = 219)
% Male Sample size	n = 116 ; % = 52	n = 116 ; % = 52	n = 120 ; % = 55
Mean age (SD) (Years (mean, SD)) Mean (SD)	55.9 (9.6)	55 (9.1)	55 (9)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
White Sample size	n = 184 ; % = 82	n = 193 ; % = 87	n = 199 ; % = 91
Hispanic or Latino Sample size	n = 39 ; % = 17	n = 34 ; % = 15	n = 35 ; % = 16
Black Sample size	n = 22 ; % = 10	n = 16 ; % = 7	n = 10 ; % = 5
Asian or Pacific Islander Sample size	n = 7 ; % = 3	n = 4 ; % = 2	n = 2 ; % = 1
Other Sample size	n = 12 ; % = 5	n = 8 ; % = 4	n = 8 ; % = 4
Time since type 2 diabetes diagnosed (Years (mean, SD)) Mean (SD)	6 (4.5)	6.4 (5.4)	6.3 (5.4)
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

Characteristic	Liraglutide 1.2 mg (N = 225)	Liraglutide 1.8 mg (N = 221)	Sitagliptin (N = 219)
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
Other antidiabetic medication used Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
Metformin use Sample size	n = 225 ; % = 100	n = 221 ; % = 100	n = 219 ; % = 100

1

2

380. Pratley, 2009

Bibliographic Reference	Pratley, R. E.; Reusch, J. E.; Fleck, P. R.; Wilson, C. A.; Mekki, Q.; Efficacy and safety of the dipeptidyl peptidase-4 inhibitor alogliptin added to pioglitazone in patients with type 2 diabetes: a randomized, double-blind, placebo-controlled study; Curr Med Res Opin; 2009; vol. 25 (no. 10); 2361-71

380.1. Study details

Secondary publication of another included study- see primary study for details	
Trial name / registration number	NCT00286494
Study type	Randomised controlled trial (RCT)
Study location	125 sites in the regions of United States, Western Europe, Australia and New Zealand, Latin America, plus Hungary, India and South Africa
Study setting	No additional information
Study dates	NR
Sources of funding	Financial support provided by Takeda Global Research and Development Center, Inc,. USA.
Inclusion criteria	Men and women 18–80 years old with type 2 diabetes and a BMI of 23–45 kg/m2 who were treated for at least 3 months (at a stable dose for at least the last month) with a TZD (pioglitazone or rosiglitazone) with or without metformin or sulfonylurea, and who were experiencing inadequate glycemic control (HbA1c of 7.0–10.0% at screening). C-peptide plasma concentrations were to be ≥0.8 ng/mL (fasting) or ≥1.5 ng/mL (post challenge by mixed-meal tolerance test, intravenous glucagon or intravenous arginine).
Exclusion criteria	Patients were excluded if they had active heart failure (New York Heart Association Class III or IV) or had undergone an invasive coronary procedure or had a myocardial infarction within 6 months before screening. Additional exclusion criteria were an abnormal laboratory test result (i.e., creatinine >2.0 mg/dL, alanine amino transferase >2.5 times the upper limit of normal, thyroid-stimulating hormone higher than the upper limit of normal, hemoglobin <12 g/dL for men or <10 g/dL for women or an albumin/creatinine ratio >1000 mg/mg); uncontrolled hypertension (i.e., systolic blood pressure4180 mm Hg or diastolic blood pressure >110 mm

	Hg); history of angioedema with angiotensin converting enzyme inhibitors or angiotensin receptor blockers, or treated diabetic gastric paresis; laser treatment for proliferative diabetic retinopathy; most cancers not in remission for ≥5 years; and pregnancy or lactation. Use of concomitant antidiabetic agents other than metformin and sulfonylurea, weight loss drugs, and non-inhaled glucocorticoids was not permitted within 3 months before assignment or during treatment
Recruitment / selection of participants	No additional information
Intervention(s)	Alogliptin 12.5 mg (n=197) Patients received 26 weeks of once daily treatment with Alogliptin 12.5 mg Alogliptin 25 mg (n=199) Patients received 26 weeks of once daily treatment with Alogliptin 25 mg
Cointervention	Pioglitazone Patients previously treated with pioglitazone continued with the same dose; patients who previously received rosiglitazone switched to an equivalent dosage of pioglitazone 30 mg or 45 mg once daily; Metformin ± sulfonylurea patients previously treated with orally administered metformin or a sulfonylurea continued those medications at the same dosage throughout the study.
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear "Patients were excluded if they had active heart failure (New York Heart Association Class III or IV)." No information in baseline characteristics.
Strata 2: People with atherosclerotic cardiovascular disease	Not stated/unclear "Patients were excluded if they had undergone an invasive coronary procedure or had a myocardial infarction within 6 months before screening." No information in baseline characteristics.
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear CKD not an inclusion/exclusion criteria. People with an abnormal lab test result (including albumin/creatinine ratio 41000mg/mg) were excluded. No information in baseline characteristics.

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 (n=97) Patients received a daily placebo for 26 weeks Patients previously treated with pioglitazone continued with the same dose; patients who previously received rosiglitazone switched to an equivalent dosage of pioglitazone 30 mg or 45 mg once daily Metformin ± sulfonylurea patients previously treated with orally administered metformin or a sulfonylurea continued those medications at the same dosage throughout the study.
Number of participants	493
Duration of follow-up	26 weeks

Indirectness	NA
Method of analysis	ITT
Additional comments	The efficacy population included all randomized patients in the safety population, which, in turn, consisted of all patients who took at least one dose of study drug. Analysis of each efficacy variable included data from patients in the efficacy population who had a baseline assessment and at least one post-baseline assessment. The last-observation-carried-forward method was used to impute missing post-baseline values. The primary efficacy endpoint was the change in HbA1c from baseline to Week 26. Secondary efficacy endpoints included changes in FPG and body weight, as well as incidences of marked hyperglycemia and rescue for hyperglycemia.

380.2. Study arms

380.2.1. Alogliptin 12.5 mg (N = 197)

Patients received a once daily dose of 12.5 mg Alogliptin to ongoing pioglitazone therapy for 26 weeks

380.2.2. Alogliptin 25 mg (N = 199)

Patients received a once daily dose of 25 mg Alogliptin to ongoing pioglitazone therapy for 26 weeks

380.2.3. Placebo (N = 97)

Patients received once daily placebo to ongoing pioglitazone therapy for 26 weeks

380.3. Characteristics

380.3.1. Arm-level characteristics

Characteristic	Alogliptin 12.5 mg (N = 197)	Alogliptin 25 mg (N = 199)	Placebo (N = 97)
% Male Sample size	n = 109 ; % = 55.3	n = 125 ; % = 62.8	n = 53 ; % = 54.6
Mean age (SD) (Years (mean, SD)) Mean (SD)	55.5 (9.4)	55.4 (10.2)	55.2 (10.8)

Characteristic	Alogliptin 12.5 mg (N = 197)	Alogliptin 25 mg (N = 199)	Placebo (N = 97)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
White Sample size	n = 143 ; % = 72.6	n = 152 ; % = 76.4	n = 71 ; % = 73.2
Asian Sample size	n = 18 ; % = 9.1	n = 24 ; % = 12.1	n = 11 ; % = 11.3
Black or African Ameircan Sample size	n = 22 ; % = 11.2	n = 13 ; % = 6.5	n = 10 ; % = 10.3
Other Sample size	n = 14 ; % = 7.1	n = 10 ; % = 5	n = 5 ; % = 5.2
Hispanic Sample size	n = 37 ; % = 18.8	n = 33 ; % = 16.6	n = 10 ; % = 10.3
Non-Hispanic Sample size	n = 160 ; % = 81.2	n = 166 ; % = 83.4	n = 87 ; % = 89.7
Time since type 2 diabetes diagnosed (Years (mean, SD)) Mean (SD)	7.7 (5.6)	7.4 (5.4)	7.8 (6.7)
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
Other antidiabetic medication used	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA

Characteristic	Alogliptin 12.5 mg (N = 197)	Alogliptin 25 mg (N = 199)	Placebo (N = 97)
Sample size			
Metformin Sample size	n = 107 ; % = 54.3	n = 114 ; % = 57.3	n = 56 ; % = 57.7
Sulfonlyurea Sample size	n = 42 ; % = 21.3	n = 44 ; % = 22.1	n = 18 ; % = 18.6
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

1

2

381. Pratley, 2019

Bibliographic Reference	Pratley, R.; Amod, A.; Hoff, S. T.; Kadowaki, T.; Lingvay, I.; Nauck, M.; Pedersen, K. B.; Saugstrup, T.; Meier, J. J.; Oral semaglutide versus subcutaneous liraglutide and placebo in type 2 diabetes (PIONEER 4): a randomised, double-blind, phase 3a trial; Lancet; 2019; vol. 394 (no. 10192); 39-50

381.1. 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	PIONEER 4 [NCT02863419]
Study type	Randomised controlled trial (RCT)
Study location	100 sites in 12 countries [Croatia, Czech Republic, Germany, Hungary, Japan, Latvia, Poland, Slovakia, South Africa, Ukraine, United Arab Emirates, USA]
Study setting	NR
Study dates	Participants were screened between August 10, 2016 and February 7, 2017
Sources of funding	Novo Nordisk
Inclusion criteria	Aged 18 years or older with type 2 diabetes and HbA1c of 7.0–9.5% (53–80.3 mmol/mol), on a stable dose of metformin (≥1500 mg or maximum tolerated) with or without an SGLT2 inhibitor.
Exclusion criteria	Patients taking any medication for diabetes or obesity within 90 days of screening (other than metformin, SGLT2 inhibitor, or short-term insulin [≤14 days]); renal impairment (estimated glomerular filtration rate <60 mL/min per 1·73 m²); proliferative retinopathy or maculopathy requiring acute treatment; and history of acute or chronic pancreatitis.

Recruitment / selection of participants	NR
Intervention(s)	• Oral semaglutide initiated once daily treatment at 3 mg with dose escalation to 7 mg at 4 weeks and to the maintenance dose of 14 mg at 8 weeks • Subcutaneous liraglutide initiated treatment at 0.6 mg once-daily with dose escalation to 1.2 mg after 1 week and to the maintenance dose of 1.8 mg after 2 weeks [Participants were instructed to take the study drug tablet in the morning in a fasted state, with up to half a glass of water, and wait 30 min or longer before their first meal, any other drinks, and taking any other oral medication.]
Cointervention	Treatment was received in addition to existing background glucose-lowering medication.
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear Exclusion criteria state: "Subjects presently classified as being in New York Heart Association Class IV" (see supplement). No information in baseline characteristics.
Strata 2: People with atherosclerotic cardiovascular disease	Not stated/unclear Exclusion criteria state: "Any of the following: myocardial infarction, stroke or hospitalisation for unstable angina or transient ischemic attack within the past 180 days prior to the day of screening" (see supplement). No information in baseline characteristics. Unclear about preceding 180 day timeframe and stable angina/PAD.
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear CKD not an inclusion/exclusion criteria. Exclusion criteria state: "Renal impairment defined as estimated glomerular filtration rate <60 mL/min/1·73 m2 as per Chronic Kidney Disease Epidemiology Collaboration formula."
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	eGFR ≥30mL/min/1.73m2
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Population subgroups	NR
Comparator	Placebo either tablet or subcutaneous to maintain double-dummy design
Number of participants	950 patients were screened and 711 were randomised. Of 285 participants allocated to semaglutide, 241 completed treatment and 277 completed the trial. Of 284 participants allocated to liraglutide, 248 participants completed treatment and 274 participants completed the trial. Of 142 participants allocated to placebo, 125 completed treatment and 134 completed the trial.
Duration of follow-up	26 and 52 weeks
Indirectness	Directly applicable
Method of analysis	ITT Described as treatment policy estimand - all participants randomly assigned to treatment regardless of study drug discontinuation or use of rescue medication. ANCOVA was used to analyse data with multiple imputation to handle missing data. Other The trial product estimand was reported for all participants randomly assigned to treatment under the assumption that all participants remained

	on the study drug for the entire planned duration of the trial and did not use rescue medication. Data were analysed using mixed model for continuous endpoints..
Additional comments	NA

381.2. Study arms

381.2.1. Semaglutide (N = 285)

381.2.2. Liraglutide (N = 284)

381.2.3. Placebo (N = 142)

381.3. Characteristics

381.3.1. Arm-level characteristics

Characteristic	Semaglutide (N = 285)	Liraglutide (N = 284)	Placebo (N = 142)
% Male Sample size	n = 147 ; % = 52	n = 149 ; % = 52	n = 74 ; % = 52
Mean age (SD) Mean (SD)	56 (10)	56 (10)	57 (10)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
White Sample size	n = 208 ; % = 73	n = 212 ; % = 75	n = 99 ; % = 70
Black or African American Sample size	n = 12 ; % = 4	n = 9 ; % = 3	n = 8 ; % = 6
Asian Sample size	n = 39 ; % = 14	n = 36 ; % = 13	n = 19 ; % = 13

Characteristic	Semaglutide (N = 285)	Liraglutide (N = 284)	Placebo (N = 142)
Other Sample size	n = 3 ; % = 1	n = 10 ; % = 4	n = 4 ; % = 3
Not available Sample size	n = 23 ; % = 8	n = 17 ; % = 6	n = 12 ; % = 8
Hispanic or Latino Sample size	n = 17 ; % = 6	n = 18 ; % = 6	n = 5 ; % = 4
Not hispanic or latino Sample size	n = 268 ; % = 94	n = 266 ; % = 94	n = 137 ; % = 96
Comorbidities Nominal	NR	NR	NR
Presence of frailty Nominal	NR	NR	NR
Time since type 2 diabetes diagnosed Mean (SD)	7.8 (5.7)	7.3 (5.3)	7.8 (5.5)
Cardiovascular risk factors Nominal	NR	*empty data*	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

Characteristic	Semaglutide (N = 285)	Liraglutide (N = 284)	Placebo (N = 142)
Other antidiabetic medication used SGLT2 Sample size	n = 74 ; % = 26	n = 73 ; % = 26	n = 36 ; % = 25
Blood pressure-lowering medication used Nominal	NR	NR	NR
Statins/lipid-lowering medication used Nominal	NR	NR	NR
Other treatment being received Nominal	NR	NR	NR

1

2

382. Pratley, 2011

Bibliographic Reference	Pratley, R; Nauck, M; Bailey, T; Montanya, E; Cuddihy, R; Filetti, S; Garber, A; Thomsen, A B; Hartvig, H; Davies, M; One year of liraglutide treatment offers sustained and more effective glycaemic control and weight reduction compared with sitagliptin, both in combination with metformin, in patients with type 2 diabetes: a randomised, parallel-group, open-label trial.; International journal of clinical practice; 2011; vol. 65 (no. 4); 397-407

382.1. Study details

Secondary publication of another included study- see primary study for details	Parent study Pratley 2010 Pratley RE, Nauck M, Bailey T, Montanya E, Cuddihy R, Filetti S, Thomsen AB, Søndergaard RE, Davies M; 1860-LIRA-DPP-4 Study Group. Liraglutide versus sitagliptin for patients with type 2 diabetes who did not have adequate glycaemic control with metformin: a 26-week, randomised, parallel-group, open-label trial. Lancet. 2010 Apr 24;375(9724):1447-56. doi: 10.1016/S0140-6736(10)60307-8.
Other publications associated with this study included in review	

383. Pratley, 2018

Bibliographic Reference	Pratley, Richard E; Aroda, Vanita R; Lingvay, Ildiko; Ludemann, Jorg; Andreassen, Camilla; Navarria, Andrea; Viljoen, Adie; Semaglutide versus dulaglutide once weekly in patients with type 2 diabetes (SUSTAIN 7): a randomised, open-label, phase 3b trial.; The lancet. Diabetes & endocrinology; 2018; vol. 6 (no. 4); 275-286

383.1. Study details

Trial name / registration number	SUSTAIN 7 / NCT02648204.
Study type	Randomised controlled trial (RCT)
Study location	194 sites in 16 countries (Bulgaria, Croatia, Finland, Germany, Greece, Hong Kong, India, Ireland, Latvia, Lithuania, Portugal, Romania, Slovakia, Spain, the UK, and the USA)
Study setting	Hospitals, clinical institutions, or private practices
Study dates	6 January 2016 to 22 June 2016
Sources of funding	Novo Nordisk. Numerous authors declare honoraria and funding from multiple pharmaceutical companies
Inclusion criteria	1. Informed consent obtained before any trial-related activities. Trial-related activities are any procedures that are carried out as part of the trial, including activities to determine suitability for the trial 2. Male or female, age ≥18 years at the time of signing informed consent 3. Patients with type 2 diabetes diagnosed clinically ≥90 days prior to screening 4. HbA1c 7·0–10·5% (53–91 mmol/mol) (both inclusive) 5. Patients on stable diabetes treatment with metformin (minimum of 1,500 mg/day or maximal tolerated dose documented in the patient medical record) for 90 days prior to screening
Exclusion criteria	1. Known or suspected hypersensitivity to trial product(s) or related products 2. Previous participation in this trial. Participation is defined as signed informed consent Female who is pregnant, breast-feeding or intends to become pregnant or is of child-bearing potential and not using an adequate contraceptive method (adequate contraceptive measures as required by local regulation or practice). Germany: Only highly effective methods of birth control are accepted (i.e. one that results in less than 1%

	per year failure rate when used consistently and correctly such as implants, injectables, combined oral contraceptives, some intrauterine device), or sexual abstinence or vasectomised partner. Ireland: Adequate contraceptive measures are defined as established use of combined oral contraceptives, injected or implanted hormonal methods of contraception, sterilisation, intrauterine device or intrauterine system or consistent use of barrier methods together with the use of spermicide and sexual abstinence. United Kingdom: Adequate contraceptive measures are defined as established use of oral, intravaginal, transdermal combined oestrogen and progestogen hormonal methods of contraception; oral, injected or implanted progestogen only hormonal methods of contraception; placement of an intrauterine device or intrauterine hormone releasing system, bilateral tubal occlusion, barrier methods of contraception (condom or occlusive cap with spermicidal foam/gel/film/cream/suppository), female sterilisation, vasectomised partner (where partner is sole partner of subject), or true abstinence (when in line with preferred and usual lifestyle). Portugal: Only highly effective methods of birth control (i.e. one that results in less than 1% per year failure rate when used consistently) are accepted, such as sexual abstinence (when in line with the preferred and usual lifestyle), combined (oestrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, transdermal), progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable), intrauterine device (IUD), intrauterine hormone-releasing system (IUS), bilateral tubal occlusion or vasectomised partner. 3. Receipt of any investigational medicinal product within 90 days before screening 4. Any condition, which in the investigator’s opinion might jeopardise subject’s safety or compliance with the protocol 5. 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. An exception is short-term insulin treatment for acute illness for a total of ≤14 days 6. History of pancreatitis (acute or chronic) 7. Screening calcitonin ≥50 ng/L 8. Family or personal history of Multiple Endocrine Neoplasia Type 2 or Medullary Thyroid Carcinoma 9. Renal impairment defined as eGFR <60 mL/min/1·73 m2 as per Chronic Kidney Disease Epidemiology Collaboration 10. Any of the following: myocardial infarction (MI), stroke or hospitalisation for unstable angina and/or transient ischaemic attack (TIA) within the past 180 days prior to the day of screening

	11. Patients presently classified as being in New York Heart Association (NYHA) Class IV 12. Planned coronary, carotid or peripheral artery revascularisation on the day of screening 13. Proliferative retinopathy or maculopathy requiring acute treatment 14. History or presence of malignant neoplasms within the last 5 years (except basal and squamous cell skin cancer and in situ carcinomas) 15. Anticipated initiation or change in concomitant medications (for more than 14 consecutive days or on a frequent basis) known to affect weight or glucose metabolism (e.g. orlistat, thyroid hormones, corticosteroids)
Recruitment / selection of participants	No additional information
Intervention(s)	Semaglutide 0.5 mg (n= 301) Semaglutide 1.0 mg (n = 300) Patients received study medication subcutaneously for 40 weeks, followed by follow-up for 5 weeks. Injections were self-administered in the thigh, abdomen, or upper arm, at any time of day irrespective of meals. Injections were administered on the same day of the week. A fixed dose-escalation procedure was used for semaglutide: the dose was doubled every 4 weeks from a starting dose of 0·25 mg until the trial maintenance dose (0·5 or 1·0 mg) was reached. Once trial maintenance doses were reached, they were not changed during the course of the trial. Patients were required to continue their pre-trial dose of metformin throughout the trial.
Cointervention	Metformin: Patients were required to continue their pre-trial dose of metformin throughout the trial.
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear People with heart failure (New York Heart Association Class IV) were excluded. No information in baseline characteristics.
Strata 2: People with atherosclerotic cardiovascular disease	Not stated/unclear Exclusion criteria state: "Any of the following: myocardial infarction (MI), stroke or hospitalisation for unstable angina and/or transient ischaemic attack (TIA) within the past 180 days prior to the day of screening" . No information in baseline characteristics. Not clear about events preceding the 180 days or stable angina/PAD.

Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear People with CKD stage 3 and above were excluded. No information in baseline characteristics. Unclear about stages 1 and 2.
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	Dulaglutide 0.75 mg (n = 300) Dulaglutide 1.5 mg (n = 300)

	Patients received study medication subcutaneously for 40 weeks, followed by follow-up for 5 weeks. Injections were self-administered in the thigh, abdomen, or upper arm, at any time of day irrespective of meals. Injections were administered on the same day of the week. Patients randomised to dulaglutide received 0·75 or 1·5 mg without dose escalation, in accordance with the dulaglutide clinical development programme and clinical product labelling. Once trial maintenance doses were reached, they were not changed during the course of the trial. Patients were required to continue their pre-trial dose of metformin throughout the trial.
Number of participants	1201
Duration of follow-up	45 weeks; Patients received study medication subcutaneously for 40 weeks, followed by follow-up for 5 weeks
Indirectness	NA
Method of analysis	ACA ITT
Additional comments	The authors used a mixed model for repeated measurements for the analysis of the primary outcome of change in continuous endpoints at week 40 from each individual baseline using data for all patients randomly assigned to treatment and exposed to at least one dose of trial product (full analysis set) obtained while on treatment and before onset of rescue medication. The primary HbA1c and confirmatory bodyweight endpoints were adjusted for multiple testing. Safety outcomes were summarised descriptively by use of data for all patients randomised to treatment who were exposed to at least one dose of trial product (safety analysis set, equivalent to the full analysis set) obtained while on treatment (on-treatment data). Fatal events, confirmed cardiovascular events by the event adjudication committee, confirmed malignant neoplasms, and diabetic retinopathy were summarised descriptively by use of data for all patients in the safety analysis set obtained from randomisation to the end of the trial regardless of treatment exposure or usage of rescue medication (in-trial data)

383.2. Study arms

383.2.1. Semaglutide 0.5 mg (N = 301)

Patients received 0.5 mg semaglutide once a week subcutaneously for 40 weeks on the same day of the week at any time of day

383.2.2. Dulaglutide 0.75 mg (N = 300)

Patients received 0.75 mg dulaglutide once a week subcutaneously for 40 weeks on the same day of the week at any time of day

383.2.3. Semaglutide 1.0 mg (N = 300)

Patients received 1.0 mg semaglutide once a week subcutaneously for 40 weeks on the same day of the week at any time of day

383.2.4. Dulaglutide 1.5 mg (N = 300)

Patients received 1.5 mg dulaglutide once a week subcutaneously for 40 weeks on the same day of the week at any time of day

383.3. Characteristics

383.3.1. Arm-level characteristics

Characteristic	Semaglutide 0.5 mg (N = 301)	Dulaglutide 0.75 mg (N = 300)	Semaglutide 1.0 mg (N = 300)	Dulaglutide 1.5 mg (N = 300)
% Male Semaglutide 0.5 mg n = 301, Dulaglutide 0.75 mg n = 299, Semaglutide 1.0 mg n = 300, Dulaglutide 1.5 mg n = 299, Sample size	n = 169 ; % = 56	n = 160 ; % = 54	n = 162 ; % = 54	n = 171 ; % = 57
Mean age (SD) (Years (mean, SD)) Semaglutide 0.5 mg n = 301, Dulaglutide 0.75 mg n = 299, Semaglutide 1.0 mg n = 300, Dulaglutide 1.5 mg n = 299, Mean (SD)	56 (10.9)	55 (10.4)	55 (10.6)	56 (10.6)
Ethnicity Semaglutide 0.5 mg n = 301, Dulaglutide 0.75 mg n = 299, Semaglutide 1.0 mg	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA

Characteristic	Semaglutide 0.5 mg (N = 301)	Dulaglutide 0.75 mg (N = 300)	Semaglutide 1.0 mg (N = 300)	Dulaglutide 1.5 mg (N = 300)
n = 300, Dulaglutide 1.5 mg n = 299, Sample size				
White Sample size	n = 233 ; % = 77	n = 232 ; % = 78	n = 243 ; % = 81	n = 220 ; % = 74
Black or African American Sample size	n = 17 ; % = 6	n = 17 ; % = 6	n = 18 ; % = 6	n = 18 ; % = 6
Asian Sample size	n = 50 ; % = 17	n = 48 ; % = 16	n = 38 ; % = 13	n = 55 ; % = 18
Other Sample size	n = 1 ; % = 0.33	n = 2 ; % = 1	n = 1 ; % = 0.33	n = 6 ; % = 2
Hispanic or Latino Sample size	n = 29 ; % = 10	n = 31 ; % = 10	n = 35 ; % = 12	n = 43 ; % = 14
Not hispanic or latino Sample size	n = 272 ; % = 90	n = 268 ; % = 90	n = 265 ; % = 88	n = 256 ; % = 86
Time since type 2 diabetes diagnosed (Years (mean, SD)) Semaglutide 0.5 mg n = 301, Dulaglutide 0.75 mg n = 299, Semaglutide 1.0 mg n = 300, Dulaglutide 1.5 mg n = 299, Mean (SD)	7.7 (5.9)	7 (5.5)	7.3 (5.7)	7.6 (5.6)
Smoking status Semaglutide 0.5 mg n = 301, Dulaglutide 0.75 mg n = 299, Semaglutide 1.0 mg n = 300, Dulaglutide 1.5 mg n = 299, Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Alcohol consumption Semaglutide 0.5 mg n = 301, Dulaglutide 0.75 mg n = 299, Semaglutide 1.0 mg	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR

Characteristic	Semaglutide 0.5 mg (N = 301)	Dulaglutide 0.75 mg (N = 300)	Semaglutide 1.0 mg (N = 300)	Dulaglutide 1.5 mg (N = 300)
n = 300, Dulaglutide 1.5 mg n = 299, Sample size				
Presence of severe mental illness Semaglutide 0.5 mg n = 301, Dulaglutide 0.75 mg n = 299, Semaglutide 1.0 mg n = 300, Dulaglutide 1.5 mg n = 299, Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
People with significant cognitive impairment Semaglutide 0.5 mg n = 301, Dulaglutide 0.75 mg n = 299, Semaglutide 1.0 mg n = 300, Dulaglutide 1.5 mg n = 299, Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
People with a learning disability Semaglutide 0.5 mg n = 301, Dulaglutide 0.75 mg n = 299, Semaglutide 1.0 mg n = 300, Dulaglutide 1.5 mg n = 299, Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Other antidiabetic medication used Semaglutide 0.5 mg n = 301, Dulaglutide 0.75 mg n = 299, Semaglutide 1.0 mg n = 300, Dulaglutide 1.5 mg n = 299, Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
Metformin Sample size	n = 301 ; % = 100	n = 299 ; % = 100	n = 300 ; % = 100	n = 299 ; % = 100
Blood pressure-lowering medication used Semaglutide 0.5 mg n = 301, Dulaglutide 0.75 mg n	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR

Characteristic	Semaglutide 0.5 mg (N = 301)	Dulaglutide 0.75 mg (N = 300)	Semaglutide 1.0 mg (N = 300)	Dulaglutide 1.5 mg (N = 300)
= 299, Semaglutide 1.0 mg n = 300, Dulaglutide 1.5 mg n = 299, Sample size				
Statins/lipid-lowering medication used Semaglutide 0.5 mg n = 301, Dulaglutide 0.75 mg n = 299, Semaglutide 1.0 mg n = 300, Dulaglutide 1.5 mg n = 299, Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Other treatment being received Semaglutide 0.5 mg n = 301, Dulaglutide 0.75 mg n = 299, Semaglutide 1.0 mg n = 300, Dulaglutide 1.5 mg n = 299, Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR

1

2

384. Punthakee, 2012

Bibliographic Reference	Punthakee, Z.; Bosch, J.; Dagenais, G.; Diaz, R.; Holman, R.; Probstfield, J.; Ramachandran, A.; Riddle, M.; Rydén, L. E.; Zinman, B.; Afzal, R.; Yusuf, S.; Gerstein, H.; Design, history and results of the Thiazolidinedione Intervention with vitamin D Evaluation (TIDE) randomised controlled trial; Diabetologia; 2012; vol. 55 (no. 1); 36-45

384.1. 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	TIDE (Thiazolidinedione Intervention with vitamin D Evaluation) [NCT00879970]
Study type	Randomised controlled trial (RCT)
Study location	Multicentre trial in 33 countries (Argentina, Brazil, Bulgaria, Canada, Chile, Columbia, Croatia, Czech Republic, Denmark, Ecuador, Finland, Germany, Greece, Hong Kong, India, Ireland, Italy, Latvia, Malaysia, Mexico, Netherlands, Norway, Pakistan, Peru, Philippines, Poland, Romania, Russia, Slovakia, South Africa, Sweden, Taiwan, Thailand, Ukraine, United Kingdom, USA)
Study setting	Participants were recruited from outpatient primary care and speciality clinics.
Study dates	Participants were recruited between June 2009 and July 2010
Sources of funding	GlaxoSmithKline
Inclusion criteria	• Type 2 diabetes and an HbA1c from 6.5% to 9.5% • Drug naive or taking up to two non-insulin glucose-lowering medications • Were at risk of cardiovascular disease on the basis of: (1) age at least 50 years with a prior cardiovascular event; (2) age at least 55 years with documented arterial stenosis, albuminuria, ankle

	brachial index <0.9 or left ventricular hypertrophy; or (3) age at least 60 years with at least two risk factors (tobacco use, high LDL-cholesterol, low HDL-cholesterol or high triacylglycerols, hypertension or obesity
Exclusion criteria	• Cardiovascular event within 30 days before randomisation • History of pulmonary oedema, symptomatic heart failure (New York Heart Association class II–IV) • Known left ventricular ejection fraction below 40% or use of a loop diuretic • Cancer diagnosed in the prior 3 years or active treatment for cancer (other than non-melanoma skin cancer or cervical carcinoma in situ) • Fracture in the prior year • Known osteomalacia, or hypercalcaemia
Recruitment / selection of participants	After 3 weeks of active rosiglitazone and vitamin D run-in, participants were randomised to either placebo, pioglitazone, or rosiglitazone.
Intervention(s)	Pioglitazone 30 mg daily to be increased to 45 mg daily by 12 months
Cointervention	The management of glucose levels and all other conditions was at the discretion of the local physician as informed by clinical practice guidelines and the relevant evidence; open label TZDs were not permitted.
Strata 1: People with type 2 diabetes mellitus and heart failure	People without heart failure Exclusion criteria state "symptomatic heart failure (New York Heart Association class II–IV), known left ventricular ejection fraction below 40%".
Strata 2: People with atherosclerotic cardiovascular disease	Not stated/unclear Inclusion criteria: "(1) age at least 50 years with a prior cardiovascular event; (2)age at least 55 years with documented arterial stenosis, albuminuria, ankle brachial index<0.9 or left ventricular hypertrophy; or (3)age at least 60 years with at least two risk factors (tobacco use, high LDL-cholesterol, low HDL-cholesterol or high triacylglycerols, hypertension or obesity)." Baseline characteristics reports 35% of people had prior cardiovascular disease. Cardiovascular disease defined as: "myocardial infarction; stroke; stable or unstable angina; valvular heart disease; arrhythmia; cardiac

	arrest; heart failure; coronary, carotid or peripheral revascularisation; amputation or intermittent claudication."
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear CKD 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 Study recruited participants at high risk of cardiovascular event due to either (1) age at least 50 years with a prior cardiovascular event; (2) age at least 55 years with documented arterial stenosis, albuminuria, ankle brachial index <0.9 or left ventricular hypertrophy; or (3) age at least 60 years with at least two risk factors (tobacco use, high LDL-cholesterol, low HDL-cholesterol or high triacylglycerols, hypertension or obesity
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	2434 participants were screened and 1332 were randomised. 392 were assigned to pioglitazone, of which 3 withdrew and 150 stopped the drug. 541 were assigned to placebo, of which 1 was lost, 3 withdrew, and 214 stopped the drug. 399 participants were assigned to rosiglitazone
Duration of follow-up	Mean of 16 days
Indirectness	Directly applicable
Method of analysis	ITT
Additional comments	The study also included a rosiglitazone arm, however, these results have not been extracted due to protocol exclusion.

384.2. Study arms

384.2.1. Pioglitazone (N = 392)

384.2.2. Placebo (N = 541)

384.3. Characteristics

384.3.1. Arm-level characteristics

Characteristic	Pioglitazone (N = 392)	Placebo (N = 541)
Mean age (SD) Mean (SD)	66.3 (6.6)	66.4 (6.8)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA
White Sample size	n = 241 ; % = 62	n = 330 ; % = 61
South Asian Sample size	n = 45 ; % = 12	n = 63 ; % = 12
Black Sample size	n = 35 ; % = 8.9	n = 45 ; % = 8.3

Characteristic	Pioglitazone (N = 392)	Placebo (N = 541)
Latin American Sample size	n = 26 ; % = 6.6	n = 33 ; % = 6.1
Wast Asian Sample size	n = 6 ; % = 1.5	n = 12 ; % = 2.3
Other Sample size	n = 38 ; % = 10	n = 57 ; % = 11
Comorbidities Sample size	n = NA ; % = NA	n = NA ; % = NA
Hypertension Sample size	n = 346 ; % = 88	n = 475 ; % = 88
Dyslipidemia Sample size	n = 299 ; % = 76	n = 408 ; % = 75
Cardiovascular disease Sample size	n = 131 ; % = 33	n = 187 ; % = 35
Myocardial infarction Sample size	n = 54 ; % = 14	n = 74 ; % = 14
Stroke Sample size	n = 15 ; % = 3.8	n = 19 ; % = 3.5
Heart failure (NYHA 1 only) Sample size	n = 11 ; % = 2.8	n = 14 ; % = 2.6
Laser/vitrectomy for retinopathy Sample size	n = 9 ; % = 2.3	n = 12 ; % = 2.2
Cancer Sample size	n = 23 ; % = 5.9	n = 32 ; % = 5.9
osteoporosis Sample size	n = 10 ; % = 2.6	n = 15 ; % = 2.8
Fracture Sample size	n = 45 ; % = 12	n = 75 ; % = 14
Presence of frailty Nominal	NA	NA

Characteristic	Pioglitazone (N = 392)	Placebo (N = 541)
Time since type 2 diabetes diagnosed Sample size	n = 8.5 ; % = 6.3	n = 8.7 ; % = 6.9
Cardiovascular risk factors Nominal	NR	NR
Smoking status Sample size	n = 46 ; % = 12	n = 64 ; % = 12
Alcohol consumption Sample size	n = 143 ; % = 37	n = 173 ; % = 32
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 BMI >30 kg/m2 Sample size	n = 187 ; % = 48	n = 258 ; % = 48
Other antidiabetic medication used Sample size	n = NA ; % = NA	n = NA ; % = NA
Biguanide Sample size	n = 313 ; % = 80	n = 442 ; % = 82
Sulfonylurea Sample size	n = 188 ; % = 48	n = 248 ; % = 46
TZD Sample size	n = 17 ; % = 4.3	n = 26 ; % = 4.8
DPP-4 inhibitor Sample size	n = 8 ; % = 2	n = 15 ; % = 2.8
Other Sample size	n = 11 ; % = 2.8	n = 12 ; % = 2.2
Blood pressure-lowering medication used	n = NA ; % = NA	n = NA ; % = NA

Characteristic	Pioglitazone (N = 392)	Placebo (N = 541)
Sample size		
ACE-inhibitor or ARB Sample size	n = 297 ; % = 76	n = 401 ; % = 74
Thiazide diuretic Sample size	n = 115 ; % = 29	n = 167 ; % = 31
Other diuretic Sample size	n = 34 ; % = 8.7	n = 51 ; % = 9.4
Statins/lipid-lowering medication used Sample size	n = 263 ; % = 67	n = 353 ; % = 65
Other treatment being received Sample size	n = NA ; % = NA	n = NA ; % = NA
Antiplatelet agent Sample size	n = 214 ; % = 55	n = 306 ; % = 57
Nitrate Sample size	n = 23 ; % = 5.9	n = 33 ; % = 6.1
Vitamin D supplement Sample size	n = 47 ; % = 12	n = 57 ; % = 11
% Female Sample size	n = 167 ; % = 43	n = 220 ; % = 41

1

2

385. Radholm, 2018

Bibliographic Reference	Radholm, Karin; Figtree, Gemma; Perkovic, Vlado; Solomon Scott, D; Mahaffey Kenneth, W; de Zeeuw, Dick; Fulcher, Greg; Barrett Terrance, D; Shaw, Wayne; Desai, Mehul; Matthews David, R; Neal, Bruce; Canagliflozin and Heart Failure in Type 2 Diabetes Mellitus: Results From the CANVAS Program.; Circulation; 2018; vol. 138 (no. 5); 458-468

385.1. Study details

Secondary publication of another included study- see primary study for details	Mahaffey Kenneth, W, Neal, Bruce, Perkovic, Vlado et al. (2018) Canagliflozin for Primary and Secondary Prevention of Cardiovascular Events: Results From the CANVAS Program (Canagliflozin Cardiovascular Assessment Study). Circulation 137(4): 323-334
Other publications associated with this study included in review	Neal, Bruce; Perkovic, Vlado; de Zeeuw, Dick et al. (2013) Rationale, design, and baseline characteristics of the Canagliflozin Cardiovascular Assessment Study (CANVAS)--a randomized placebo-controlled trial. American heart journal; 2013; vol. 166 (no. 2); 217-223e11 Neal, Bruce, Perkovic, Vlado, Matthews David, R et al. (2017) Rationale, design and baseline characteristics of the CANagliflozin cardioVascular Assessment Study-Renal (CANVAS-R): A randomized, placebo-controlled trial. Diabetes, obesity & metabolism 19(3): 387-393 Zhou, Z, Lindley R, I, Radholm, K et al. (2019) Canagliflozin and Stroke in Type 2 Diabetes Mellitus: Results from the Randomized CANVAS Program Trials. Stroke 50(2): 396-404
Trial name / registration number	CANVAS Program combines the CANVAS trial (NCT01032629) and the CANVAS-R trial (NCT01989754)

385.2. Study arms

385.2.1. Canagliflozin (N = 5795)

Oral canagliflozin 100mg once a day or 300mg once a day (groups combined in the study analysis). Mean duration of follow up was 188 weeks. Concomitant therapy: Use of other background therapy for glycaemic management and other risk factor control was according to best practice instituted in line with local guidelines.

385.2.2. Placebo (N = 4347)

Oral matching placebo once a day. Mean duration of follow up was 188 weeks. Concomitant therapy: Use of other background therapy for glycaemic management and other risk factor control was according to best practice instituted in line with local guidelines.

386. Raman, 2022

Bibliographic Reference	Raman, R.B.; Kumar, D.; Roushan, R.; Comparative Study of Efficacy and Safety of Empagliflozin vs Linagliptin as Add on Therapy to Insulin in Patients of Type 2 Diabetes Mellitus and Chronic Kidney Disease in Tertiary Care Centre of Eastern India; International Journal of Pharmaceutical Sciences Review and Research; 2022; vol. 77 (no. 2); 139-145

386.1. Study details

Secondary publication of another included study- see primary study for details	No
Other publications associated with this study included in review	N/A
Trial name / registration number	Raman 2022
Study type	Randomised controlled trial (RCT) Open label, single centre RCT
Study location	Eastern India
Study setting	Tertiary care setting
Study dates	October 2021 - September 2022
Sources of funding	Unclear. Statement that the authors received no financial support for the research, authorship, and /or publication of this article.
Inclusion criteria	• Age over 18 years • Diagnosis of T2DM and diagnosis of CKD • HbA1c of 7.5-10% • eGFR <60ml/min per 1.73m2 • Patients on insulin: "any insulin regimen as per equipment to achieve their glycaemia control"

Exclusion criteria	• eGFR <15 ml/min per 1.73m2 • Renal transplant • Patients on dialysis • Urinary tract infections or other systemic infections • Haematuria • Decompensated heart failure • Liver failure • Debilitating illness that may adversely affect renal function • BMI <18.5kg/m2
Recruitment / selection of participants	No information
Intervention(s)	Empagliflozin (10 mg daily) added to background insulin therapy
Strata 1: People with type 2 diabetes mellitus and heart failure	People without heart failure Exclusion criteria: Decompensated heart failure
Strata 2: People with atherosclerotic cardiovascular disease	Not stated/unclear No information
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	People with chronic kidney disease Inclusion criteria: diagnosed case of 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 No information

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	Not stated/unclear No information
Subgroup 4: People with obesity	Not stated/unclear No information
Subgroup 5: eGFR category at baseline	Not stated/unclear eGFR <60ml/min per 1.73m2 an inclusion criteria. eGFR <15ml/min per 1.73 m2 and exclusion criteria eGFR must be between 15-60ml/min per 1.73m2, does not align with specified categories Only mean baseline eGFR reported
Subgroup 6: Albuminuria category at baseline	Not stated/unclear Mean baseline UPCR reported (not UACR)
Comparator	Linagliptin (5mg daily) added to background insulin therapy
Number of participants	N= 107
Duration of follow-up	1 year
Indirectness	None
Additional comments	Not specified

386.2. Study arms

386.2.1. Empagliflozin + insulin (N = 52)

Empagliflozin (10mg daily) added to background insulin therapy

386.2.2. Linagliptin + insulin (N = 55)

Linagliptin (5mg daily) added to background insulin therapy

386.3. Characteristics

386.3.1. Arm-level characteristics

Characteristic	Empagliflozin + insulin (N = 52)	Linagliptin + insulin (N = 55)
% Male Sample size	n = 24 ; % = 46	n = 26 ; % = 47
Mean age (SD) (years) Mean (SD)	61.58 (7.52)	63.32 (7.47)
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)	13.16 (5.96)	13.67 (5.13)
HbA1c (%) Mean (SD)	8.47 (1.23)	8.42 (1.12)
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
Alcohol consumption	n = NR ; % = NR	n = NR ; % = NR

Characteristic	Empagliflozin + insulin (N = 52)	Linagliptin + insulin (N = 55)
Sample size		
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)	NR (NR)	NR (NR)
BMI Mean (SD)	NR (NR)	NR (NR)
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)	41.32 (12.77)	40.94 (11.42)
Other antidiabetic medication used Sample size	n = NR ; % = NR	n = NR ; % = NR
Blood pressure-lowering medication used Sample size	n = NA ; % = NA	n = NA ; % = NA
ACE inhibitors or ARB Sample size	n = 39 ; % = 75	n = 43 ; % = 78
Beta-blockers Sample size	n = 20 ; % = 38	n = 18 ; % = 33
Loop diuretics	n = 2 ; % = 4	n = 3 ; % = 5

Characteristic	Empagliflozin + insulin (N = 52)	Linagliptin + insulin (N = 55)
Sample size		
Thiazide diuretics Sample size	n = 15 ; % = 29	n = 13 ; % = 24
Calcium channel blockers Sample size	n = 17 ; % = 33	n = 20 ; % = 36
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

1

2

387. Rasouli, 2024

Bibliographic Reference	Rasouli, N; Younes, N; Ghosh, A; Albu, J; Cohen, RM; DeFronzo, RA; Diaz, E; Sayyed Kassem, L; Luchsinger, JA; McGill, JB; et, al.; Longitudinal Effects of Glucose-Lowering Medications on β-Cell Responses and Insulin Sensitivity in Type 2 Diabetes: the GRADE Randomized Clinical Trial; Diabetes care; 2024

387.1. Study details

Secondary publication of another included study- see primary study for details	Group 2022 (Grade Study Research Group). Glycemia Reduction in Type 2 Diabetes - Microvascular and Cardiovascular Outcomes. New England Journal of Medicine; 2022; vol. 387 (no. 12); 1075-1088.
Trial name / registration number	The Grade Research Study Group [NCT01794143]

388. Raz, 2008

Bibliographic Reference	Raz, I.; Chen, Y.; Wu, M.; Hussain, S.; Kaufman, K. D.; Amatruda, J. M.; Langdon, R. B.; Stein, P. P.; Alba, M.; Efficacy and safety of sitagliptin added to ongoing metformin therapy in patients with type 2 diabetes; Curr Med Res Opin; 2008; vol. 24 (no. 2); 537-50

388.1. 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	NCT00337610
Study type	Randomised controlled trial (RCT)
Study location	Multinational trial
Study setting	NR
Study dates	NR
Sources of funding	Merck & Co.
Inclusion criteria	• Patients with T2DM • 18–78 years of age • Currently on metformin monotherapy or any other single OHA, or being treated with metformin in combination with another OHA • HbA1c 8-11% at screening
Exclusion criteria	• Patient received treatment with insulin within 8 weeks prior to screening • Treatment with a PPAR agent (e.g., pioglitazone or rosiglitazone) or incretin mimetics (e.g., exenatide) within 12 weeks • Had type 1 diabetes

	• Body mass index (BMI) < 20 kg/m2 or > 43 kg/m2 • Fasting plasma glucose (FPG) during run-in that was consistently < 7.2 mmol/L or > 15.6 mmol/L. • Pregnant or breastfeeding
Recruitment / selection of participants	Participants on other OHAs: run-in period where OHAs were switched to metformin monotherapy, which was then titrated upward to a dose of at least 1500 mg per day (maximum, 2550 mg per day). Participants then entered a metformin dose-stable diet and exercise period of at least 6 weeks Participants already on metformin at stable dose of at least 1500 mg per day: entered directly into the 6-week dose-stable diet and exercise period. At the end of the run-in period, participants with HbA1c 8.0-11.0% were eligible to continue into a 2-week single-blind placebo run-in period. Participants who showed adequate treatment compliance and a fasting fingerstick glucose ≥7.2 mmol/L and ≤15.6 mmol/L were randomised to either placebo or sitagliptin.
Intervention(s)	Sitagliptin 100 mg once daily
Cointervention	Participants received ongoing stable metformin dose. Use of other OHAs was not permitted, but participants were allowed stable doses of lipid lowering medications, anti-hypertensive drugs, thyroid hormone medications, and hormonal contraceptives. Participants who failed to achieve or maintain pre-specified FPG levels after randomization received rescue therapy with glipizide (administered according to the product label).
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	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	Mixed population
Subgroup 5: eGFR category at baseline	Not stated/unclear
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Population subgroups	Prespecified subgroup analysis based on median BMI (30.7 kg/m2)
Comparator	Placebo
Number of participants	544 participants were screened and 190 were randomised. 96 participants were assigned to sitagliptin, 17 discontinued, 6 received rescue therapy, and 79 completed. 94 participants were assigned to placebo, 14 discontinued, 23 received rescue therapy, and 80 completed
Duration of follow-up	30 weeks
Indirectness	Directly applicable

Method of analysis	Not stated/unclear Efficacy outcomes: full-analysis set populations comprised of all randomised patients who had received at least one dose of sitagliptin or placebo and had a baseline plus at least on post randomization measurement. ANCOVA was used to compare treatment groups for continuous efficacy parameters. Missing data were handled using the last-observation-carried-forward (LOCF) method. Safety and tolerability: all-patients-as-treated population composed of all randomized patients who had received at least one dose of double-blind study medication.
Additional comments	NA

388.2. Study arms

388.2.1. Sitagliptin (N = 96)

388.2.2. Placebo (N = 94)

388.3. Characteristics

388.3.1. Arm-level characteristics

Characteristic	Sitagliptin (N = 96)	Placebo (N = 94)
Mean age (SD) Mean (SD)	53.6 (9.5)	56.1 (9.5)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA
White Sample size	n = 40 ; % = 42	n = 44 ; % = 47
Hispanic Sample size	n = 31 ; % = 32	n = 24 ; % = 25
Black Sample size	n = 3 ; % = 3	n = 1 ; % = 1

Characteristic	Sitagliptin (N = 96)	Placebo (N = 94)
Multiracial Sample size	n = 21 ; % = 22	n = 23 ; % = 25
Other Sample size	n = 1 ; % = 1	n = 2 ; % = 2
Comorbidities Nominal	NR	NR
Presence of frailty Nominal	NA	NA
Time since type 2 diabetes diagnosed (years) Mean (SD)	8.4 (6.5)	7.3 (5.3)
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
Weight (kg) Mean (SD)	81.5 (16.8)	81.2 (19.4)
BMI (kg/m2) Mean (SD)	30.1 (4.4)	30.4 (5.3)
Number of people with obesity BMI>30.1 kg/m2 Sample size	n = 47 ; % = 50	n = 46 ; % = 50
Other antidiabetic medication used	n = NA ; % = NA	n = NA ; % = NA

Characteristic	Sitagliptin (N = 96)	Placebo (N = 94)
Sample size		
Metformin monotherapy Sample size	n = 54 ; % = 56.3	n = 45 ; % = 47.9
Other monotherapy Sample size	n = 4 ; % = 4.2	n = 2 ; % = 2.1
Combination therapy Sample size	n = 39 ; % = 40.6	n = 47 ; % = 50
None Sample size	n = 0 ; % = 0	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
% Female Sample size	n = 47 ; % = 49	n = 55 ; % = 58.5

1

2

389. Retnakaran, 2010

Bibliographic Reference	Retnakaran, R.; Qi, Y.; Opsteen, C.; Vivero, E.; Zinman, B.; Initial short-term intensive insulin therapy as a strategy for evaluating the preservation of beta-cell function with oral antidiabetic medications: a pilot study with sitagliptin; Diabetes Obes Metab; 2010; vol. 12 (no. 10); 909-15

389.1. 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	BEST trial. NCT00420511
Study type	Randomised controlled trial (RCT)
Study location	Canada
Study setting	Unspecified clinical setting
Study dates	2007-01-11 to 2009-01-09
Sources of funding	Samuel Lunenfeld Research Institute, Mount Sinai Hospital
Inclusion criteria	1. Men and women between the ages of 30 and 75 inclusive 2. Physician-diagnosed type 2 diabetes on 0-2 oral hypoglycemic agents 3. Negative for anti-glutamic acid decarboxylase (anti-GAD_ antibodies (to rule out Latent Autoimmune Diabetes of Adults (LADA) 4. A1c at screening between 6.5% and 9% inclusive if on no oral hypoglycemic agents or 6.0% and 9.0% inclusive if on 1-2 oral hypoglycemic agents

Exclusion criteria	1. Current insulin therapy 2. Type 1 diabetes or secondary forms of diabetes 3. Any major illness with a life expectancy of < 5 years or that may interfere with the patient's participation in the study 4. Involvement in any other study requiring drug therapy 5. Renal dysfunction as evidenced by serum creatinine >/= 136 umol/L for males or >/= 124 umol/L for females or abnormal creatinine clearance (< 60 ml/min by Modification of Diet in Renal Disease (MDRD) formula) 6. Hepatic disease considered to be clinically significant (includes jaundice, chronic hepatitis, or previous liver transplant) or transaminases > 2.5 times the upper limit of normal 7. Excessive alcohol consumption, defined as > 14 alcoholic drinks per week for males and > 9 alcoholic drinks per week for females 8. Pregnancy or unwillingness to use reliable contraception. Women should not be planning pregnancy for the duration of the study. Reliable contraception includes: birth control pill, intra-uterine device, abstinence, tubal ligation, partner vasectomy, or condoms with spermicide. Any women who miss a menstrual period or think that they may be pregnant must have a pregnancy test as soon as possible 9. History of serious arrhythmia or atrioventricular block on baseline electrocardiogram 10. Uncontrolled hypertension (systolic blood pressure > 180 mm Hg or diastolic blood pressure > 110 mm Hg) 11. Unwillingness to undergo multiple daily insulin injection therapy for 4 weeks 12. Unwillingness to perform capillary blood glucose monitoring at least 4 times per day during intensive insulin therapy
Recruitment / selection of participants	The study population consisted of 37 adult patients with T2DM, who were negative for antiglutamic acid decarboxylase antibodies and had screening A1c <9.0% on 0–2 OADs
Intervention(s)	37 patients with T2DM of 6.0 + 6.4 years duration and A1c 7.0 + 0.8% on 0–2 OADs were put on 4–8 weeks of IIT consisting of basal detemir and premeal insulin aspart. Subjects achieving fasting glucose <7.0 mmol/l 1 day after completing IIT (n = 21) were then randomized to metformin with either sitagliptin or placebo
Cointervention	Metformin (over 70% were on metformin at baseline). Baseline OADs were then stopped during the pre-randomisation insulin therapy. Metformin given to everyone alongside randomised treatment so treated in this review as a concomitant therapy. Metformin initiated at 500 mg twice a day for the first 2 weeks, before increasing to 1000 mg twice a day for the duration of the study.
Strata 1: People with type 2	Not stated/unclear

diabetes mellitus and heart failure	
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 Renal dysfunction as an exclusion criteria, but unclear if this includes 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	People without non-alcoholic fatty liver disease Excluded: Hepatic disease considered to be clinically significant
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	none
Comparator	placebo
Number of participants	Thirty-seven participants (23 males, 14 females) with mean age of 56.6 ± 10.0 years, T2DM of 6.0 ± 6.4 years duration and mean A1c 7.0 ± 0.8% on 0–2 OADs entered the pre-randomization IIT phase. After 4–8 weeks of IIT, the 21 participants meeting the randomization criterion (venous fasting glucose <7.0 mmol/l 1 day after completing IIT) were randomized to either (i) sitagliptin and metformin or (ii) placebo and metformin
Duration of follow-up	48 weeks
Indirectness	Stopped all baseline OADs prior to a pre-randomisation intensive insulin therapy (insulin stopped at randomisation), then randomised sitagliptin v placebo with concomitant metformin in both arms. Allocated in review as a switching strategy (switching from original OADs to Sitagliptin). But, downgraded for indirectness as although switched from their original therapy to a new therapeutic plan, this included an initial high intensity insulin boost followed by the randomised treatment.
Method of analysis	Modified ITT
Additional comments	ITT LOCF

389.2. Study arms

389.2.1. Sitagliptin (N = 10)

Intervention(s)	37 patients with T2DM of 6.0 + 6.4 years duration and A1c 7.0 + 0.8% on 0–2 OADs were switched to 4–8 weeks of IIT consisting of basal detemir and premeal insulin aspart. Subjects achieving fasting glucose <7.0 mmol/l 1 day after completing IIT (n = 21) were then randomized to metformin with either sitagliptin or placebo

Sitagliptin 100mg once a day (od) by mouth (po)

389.2.2. Placebo (N = 11)

Intervention(s)	37 patients with T2DM of 6.0 + 6.4 years duration and A1c 7.0 + 0.8% on 0–2 OADs were switched to 4–8 weeks of IIT consisting of basal detemir

	and premeal insulin aspart. Subjects achieving fasting glucose <7.0 mmol/l 1 day after completing IIT (n = 21) were then randomized to metformin with either sitagliptin or placebo

Placebo once a day (od) by mouth (po)

389.3. Characteristics

389.3.1. Arm-level characteristics

Characteristic	Sitagliptin (N = 10)	Placebo (N = 11)
% Male Nominal	60	72.7
Mean age (SD) Median (IQR)	61.3 (45.5 to 69.5)	60.8 (51.3 to 61.4)
White Nominal	40	81.8
Other Nominal	60	18.2
Comorbidities Nominal	NR	NR
Presence of frailty Nominal	NR	NR
Time since type 2 diabetes diagnosed Median (IQR)	2.8 (2 to 4)	3.5 (2 to 8)
HbA1c (%) Median (IQR)	6.2 (5.8 to 6.9)	6.1 (5.9 to 6.9)
Cardiovascular risk factors Nominal	NR	NR
Smoking status Nominal	NR	NR

Characteristic	Sitagliptin (N = 10)	Placebo (N = 11)
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 Nominal	NR	NR
People with a learning disability Nominal	NR	NR
BMI Median (IQR)	34.3 (27.3 to 42.6)	32.7 (31 to 41.1)
Number of people with obesity Nominal	NR	NR
diet alone diet alone Nominal	20	0
Metformin Nominal	40	45.5
TZD Nominal	20	0
SU Nominal	0	9.1
metformin + TZD Nominal	10	9.1
metformin + SU Nominal	10	27.3
TZD + SU Nominal	0	9.1
Blood pressure-lowering medication used Nominal	NR	NR
Statins/lipid-lowering medication used	NR	NR

Characteristic	Sitagliptin (N = 10)	Placebo (N = 11)
Nominal		
Other treatment being received Nominal	NR	NR

1

2

390. Ridderstrale, 2014

Bibliographic Reference	Ridderstrale, M.; Andersen, K. R.; Zeller, C.; Kim, G.; Woerle, H. J.; Broedl, U. C.; Comparison of empagliflozin and glimepiride as add-on to metformin in patients with type 2 diabetes: A 104-week randomised, active-controlled, double-blind, phase 3 trial; Lancet Diabetes Endocrinol; 2014; vol. 2 (no. 9); 691-700

390.1. 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	Ridderstrale, Martin; Svaerd, Robbyna; Zeller, Cordula; Kim, Gabriel; Woerle, Hans J; Broedl, Uli C. Rationale, design and baseline characteristics of a 4-year (208-week) phase III trial of empagliflozin, an SGLT2 inhibitor, versus glimepiride as add-on to metformin in patients with type 2 diabetes mellitus with insufficient glycemic control. Cardiovascular diabetology; 2013; vol. 12; 129. Ridderstrale, Martin; Rosenstock, Julio; Andersen Knut, R; Woerle Hans, J; Salsali, Afshin. Empagliflozin compared with glimepiride in metformin-treated patients with type 2 diabetes: 208-week data from a masked randomized controlled trial. Diabetes, obesity & metabolism; 2018; vol. 20 (no. 12); 2768-2777
Trial name / registration number	NCT01167881
Study type	Randomised controlled trial (RCT)
Study location	23 countries: • Argentina • Austria • Canada • Colombia • Czech Republic • Finland • Hong Kong • India • Italy • Malaysia

	• Mexico • the Netherlands • Norway • Philippines • Portugal • South Africa • Spain • Sweden • Switzerland • Taiwan • Thailand • UK • USA
Study setting	Diabetes centres and clinics.
Study dates	08/2010 - 06/2011
Sources of funding	Boehringer Ingelheim - involved in the study design, data gathering and analysis. Eli-Lilly co-sponsored the trial but was not involved in the study design, and data gathering analysis.
Inclusion criteria	• Adults (aged ≥18 years) with type 2 diabetes • BMI less than or equal to 45 kg/m² • HbA1c concentrations of 7–10%, receiving an unchanged dose of metformin immediate release (≥1500 mg/day, maximum tolerated dose, or maximum dose according to the local label) for at least 12 weeks before randomisation
Exclusion criteria	• Estimated glomerular filtration rate (eGFR) of less than 60 mL/min per 1·73 m² (Modified Diet Renal Disease formula) during screening or placebo run-in • Blood glucose concentration greater than 13·3 mmol/L after an overnight fast during the placebo run-in, confirmed by a second measurement • Use of antidiabetic drugs other than metformin immediate release any time during the 12 weeks before randomisation
Recruitment / selection of participants	After a 2-week, open-label, placebo run-in, eligible patients were randomly assigned in a 1:1 ratio to receive empagliflozin (25 mg once daily, orally) or glimepiride (1–4 mg once daily, orally) in a double-blind, double-dummy manner for 104 weeks, in addition to metformin immediate release and diet and exercise counselling.
Intervention(s)	Glimepiride 1 - 4 mg daily, orally. Glimepiride was initiated at a dose of 1 mg/day, with a recommendation for up-titration if fasting plasma glucose (assessed with home monitoring) was

	greater than 6·1 mmol/L to 2 mg/day at week 4, 3 mg/day at week 8, and 4 mg/day at week 12.
Cointervention	Metformin immediate release (≥1500 mg/day, maximum tolerated dose or maximum dose according to the local label)
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 "Acute coronary syndrome, stroke or transient ischemic attack within 3 months of informed consent", 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 "estimated glomerular filtration rate (eGFR) of less than 60 mL/min per 1·73 m² (Modified Diet Renal Disease formula) during screening or placebo run-in", otherwise unclear. Baseline characteristics only give eGFR categories.
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	eGFR ≥30mL/min/1.73m2
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Population subgroups	
Comparator	Empagliflozin 25 mg once daily, orally.
Number of participants	N=1549
Duration of follow-up	104 weeks (24 months)
Indirectness	
Method of analysis	Modified ITT
Additional comments	Patients treated with at least one dose of study drug who had a baseline HbA1c value were included in the efficacy analysis.

390.2. Study arms

390.2.1. Glimepiride 1 - 4 mg once daily (N = 780)

Administered orally

390.2.2. Empagliflozin 25 mg once daily (N = 765)

Administered orally

390.3. Characteristics

390.3.1. Arm-level characteristics

Characteristic	Glimepiride 1 - 4 mg once daily (N = 780)	Empagliflozin 25 mg once daily (N = 765)
% Male No of events	n = 421 ; % = 54	n = 432 ; % = 56
Mean age (SD) (year) Mean (SD)	55.7 (10.4)	56.2 (10.3)
Hispanic or Latino No of events	n = 159 ; % = 20	n = 153 ; % = 20
Non-hispanic or non-latino No of events	n = 621 ; % = 80	n = 612 ; % = 80
White No of events	n = 519 ; % = 67	n = 498 ; % = 65
Asian No of events	n = 253 ; % = 32	n = 254 ; % = 33
Black or African-American No of events	n = 8 ; % = 1	n = 12 ; % = 2
Hawaiian or pacific islander No of events	n = 0 ; % = 0	n = 1 ; % = 1
Presence of frailty Nominal	NR	NR
1 or fewer No of events	n = 93 ; % = 12	n = 79 ; % = 10
more than 1 to 5 No of events	n = 336 ; % = 43	n = 341 ; % = 45
more than 5 to 10 No of events	n = 211 ; % = 27	n = 214 ; % = 28
More than 10 No of events	n = 140 ; % = 18	n = 131 ; % = 17

Characteristic	Glimepiride 1 - 4 mg once daily (N = 780)	Empagliflozin 25 mg once daily (N = 765)
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
Metformin modified release No of events	n = 780 ; % = 100	n = 765 ; % = 100

1

2

391. Ridderstrale, 2018

Bibliographic Reference	Ridderstrale, Martin; Rosenstock, Julio; Andersen Knut, R; Woerle Hans, J; Salsali, Afshin; EMPA-REG H2H-SU, trial; investigators; Empagliflozin compared with glimepiride in metformin-treated patients with type 2 diabetes: 208-week data from a masked randomized controlled trial.; Diabetes, obesity & metabolism; 2018; vol. 20 (no. 12); 2768-2777

391.1. Study details

Secondary publication of another included study- see primary study for details	Ridderstrale, M.; Andersen, K. R.; Zeller, C.; Kim, G.; Woerle, H. J.; Broedl, U. C. Comparison of empagliflozin and glimepiride as add-on to metformin in patients with type 2 diabetes: A 104-week randomised, active-controlled, double-blind, phase 3 trial. Lancet Diabetes Endocrinol; 2014; vol. 2 (no. 9); 691-700.
Other publications associated with this study included in review	Ridderstrale, Martin; Svaerd, Robbyna; Zeller, Cordula; Kim, Gabriel; Woerle, Hans J; Broedl, Uli C. Rationale, design and baseline characteristics of a 4-year (208-week) phase III trial of empagliflozin, an SGLT2 inhibitor, versus glimepiride as add-on to metformin in patients with type 2 diabetes mellitus with insufficient glycemic control. Cardiovascular diabetology; 2013; vol. 12; 129

391.2. Study arms

391.2.1. Glimepiride 1 - 4 mg once daily (N = 780)

Administered orally

391.2.2. Empagliflozin 25 mg once daily (N = 765)

Administered orally

392. Ridderstrale, 2013

Bibliographic Reference	Ridderstrale, Martin; Svaerd, Robbyna; Zeller, Cordula; Kim, Gabriel; Woerle, Hans J; Broedl, Uli C; Rationale, design and baseline characteristics of a 4-year (208-week) phase III trial of empagliflozin, an SGLT2 inhibitor, versus glimepiride as add-on to metformin in patients with type 2 diabetes mellitus with insufficient glycemic control.; Cardiovascular diabetology; 2013; vol. 12; 129

392.1. Study details

Secondary publication of another included study- see primary study for details	Parent study Ridderstrale 2014

393. Riddle, 2013

Bibliographic Reference	Riddle, M. C.; Aronson, R.; Home, P.; Marre, M.; Niemoeller, E.; Miossec, P.; Ping, L.; Ye, J.; Rosenstock, J.; Adding once-daily lixisenatide for type 2 diabetes inadequately controlled by established basal insulin: a 24-week, randomized, placebo-controlled comparison (GetGoal-L); Diabetes Care; 2013; vol. 36 (no. 9); 2489-96

393.1. 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-L (NCT00715624)
Study type	Randomised controlled trial (RCT)
Study location	111 centres in 15 countries (Brazil, Canada, Chile, Egypt, France, Germany, India, Italy, Republic of Korea, Mexico, Puerto Rico, Russian Federation, Turkey, U.K., and U.S)
Study setting	NR
Study dates	July 2008 to February 2011
Sources of funding	Sanofi
Inclusion criteria	• Adults with type 2 diabetes diagnosed ≥1 year at the time of screening • Basal insulin regimen for ≥3 months with a stable dose (±20%) ≥30 units/day for ≥2 months before screening • HbA1c 7-10% • Patients using metformin must have taken a stable dose of at least 1.5 g/day (South Korea, at least 1.0 g/day) for at least 3 months before screening

Exclusion criteria	• FPG > 13.9 mmol/L (250 mg/dL) • BMI ≤ 20.0 kg/m2 • Weight change > 5.0 kg over the 3 months before screening • History of unexplained pancreatitis, end-stage renal disease, or allergic reaction to any GLP-1RA in the past • Pregnancy.
Recruitment / selection of participants	NR
Intervention(s)	Lixisenatide once daily in a two-step dose-increase regimen (10 ug for 1 week, 15 ug for 1 week, and then 20 ug if tolerated. [Lixisenatide/placebo was given subcutaneously within 1 hour before the morning meal.]
Cointervention	If used at enrolment, metformin was continued at a stable dose throughout the study. In general, basal insulin dosage was to remain relatively stable (±20%) throughout the study. However, if HbA1c was ≤7.5% at screening, daily basal insulin was initially reduced by 20% at randomization and thereafter progressively increased between weeks 4 and 12 to the dosage used at the screening visit, unless prevented by the occurrence of hypoglycemia. After week 12, no further dose adjustments of basal insulin were to be made except for reductions in response to hypoglycemia. Rescue therapy, preferably with rapid-acting insulin, was permitted if FPG was >15.0 mmol/L any time between randomization and week 8, FPG was >13.3 mmol/L from week 8 through 12, and FPG was >11.1mmol/L or HbA1c >8.5% from week 12 through 24.
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 Exclusion criteria for people with end-stage kidney disease but no information about people with chronic kidney 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
Population subgroups	NA
Comparator	Placebo
Number of participants	879 patients were screened and 518 entered the run-in, and 496 were randomised. 329 participants were allocated to lixisenatide, where 275 completed (84%). 167 participants were allocated to placebo, where 147 completed (88%).
Duration of follow-up	24 weeks
Indirectness	Directly applicable
Method of analysis	Modified ITT

	Defined as participants who received one or more doses of the allocated treatment and had a measurement at baseline and at least one on-treatment measurement of any primary and secondary efficacy endpoint. Data obtained after rescue therapy were excluded from the efficacy analyses. Analysed using ANCOVA, and LS mean change was calculated with last observation carried forward.
Additional comments	Rescue therapy was required by 19 (6%) of participants in the lixisenatide arm and 12 (7%) of participants in the placebo arm.

393.2. Study arms

393.2.1. Lixisenatide (N = 329)

393.2.2. Placebo (N = 167)

393.3. Characteristics

393.3.1. Arm-level characteristics

Characteristic	Lixisenatide (N = 329)	Placebo (N = 167)
% Male Sample size	n = 146 ; % = 45	n = 82 ; % = 49
Mean age (SD) Mean (SD)	57 (10)	57 (10)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA
Caucasian Sample size	n = 254 ; % = 77	n = 130 ; % = 78
Black Sample size	n = 14 ; % = 4	n = 6 ; % = 4
Asian Sample size	n = 53 ; % = 16	n = 30 ; % = 18
Other Sample size	n = 7 ; % = 2	n = 1 ; % = 1

Characteristic	Lixisenatide (N = 329)	Placebo (N = 167)
Hispanic Sample size	n = 94 ; % = 29	n = 40 ; % = 24
Not Hispanic Sample size	n = 234 ; % = 71	n = 127 ; % = 76
Comorbidities Nominal	NR	NR
Presence of frailty Nominal	NR	NR
Time since type 2 diabetes diagnosed Mean (SD)	12.5 (7)	12.4 (6.3)
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
BMI Mean (SD)	31.9 (6.2)	32.6 (6.3)
Number of people with obesity BMI >=30 kg/m2 Sample size	n = 191 ; % = 58	n = 106 ; % = 63
Other antidiabetic medication used Sample size	n = NA ; % = NA	n = NA ; % = NA
Insulin - Glargine	n = 165 ; % = 50	n = 83 ; % = 50

Characteristic	Lixisenatide (N = 329)	Placebo (N = 167)
Sample size		
Insulin - Detemir Sample size	n = 24 ; % = 7	n = 19 ; % = 11
Insulin - NPH Sample size	n = 134 ; % = 41	n = 64 ; % = 38
Insulin - Premix Sample size	n = 5 ; % = 2	n = 3 ; % = 2
Metformin Sample size	n = 80 ; % = 20	n = 78 ; % = 22
Blood pressure-lowering medication used Nominal	NR	NR
Statins/lipid-lowering medication used Nominal	NR	NR
Other treatment being received Nominal	NR	NR

1

2

394. Riddle, 2013

Bibliographic Reference	Riddle, M. C.; Forst, T.; Aronson, R.; Sauque-Reyna, L.; Souhami, E.; Silvestre, L.; Ping, L.; Rosenstock, J.; Adding once-daily lixisenatide for type 2 diabetes inadequately controlled with newly initiated and continuously titrated basal insulin glargine: a 24-week, randomized, placebo-controlled study (GetGoal-Duo 1); Diabetes Care; 2013; vol. 36 (no. 9); 2497-503

394.1. 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-Duo 1 [NCT00975286]
Study type	Randomised controlled trial (RCT)
Study location	140 centres in 25 countries
Study setting	NR
Study dates	October 2009 to August 2011
Sources of funding	Sanofi
Inclusion criteria	• Adults with type 2 diabetes for at least 1 year at the time of screening • Use of metformin at a stable dose of at least 1.5 mg/day for at least 3 months alone or in combination with a sulfonylurea or glinide or a thiazolidinedione (TZD), or a combination of these • HbA1c ≥ 7 and ≤10% and BMI >20 kg/m2

Exclusion criteria	• Use of oral or injectable antihyperglycemic agents other than metformin, sulfonylureas, glinides, and TZDs within 3 months • Use of weight-loss drugs if not at a stable dose for ≥3 months • History of hypoglycemia unawareness, gastrointestinal disease associated with prolonged nausea, and vomiting • Hypersensitivity to insulin glargine or allergic reaction to any GLP-1RAs#7.8 mmol/L (140 mg/dL)
Recruitment / selection of participants	After enrolment, participants continued metformin and a TZD if previously used but stopped any secretagogue. Morning administration of insulin glargine was started at 10 units daily and was titrated weekly, targeting a fasting range of 4.4–5.6 mmol/L (80–100 mg/dL). At completion of the 12-week run-in, participants were eligible for randomization if they had HbA1c ≥7% and ≤9% and fasting self-measurement of plasma-referenced glucose (SMPG) for the past 7 days averaging 7.0mmol/L (126mg/dL) early in the trial or ≤7.8 mmol/L (140 mg/dL).
Intervention(s)	Lixisenatide - A two-step dosage increase was used with both placebo and lixisenatide (10 mcg for 1 week, 15 mg for 1 week, and then 20-mcg maintenance dosage if tolerated), with injections self administered by participants ≤1 h before breakfast.
Cointervention	Adjustment of dosage of insulin glargine was permitted throughout randomized treatment targeting fasting SMPG 4.4–5.6 mmol/L. Rescue therapy with short-acting insulin was permitted through week 8 if FPG was repeatedly >11.1 mmol/L or if HbA1c was >9.0% and after week 8 if FPG was >10.0mmol/L or if HbA1c was >8.5%.
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	Not stated/unclear

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	NA
Comparator	Placebo
Number of participants	1470 patients were screened and 898 entered the 12-week run-in period. 446 participants were randomised. 223 participants were allocated to lixisenatide, and 194 (87%) completed. 223 participants were allocated to placebo, and 211 (95%) completed.
Duration of follow-up	24 weeks

Indirectness	Directly applicable
Method of analysis	Modified ITT Efficacy variables defined as all randomised participants who received at least one dose of double-blind study drug, and had both a baseline assessment and at least on postbaseline assessment of any primary or secondary efficacy variable using the last observation carried forward procedure. The primary and secondary efficacy assessment used an ANCOVA model. Safety variables were assessed in the safety population defined as all randomised participants exposed to at least one dose of the double-blind study drug regardless of the amount of treatment administered.
Additional comments	NA

394.2. Study arms

394.2.1. Lixisenatide (N = 223)

394.2.2. Placebo (N = 223)

394.3. Characteristics

394.3.1. Arm-level characteristics

Characteristic	Lixisenatide (N = 223)	Placebo (N = 223)
% Male Sample size	n = 109 ; % = 49	n = 113 ; % = 51
Mean age (SD) Mean (SD)	56 (10)	56 (10)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA

Characteristic	Lixisenatide (N = 223)	Placebo (N = 223)
Caucasian Sample size	n = 165 ; % = 74	n = 167 ; % = 75
Black Sample size	n = 9 ; % = 4	n = 11 ; % = 5
Asian Sample size	n = 44 ; % = 20	n = 43 ; % = 19
Other Sample size	n = 5 ; % = 2	n = 2 ; % = 1
Hispanic Sample size	n = 52 ; % = 23	n = 49 ; % = 22
Not Hispanic Sample size	n = 171 ; % = 77	n = 174 ; % = 78
Comorbidities Nominal	NR	NR
Presence of frailty Nominal	NR	NR
Time since type 2 diabetes diagnosed (years) Mean (SD)	9.6 (6)	8.7 (5.8)
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

Characteristic	Lixisenatide (N = 223)	Placebo (N = 223)
BMI (kg/m2) Mean (SD)	32 (6.6)	31.7 (6)
Number of people with obesity BMI>=30 kg/m2 Sample size	n = 120 ; % = 53.8	n = 120 ; % = 53.8
Other antidiabetic medication used TZD use Sample size	n = 27 ; % = 12	n = 27 ; % = 12
Blood pressure-lowering medication used Nominal	NR	NR
Statins/lipid-lowering medication used Nominal	NR	NR
Other treatment being received Nominal	NR	NR

1

2

395. Riddle, 1998

Bibliographic Reference	Riddle, M. C.; Schneider, J.; Beginning insulin treatment of obese patients with evening 70/30 insulin plus glimepiride versus insulin alone.; Diabetes Care; 1998; vol. 21 (no. 7); 1052-7

395.1. 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, treat-to-target, RCT
Study location	Not reported but probably USA (multisite)
Study setting	Outpatient
Study dates	Not reported but likely before 1997
Sources of funding	Funded by Hoechst Marion Roussel Pharmaceuticals.
Inclusion criteria	• Type 2 diabetes diagnosis • Aged 45-70 years • Inadequate glycaemic control on at least 6-mo of sulphonylurea treatment ○ Between 130-170% inclusive of desirable weight at entry (article states that trial is in participants living with obesity but this is not defined • If female, then postmenopausal, infertile, or using adequate contraception

Exclusion criteria	• Pregnancy or lactating • Diabetes diagnosis>15 years before screening • History of ketoacidosis, autoimmune disease or major systemic illness other than diabetes • Use of glucocorticoid agents, phenytoin, nicotinic acid, sympathomimetics, phenothiazines, or isoniazid • Serum creatinine or serum alanine aminotransferase>1.5 times upper limit of normal • Fasting C-peptide<0.4 pmol/ml
Recruitment / selection of participants	Eligible participants entered initial open-label phase of 8 weeks in which they discontinued any current hypoglycaemic therapy and received glimepiride titrated up to 8 mg twice daily (initial dose 8 mg before breakfast). If FPG>8.3 mmol/L at weekly testing, dose increased incrementally to 12 mg once daily, 16 mg once daily, and then to 8 mg before breakfast and 8 mg before dinner after 3 weeks treatment. If FPG<8.3 mmol/L on 2 consecutive visits, participants were excluded; participants also excluded if FPG≤10 mmol/L or >16.7 mmol/L after 2-wks of glimepiride 8 mg twice daily. Eligible participants continued on glimepiride 8 mg twice daily to end of 8-wk open-label period. After this, eligible participants randomised to glimepiride or placebo.
Intervention(s)	• Glimepiride 16 mg daily Oral glimepiride 8 mg twice daily, before breakfast and dinner, for 24 weeks, in addition to insulin human 70/30.
Cointervention	• Insulin human 70/30 All participants received insulin human 70/30 (NPH insulin 70% and regular insulin 30%), 30 min before dinner, for duration of trial. Initial dosage of 10 U daily for first 2 weeks, then titrated according to fasting blood glucose (FBG) by 10 U weekly until FBG≤7.8 mmol/L for 2 consecutive days, then 5 U weekly until ≤6.7 mmol/L for 2 consecutive days. When FBG consistently 5.5-6.7 mmol/L constant insulin dosage maintained. Small decreases of insulin permitted to prevent hypoglycaemia.
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	Not stated/unclear

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	People with obesity Article states trial in participants with obesity but this is not defined
Subgroup 5: eGFR category at baseline	Not stated/unclear
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Comparator	• Placebo Matching placebo twice daily before breakfast and dinner for 24 weeks, in addition to insulin human 70/30.
Number of participants	N=145 randomised
Duration of follow-up	24 weeks

Indirectness	None
Method of analysis	ITT Safety outcomes used ITT population Modified ITT mITT observed cases analysis (all randomised participants with baseline and at least one post-baseline measurement) for all efficacy outcomes.
Additional comments	

395.2. Study arms

395.2.1. Glimepiride 16 mg daily (N = 72)

Oral glimepiride 8 mg twice daily for 24 weeks, in addition to insulin 70/30 (NPH insulin 70%/regular insulin 30%).

395.2.2. Placebo (N = 73)

Matching placebo twice daily for 24 weeks, in addition to insulin 70/30 (NPH insulin 70%/regular insulin 30%).

395.3. Characteristics

395.3.1. Arm-level characteristics

Characteristic	Glimepiride 16 mg daily (N = 72)	Placebo (N = 73)
% Male Sample size	n = 45 ; % = 62.5	n = 40 ; % = 54.8
Mean age (SD) (years) Mean (SD)	58 (8)	58 (8)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA
Latino, African American, or Native American Sample size	n = 15 ; % = 20.8	n = 15 ; % = 20.5

Characteristic	Glimepiride 16 mg daily (N = 72)	Placebo (N = 73)
White Sample size	n = 57 ; % = 79.2	n = 58 ; % = 79.5
Comorbidities Nominal	NR	NR
Presence of frailty Nominal	NR	NR
Time since type 2 diabetes diagnosed (years) Mean (SD)	7 (4)	7 (4)
Cardiovascular risk factors Nominal	NR	NR
Smoking status Nominal	NR	NR
Alcohol consumption Nominal	NR	NR
People with significant cognitive impairment Nominal	NR	NR
People with a learning disability Nominal	NR	NR
Number of people with obesity Sample size	n = 72 ; % = 100	n = 73 ; % = 100
Other antidiabetic medication used Nominal	NR	NR
Blood pressure-lowering medication used Nominal	NR	NR
Statins/lipid-lowering medication used Nominal	NR	NR
Other treatment being received	NR	NR

Characteristic	Glimepiride 16 mg daily (N = 72)	Placebo (N = 73)
Nominal		

1

2

396. Roberts, 2005

Bibliographic Reference	Roberts, V. L.; Stewart, J.; Issa, M.; Lake, B.; Melis, R.; Triple therapy with glimepiride in patients with type 2 diabetes mellitus inadequately controlled by metformin and a thiazolidinedione: results of a 30-week, randomized, double-blind, placebo-controlled, parallel-group study; Clin Ther; 2005; vol. 27 (no. 10); 1535-47

396.1. 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 treat-to-target RCT
Study location	USA (multisite)
Study setting	Outpatient
Study dates	Not reported by trial likely began before 2005
Sources of funding	Supported by Aventis Pharmaceuticals, Bridgewater, NJ, USA; Innovus Research Inc., Medford, MA, USA performed health-related quality of life analysis.
Inclusion criteria	• Type 2 diabetes diagnosis≥1 year prior to screening • Aged 18-80 years inclusive • Performing self-monitored blood glucose testing at home • Receiving stable dose of immediate-release (1000-2500 mg daily) or extended-release (up to 2000 mg daily) metformin and half-max dose of a thiazolidinedione (up to 8 mg daily rosiglitazone; up to 45 mg daily pioglitazone) for at least 3-mo before screening • HbA1c 7.5-9.5 inclusive at screening • BMI 26-42 kg/m2 inclusive at screening

	• Fasting C-peptide≥0.27 nmol/L during 4-wk stabilization period • Fasting plasma glucose 130-235 mg/dL inclusive within 2-3 days of randomisation
Exclusion criteria	• Requiring insulin therapy • Receiving other sulphonylurea treatment • History of hypersensitivity to sulphonylurea • History of severe hypoglycaemia when taking oral anti-diabetics • Acute metabolic complication • Increase in thiazolidinedione dose during past 2-mo of screening • Increase in metformin dose in past 1-mo of screening • Clinically significant lab abnormalities at baseline
Recruitment / selection of participants	Potential participants entered 4-wk stabilization and eligibility period in which they continued to take fixed doses of current oral anti-diabetic drugs. Eligible participants then randomised in blocks of 2 to glimepiride or placebo. All participants were advised to follow American Diabetes Association diet to maintain body weight.. Doses of study drug reduced once in case of hypoglycaemia and FPG level <70 mg/dL, random capillary BG level<60 mg/dL, or mean of 3 consecutive self-monitored BG <70 mg/dL before study visit. Participants with excessive hyperglycaemia discontinued study,
Intervention(s)	• Glimepiride 2-8 mg daily titrated Oral glimepiride 2-8 mg daily titrated for 26 weeks, in addition to metformin and a thiazolidinedione. Initial 6-wk titration phase in which glimepiride titrated every 2 weeks to 4 mg daily and then to 8 mg daily until target serum glucose reached of <6.7 mmol/L. Titration phase followed by 20-week maintenance phase.
Cointervention	• Metformin • Thiazolidinedione All participants received immediate- (1000-2500 mg daily) or extended- (up to 2000 mg daily) release metformin and half-max dose of a thiazolidinedione (up to 8 mg daily rosiglitazone; up to 45 mg daily pioglitazone) 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	Not stated/unclear

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	Not stated/unclear
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Comparator	• Placebo Matching placebo for 26 weeks following same 6-wk titration and 20-wk maintenance phases as glimepiride arm.
Number of participants	N=170 randomised (131 completed)
Duration of follow-up	26 weeks

Indirectness	None
Method of analysis	Modified ITT mITT analysis (all randomised participants who received at least one dose of study drug and had at least 1 post-baseline HbA1c assessment) for all efficacy outcomes; safety population was all randomised participants who received at least 1 dose of study drug. Missing data strategy unclear.

396.2. Study arms

396.2.1. Glimepiride 2-8 mg daily (N = 85)

Oral glimepiride 2-8 mg daily titrated for 26 weeks, in addition to background metformin and a thiazolidinedione.

396.2.2. Placebo (N = 85)

Matching placebo daily for 26 weeks, in addition to background metformin and a thiazolidinedione.

396.3. Characteristics

396.3.1. Arm-level characteristics

Characteristic	Glimepiride 2-8 mg daily (N = 85)	Placebo (N = 85)
% Male Sample size	n = 50 ; % = 61	n = 48 ; % = 62.3
Mean age (SD) (years) Mean (SD)	56.5 (9.8)	56.4 (10)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA
Black Sample size	n = 11 ; % = 13.4	n = 7 ; % = 9.1
Other Sample size	n = 16 ; % = 19.5	n = 14 ; % = 18.2

Characteristic	Glimepiride 2-8 mg daily (N = 85)	Placebo (N = 85)
White Sample size	n = 55 ; % = 67.1	n = 56 ; % = 72.7
Comorbidities Nominal	NR	NR
Presence of frailty Nominal	NR	NR
Time since type 2 diabetes diagnosed (years) Mean (SD)	7.9 (4.9)	8.7 (6.8)
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 Nominal	NR	NR
Blood pressure-lowering medication used Nominal	NR	NR
Statins/lipid-lowering medication used	NR	NR

Characteristic	Glimepiride 2-8 mg daily (N = 85)	Placebo (N = 85)
Nominal		
Other treatment being received Nominal	NR	NR

1 Baseline characteristics data are for mITT population: Glimepiride, N=82; Placebo,
2 N=77

3

4

397. Rodbard Helena, 2019

Bibliographic Reference	Rodbard Helena, W; Rosenstock, Julio; Canani Luis, H; Deerochanawong, Chaicharn; Gumprecht, Janusz; Lindberg Soren, Ostergaard; Lingvay, Ildiko; Sondergaard Anette, Luther; Treppendahl Marianne, Bach; Montanya, Eduard; PIONEER, 2; Investigators; Oral Semaglutide Versus Empagliflozin in Patients With Type 2 Diabetes Uncontrolled on Metformin: The PIONEER 2 Trial.; Diabetes care; 2019; vol. 42 (no. 12); 2272-2281

397.1. 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	PIONEER 2/NCT02863328
Study type	Randomised controlled trial (RCT) Open-label, parallel-group, RCT
Study location	International (108 sites in 12 countries: Argentina, Brazil, Croatia, Greece, Hungary, Italy, Poland, Russia, Serbia, Spain, Thailand, U.S.A.)
Study setting	Outpatient
Study dates	08/2016 to 03/2018
Sources of funding	Novo Nordisk A/S, Denmark.
Inclusion criteria	• Aged≥18 years • Type 2 diabetes diagnosis≥90 days before screening • HbA1c level 7.0–10.5% inclusive • Stable dose of metformin (≥1,500 mg or maximum tolerated)≥90 days before screening

Exclusion criteria	• Any medication for diabetes or obesity within the previous 90 days other than metformin or short-term (≤14 days) insulin • Renal impairment (eGFR<60 mL/min/1.73 m2) • If female, then pregnancy, breast-feeding or intends to become pregnant, or of child-bearing potential and not using adequate contraceptives • Proliferative retinopathy or maculopathy requiring acute treatment verified by fundus photography or dilated fundoscopy • History of pancreatitis, major surgical procedure involving stomach, diabetic ketoacidosis, malignant neoplasms • NYHA class 4 • Planned coronary, carotid or peripheral artery revascularization known on the day of screening • Subjects with alanine aminotransferase >2.5x upper normal limit
Recruitment / selection of participants	A total of 1,122 patients were screened, with 822 randomized (1:1) to oral semaglutide 14mg once daily (n= 412) or empagliflozin 25 mg once daily (n= 410), using an interactive web response system; Open label trial. Additional antidiabetic medication was available for patients with persistent or unacceptable hyperglycemia on trial product and for patients who prematurely discontinued trial product and remained in the trial. Additional antidiabetic medication was defined as that initiated (or intensification of existing antidiabetic background medication by a dose increase of .20%) during the planned treatment period (i.e., from randomization to the planned end-of-treatment visit) either as add-on to trial product or initiated after premature discontinuation of trial product. The subset of additional antidiabetic medication (or intensification of existing antidiabetic background medication) used as add-on to trial product is defined as rescue medication. Short-term use (≤21 days) of antidiabetic medication (e.g., in connection with intercurrent illness) was not considered as additional antidiabetic medication (including rescue medication). Rescue criteria were fasting plasma glucose .260 mg/dL (14.4 mmol/L) from week 8 to 13, .240 mg/dL (13.3 mmol/L) from week 14 to 25, and .200 mg/dL (11.1 mmol/L) (or HbA1c .8.5% [69.4 mmol/mol]) from week 26 onward. Rescue medication was prescribed at the investigator's discretion (excluding GLP1RAs, dipeptidyl peptidase 4 inhibitors, and amylin analogues in the oral semaglutide arm and SGLT-2 inhibitors in the empagliflozin arm). Patients who prematurely discontinued trial product remained in the trial and could receive any other antidiabetic medications at the investigator's discretion (excluding GLP-1RAs in the oral semaglutide arm before completion of the follow-up visit 5 weeks after the last date on trial product).
Intervention(s)	• Empagliflozin 25 mg daily Oral empagliflozin 25 mg once daily for 52 weeks in addition to stable metformin dose. Empagliflozin was initiated at 10 mg once daily in the morning and escalated to 25 mg at week 8.
Cointervention	• Metformin

	All participants received oral metformin ≥1500 mg or max tolerated dose daily for 52 weeks.
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear Excluded " New York Heart Association Class IV", otherwise 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, or transient ischemic 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 with an estimated glomerular filtration rate <60 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	People with type 2 diabetes first diagnosed above 40 years of age Based on mean age (SD) 58 (10) years and duration of diagnosis for mean (SD) 7 (6.1) years
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	• Semaglutide 14 mg daily Oral semaglutide 14 mg daily for 52 weeks, in addition to stable metformin dose. Oral semaglutide was initiated at 3 mg once daily, escalated to 7 mg at week 4 and 14 mg after week 8. Patients were instructed to administer oral semaglutide in the morning in a fasted state with up to 120 mL of water at least 30 min before breakfast and any other oral medication.
Number of participants	822 participants were randomized to oral semaglutide 14mg once daily (n= 412) or empagliflozin 25 mg once daily (n= 410)
Duration of follow-up	52 weeks + 5-wk follow up
Indirectness	None
Method of analysis	Modified ITT Reports both treatment and trial policy results for all outcomes. Treatment policy evaluates all randomized patients, regardless of trial product discontinuation or use of rescue medication with multiple imputation for missing data. Trial policy estimand evaluates all randomised participants using data collected before premature trial product discontinuation or initiation of rescue medication from all randomized patients and assumes participants with missing data behave similarly to other participants in same treatment group. Other

397.2. Study arms

397.2.1. Empagliflozin 25 mg daily (N = 410)

Oral empagliflozin 25 mg for 52 weeks, in addition to stable metformin.

397.2.2. Semaglutide 14 mg (N = 412)

Oral semaglutide 14 mg weekly for 52 weeks, in addition to stable metformin.

397.3. Characteristics

397.3.1. Arm-level characteristics

Characteristic	Empagliflozin 25 mg daily (N = 410)	Semaglutide 14 mg (N = 412)
% Male Sample size	n = 206 ; % = 50	n = 209 ; % = 51
Mean age (SD) (years) Mean (SD)	57 (10)	58 (10)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA
Asian Sample size	n = 21 ; % = 5.1	n = 28 ; % = 6.8
Black/African-American Sample size	n = 33 ; % = 8	n = 26 ; % = 6.3
Hispanic or Latino Sample size	n = 108 ; % = 26.3	n = 91 ; % = 22.1
Other Sample size	n = 3 ; % = 0.7	n = 2 ; % = 0.5
White Sample size	n = 353 ; % = 86.1	n = 355 ; % = 86.4
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)	7.2 (5.8)	7.7 (6.3)
Cardiovascular risk factors Sample size	n = NR ; % = NR	n = NR ; % = NR
Smoking status Sample size	n = NR ; % = NR	n = NR ; % = NR

Characteristic	Empagliflozin 25 mg daily (N = 410)	Semaglutide 14 mg (N = 412)
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
eGFR mL/min/1.73m2 Mean (SD)	96 (15)	95 (15)
Other antidiabetic medication used Nominal	NR	NR
Blood pressure-lowering medication used Nominal	NR	NR
Statins/lipid-lowering medication used Nominal	NR	NR
Other treatment being received Nominal	NR	NR

1

2

398. Rodbard, 2017

Bibliographic Reference	Rodbard, H W; Bode, B W; Harris, S B; Rose, L; Lehmann, L; Jarlov, H; Thurman, J; Safety and efficacy of insulin degludec/liraglutide (IDegLira) added to sulphonylurea alone or to sulphonylurea and metformin in insulin-naive people with Type 2 diabetes: the DUAL IV trial.; Diabetic medicine : a journal of the British Diabetic Association; 2017; vol. 34 (no. 2); 189-196

398.1. 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	DUAL IV/NCT01618162
Study type	Randomised controlled trial (RCT) Double-blind, parallel-group, RCT
Study location	International (77 sites in 7 countries: Bulgaria, Canada, Germany, India, Israel, Turkey, USA)
Study setting	Outpatient
Study dates	08/2012 to 10/2013
Sources of funding	Sponsored by Novo Nordisk.
Inclusion criteria	• Aged≥18 years • Type 2 diabetes diagnosis • HbA1c level 7-9% inclusive • BMI≤40 kg/m2 • Previous treatment with stable dose of a sulphonylurea (≥half maximum approved dose according to local label) with or without metformin (≥1500 mg or max tolerated dose) for at least 90 days before screening

	• Insulin and GLP-1RA naive
Exclusion criteria	• Known or suspected hypersensitivity to trial product(s) or related products • Females of child-bearing 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).(Visit 1) • Any use of OADs (other than SU in monotherapy or in combination with metformin) ≤90 days prior to screening visit (Visit 1) • Use of any drug (other than SU in monotherapy or in combination with metformin), which in the Investigators opinion could interfere with the blood glucose level (e.g. systemic corticosteroids) • Previous treatment with GLP-1 receptor agonist (e.g. exenatide, liraglutide) • Treatment with any insulin regimen other than short term treatment due to intercurrent illness including gestational diabetes • Impaired liver function(ALAT≥2.5 times upper normal range) • Impaired renal function (serum-creatinine (≥133 µmol/l for males and ≥125 µmol/l for females), or as allowed according to local contraindications for metformin • Screening calcitonin ≥50 ng/l • Personal or family history of medullary thyroid carcinoma (MTC) or multiple endocrine neoplasia type 2 (MEN2) • Cardiovascular disorders defined as; congestive heart failure (NYHA class III-IV), diagnosis of unstable angina pectoris, cerebral stroke and/or myocardial infarction within the past 52 weeks prior to Visit 1 and/or planned coronary, carotid or peripheral artery revascularization procedures • Severe uncontrolled treated or untreated hypertension (systolic blood pressure ≥180 mmHg or diastolic blood pressure ≥100 mmHg) • Proliferative retinopathy requiring acute treatment or maculopathy (macular edema) according to the Investigator’s opinion • Participants with a clinical significant, active (during the past 12 months) disease of the gastrointestinal, pulmonary, endocrinological (other than Type 2 Diabetes Mellitus), neurological, genitourinary or haematological system that in the opinion of the Investigator, may confound the results of the trial or pose additional risk in administering trial product • Mental incapacity, unwillingness or language barrier precluding adequate understanding of the trial procedures or cooperation with the trial personnel • Known or suspected abuse of prescription drugs, alcohol or illicit substances • History of chronic pancreatitis or idiopathic acute pancreatitis • Suffer from a life threatening disease including malignant neoplasms and medical history of malignant neoplasms within the last 5 years (except basal and squamous cell skin cancer)

Recruitment / selection of participants	Participants randomised 2:1 using central interactive voice/web system to IDegLira or Placebo. Treatment masked for investigators and participants using PDS290 pen-injector to administer drugs. Masking maintained for participants and personnel during trial. IDegLira or placebo initiated at 10 dose steps with 1 dose step of IDegLira containing 1 unit insulin degludec and 0.036 mg liraglutide. Doses of IDegLira or placebo adjusted twice per week according to pre-defined algorithm based on breakfast self-monitored blood glucose from 3 consecutive days (aim to achieve 4-6 mmol/l). Maximum allowed dose steps were 50.
Intervention(s)	• IDegLira titrated daily Subcutaneous injection of IDeg Lira (100 U/ml insulin degludec and 3.6 mg/ml liraglutide) once daily, independent of meals in 3 ml prefilled pen (preferably at same time of day).
Cointervention	• Sulphonylurea All participants received a sulphonylurea with or without metformin for duration of trial.
Strata 1: People with type 2 diabetes mellitus and heart failure	People without heart failure Exclusion criteria for NYHA class III-IV congestive heart failure - likely intention to exclude symptomatic heart failure
Strata 2: People with atherosclerotic cardiovascular disease	People without atherosclerotic cardiovascular diseases Exclusion criteria for unstable angina, stroke, myocardial infarction within the past 52 weeks and planned coronary, carotid or peripheral artery revascularisation procedures
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear Exclusion criteria for impaired renal function, but not specifically for 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
Comparator	• Placebo Subcutaneous placebo injection for 26 weeks once daily, independent of meals in 3 ml prefilled pen (preferably at same time of day).
Number of participants	N=435
Duration of follow-up	26 weeks
Indirectness	None
Method of analysis	ITT ITT LOCF analysis (full analysis set) for all outcomes

398.2. Study arms

398.2.1. IDegLira titrated (N = 289)

Subcutaneous injection of IDegLira (insulin degludec 100 U/ml and liraglutide 3.6 mg/ml) in 3ml prefilled pen for 26 weeks, in addition to a sulphonylurea with or without metformin.

398.2.2. Placebo (N = 146)

Subcutaneous placebo for 26 weeks in addition to a sulphonylurea with or without metformin,

398.3. Characteristics

398.3.1. Arm-level characteristics

Characteristic	IDegLira titrated (N = 289)	Placebo (N = 146)
% Male Sample size	n = 154 ; % = 53.3	n = 73 ; % = 50
Mean age (SD) (years) Mean (SD)	60 (9.6)	59.4 (10.8)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA
Asian Sample size	n = 52 ; % = 18	n = 20 ; % = 13.7
Black/African-American Sample size	n = 16 ; % = 5.5	n = 13 ; % = 8.9
Hispanic or Latin American Sample size	n = 24 ; % = 8.3	n = 16 ; % = 11
Other Sample size	n = 1 ; % = 1.4	n = 1 ; % = 1.4
White Sample size	n = 217 ; % = 75.1	n = 111 ; % = 76
Presence of severe mental illness Sample size	n = 0 ; % = 0	n = 0 ; % = 0
People with significant cognitive impairment	n = 0 ; % = 0	n = 0 ; % = 0

Characteristic	IDegLira titrated (N = 289)	Placebo (N = 146)
Sample size		
People with a learning disability Sample size	n = 0 ; % = 0	n = 0 ; % = 0
Other antidiabetic medication used Sample size	n = NA ; % = NA	n = NA ; % = NA
Sulphonylurea only Sample size	n = 30 ; % = 10.4	n = 17 ; % = 11.6
Sulphonylurea + metformin Sample size	n = 259 ; % = 89.6	n = 129 ; % = 88.4

1

2

399. Rodbard, 2018

Bibliographic Reference	Rodbard, H. W.; Lingvay, I.; Reed, J.; de la Rosa, R.; Rose, L.; Sugimoto, D.; Araki, E.; Chu, P. L.; Wijayasinghe, N.; Norwood, P.; Semaglutide Added to Basal Insulin in Type 2 Diabetes (SUSTAIN 5): a Randomized, Controlled Trial; J Clin Endocrinol Metabol; 2018; vol. 103 (no. 6); 2291-2301

399.1. 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 5/NCT02305381
Study type	Randomised controlled trial (RCT) Double-blind, parallel-group, RCT
Study location	International (90 sites in Germany, Japan, Serbia, Slovakia, and USA)
Study setting	Outpatient
Study dates	12/2014 to 11/2015
Sources of funding	Funded by Novo Nordisk
Inclusion criteria	• Aged≥18 years (≥20 years in Japan) • Type 2 diabetes diagnosis • Stable basal insulin therapy (min 0.25 IU/kg/d and/or 20 IU/d of insulin glargine, insulin detemir, insulin degludec and/or npH insulin) with or without metformin for 90 days before screening • HbA1c level 7-10% inclusive

Exclusion criteria	• Treatment with any glucose-lowering agent other than basal insulin with or without metformin in the 90 days prior to screening (excepting short-term bolus insulin therapy of less than 7 days) • History of pancreatitis (acute or chronic) • Family history of medullary thyroid carcinoma or multiple endocrine neoplasia type 2 • Severe renal impairment (eGFR<30 mL/min/1.73 m2, MDRD) • More than three episodes of severe hypoglycemia within the 6 months prior to screening • Known proliferative retinopathy or maculopathy requiring acute treatment • Pregnant, breastfeeding, or intending to become pregnant
Recruitment / selection of participants	Participants randomised 2:2:1:1 to semaglutide (0.5 or 1.0 mg) or volume matched placebo (0.5 or 1.0 mg) using interactive voice/web-response system, stratified by baseline HbA1c level (<8/≥8%) and use of metformin (yes; no). Drugs were visually identical and had same packaging. Five-week follow period after treatment.
Intervention(s)	• Semaglutide 1.0 mg weekly • Semaglutide 0.5 mg weekly Subcutaneous injection of semaglutide 1.0 mg or 0.5 mg weekly for 30 weeks, in addition to basal insulin with or without metformin. For 0.5 mg , maintenance dose reached after 4 weeks of 0.25 mg or matching placebo weekly; for 1.0 mg maintenance dose reached after 4 weeks of 0.25 mg, followed by 0.5 mg for or matching placebo once weekly for 4 weeks.
Cointervention	• Basal insulin All participants received basal insulin (glargine, detemir, degludec or NPH) for duration of trial, with or without metformin. Participants with HbA1c≤8% had background basal insulin dose reduced 20% at trial start. Insulin titrations based on self-measured blood glucose according to protocol. Background basal insulin and metformin remained stable for trial except for i) dose reduction due to hypoglycaemia or ii) dose intensification (rescue medication).
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear Heart failure, New York Heart Association Class IV in the exclusion criteria. Unclear if this applies to all forms of heart failure.
Strata 2: People with atherosclerotic cardiovascular disease	People without atherosclerotic cardiovascular diseases Acute coronary or cerebrovascular event within 90 days before randomisation in the exclusion criteria
Strata 3: People with type 2	Not stated/unclear Severe renal impairment in the exclusion criteria - unclear if this relates to 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	eGFR ≥30mL/min/1.73m2
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Comparator	• Placebo Matching placebo for 30 weeks with fixed-dose escalation regimen same as for semaglutide groups.
Number of participants	N=397 randomised
Duration of follow-up	30 weeks + 5-wk follow up

Indirectness	None
Method of analysis	Modified ITT mITT analysis (all randomised participants who received at least one study drug dose) for efficacy and safety outcomes; primary analysis trial product estimand using data collected before premature trial product discontinuation or initiation of rescue medication from all randomized patients and assumes participants with missing data behave similarly to other participants in same treatment group. Secondary analysis treatment policy estimand evaluates all randomized patients, regardless of trial product discontinuation or use of rescue medication with multiple imputation for missing data.

399.2. Study arms

399.2.1. Semaglutide 1.0 mg weekly (N = 132)

Subcutaneous injection of semaglutide 1.0 mg weekly for 30 weeks, in addition to basal insulin with or without metformin.

399.2.2. Semaglutide 0.5 mg weekly (N = 132)

Subcutaneous injection of semaglutide 0.5 mg weekly for 30 weeks, in addition to basal insulin with or without metformin.

399.2.3. Placebo (N = 133)

Two arms combined of matched placebo (0.5 or 1.0 mg) weekly injections for 30 weeks, in addition to basal insulin with or without metformin.

399.3. Characteristics

399.3.1. Arm-level characteristics

Characteristic	Semaglutide 1.0 mg weekly (N = 132)	Semaglutide 0.5 mg weekly (N = 132)	Placebo (N = 133)
% Male Sample size	n = 77 ; % = 58.8	n = 74 ; % = 56.1	n = 71 ; % = 53.4
Mean age (SD) (years) Custom value	mean 58.5 (range 33-80)	mean 59.1 (range 28-84)	mean 58.8 (range 19-86(

Characteristic	Semaglutide 1.0 mg weekly (N = 132)	Semaglutide 0.5 mg weekly (N = 132)	Placebo (N = 133)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
Asian Sample size	n = 23 ; % = 17.6	n = 19 ; % = 14.4	n = 24 ; % = 18
Black/African-American Sample size	n = 9 ; % = 6.9	n = 4 ; % = 3	n = 8 ; % = 6
Other Sample size	n = 1 ; % = 0.8	n = 0 ; % = 0	n = 0 ; % = 0
White Sample size	n = 98 ; % = 74.8	n = 108 ; % = 81.8	n = 101 ; % = 75.9
Comorbidities Nominal	NR	NR	NR
Presence of frailty Nominal	NR	NR	NR
Time since type 2 diabetes diagnosed (years) Custom value	mean 13.7 (range 0.6-36.9)	mean 12.9 (range 0.4-37.1)	mean 13.3 (range 0.8-39.6)
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

Characteristic	Semaglutide 1.0 mg weekly (N = 132)	Semaglutide 0.5 mg weekly (N = 132)	Placebo (N = 133)
People with a learning disability Nominal	NR	NR	NR
Number of people with obesity Nominal	NR	NR	NR
Other antidiabetic medication used Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
Metformin Sample size	n = 110 ; % = 84	n = 110 ; % = 93.3	n = 110 ; % = 82.7
Sulphonylurea Participant was randomised in error and excluded from trial Sample size	n = 0 ; % = 0	n = 0 ; % = 0	n = 1 ; % = 0.8
Insulin glargine Sample size	n = 70 ; % = 53.4	n = 76 ; % = 57.6	n = 67 ; % = 50.4
Insulin detemir Sample size	n = 27 ; % = 20.6	n = 20 ; % = 15.2	n = 28 ; % = 21.1
Insulin degludec Sample size	n = 19 ; % = 14.5	n = 10 ; % = 7.6	n = 14 ; % = 10.5
NPH insulin Sample size	n = 15 ; % = 11.5	n = 27 ; % = 20.5	n = 24 ; % = 18
Blood pressure-lowering medication used Nominal	NR	NR	NR
Statins/lipid-lowering medication used Nominal	NR	NR	NR
Other treatment being received Nominal	NR	NR	NR

1

2

400. Rodbard, 2016

Bibliographic Reference	Rodbard, H. W.; Seufert, J.; Aggarwal, N.; Cao, A.; Fung, A.; Pfeifer, M.; Alba, M.; Efficacy and safety of titrated canagliflozin in patients with type 2 diabetes mellitus inadequately controlled on metformin and sitagliptin; Diabetes Obes Metab; 2016; vol. 18 (no. 8); 812-819

400.1. 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 provided
Study type	Randomised controlled trial (RCT) Double-blind, parallel-group, RCT
Study location	International (47 sites in Canada, Germany, USA and 2 other countries)
Study setting	Outpatient
Study dates	02/2014 to 09/2015
Sources of funding	Supported by Janssen Research and Development, LLC
Inclusion criteria	• Aged 18-75 years inclusive • Type 2 diabetes diagnosis • HbA1c 7.5-10.5% inclusive • Stable metformin dose (≥1500 mg/day) and sitagliptin (100 mg/day) for more than 12 weeks before screening
Exclusion criteria	• History of diabetic ketoacidosis or type 1 diabetes • Fasting self-monitored blood glucose (SMBG) levels≥15.0 mmol/l(≥270 mg/dl) at baseline

	• Myocardial infarction, unstable angina, a revascularization procedure or cerebrovascularaccident≤12 weeks before screening • History of NYHA Class III or IV cardiac disease • Uncontrolled hypertension • eGFR<60 ml/min/1.73 m2 or serum creatinine≥124µmol/l (≥1.4 mg/dl) in men or≥115µmol/l(≥1.3 mg/dl) in women • Taking loop diuretics • Taking any antihyperglycaemic agent other than metformin and sitagliptin≤12 weeks before screening
Recruitment / selection of participants	Initial 3-wk pretreatment phase (1-wk screening, 2-wk single-blind placebo run-in period), then permuted block randomisation 1:1, using computer-generated randomisation schedule and stratified by HbA1c level (<8%≥8%). Participants who had hypoglycaemia before 6 weeks increased dose (canagliflozin or matching placebo) if titration criteria met.
Intervention(s)	• Canagliflozin 100-300 mg daily Oral canagliflozin 100 mg until week 6. Participants who met following criteria were increased to 300 mg until week 26 if they had: • baseline eGFR≥70 mL/min/1.73 m2 • fasting SMBG ≥5.6 mmol/L (≥2 measurements in past 2 weeks) • no volume-depletion adverse events Participants who did not meet criteria stayed on 100 mg and were reassessed every 2 weeks until week 8 to determine dose titration eligibility.
Cointervention	• Metformin ≥1500 mg daily • Sitagliptin 100 mg daily All participants received background metformin and sitagliptin for duration of trial.
Strata 1: People with type 2 diabetes mellitus and heart failure	People without heart failure Exclusion criteria for people with New York Association Class III or IV cardiac disease - likely intention to exclude symptomatic heart failure
Strata 2: People with atherosclerotic cardiovascular disease	People without atherosclerotic cardiovascular diseases Exclusion criteria of unstable angina, myocardial infarction, a revascularisation procedure or a cerebrovascular accident in the 12 weeks before screening
Strata 3: People with type 2 diabetes mellitus and	Not stated/unclear eGFR and creatinine based exclusion criteria but no clear statement about CKD

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	eGFR ≥30mL/min/1.73m2 Exclusion criteria: eGFR<60 ml/min/1.73m2
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Comparator	• Placebo Matched placebo for 26 weeks.
Number of participants	N=213 (218 randomised, 6 excluded from mITT analysis set)
Duration of follow-up	26 weeks
Indirectness	None

Method of analysis	Modified ITT mITT observed data analysis (all randomised participants who received at least one study drug dose) for HbA1c and weight, and safety outcomes

400.2. Study arms

400.2.1. Canagliflozin 100 mg/300 mg titrated (N = 107)

Oral canagliflozin 100 mg/300 mg titrated for 26 weeks, in addition to metformin and sitagliptin.

400.2.2. Placebo (N = 106)

Matched placebo for 26 weeks, in addition to metformin and sitagliptin.

400.3. Characteristics

400.3.1. Arm-level characteristics

Characteristic	Canagliflozin 100 mg/300 mg titrated (N = 107)	Placebo (N = 106)
% Male Sample size	n = 66 ; % = 61.7	n = 55 ; % = 51.9
Mean age (SD) (years) Mean (SD)	57.4 (9.3)	57.5 (10.1)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA
Asian Sample size	n = 20 ; % = 18.7	n = 12 ; % = 11.3
Black/African-American Sample size	n = 6 ; % = 5.6	n = 16 ; % = 15.1
Other Sample size	n = 1 ; % = 0.9	n = 1 ; % = 0.9
White Sample size	n = 80 ; % = 74.8	n = 77 ; % = 72.6

Characteristic	Canagliflozin 100 mg/300 mg titrated (N = 107)	Placebo (N = 106)
Comorbidities Nominal	NR	NR
Presence of frailty Nominal	NR	NR
Time since type 2 diabetes diagnosed (years) Mean (SD)	9.8 (5.4)	10.1 (5.9)
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 Nominal	NR	NR
Blood pressure-lowering medication used Nominal	NR	NR
Statins/lipid-lowering medication used Nominal	NR	NR

Characteristic	Canagliflozin 100 mg/300 mg titrated (N = 107)	Placebo (N = 106)
Other treatment being received Nominal	NR	NR

1

2

401. Roden, 2005

Bibliographic Reference	Roden, M; Laakso, M; Johns, D; Widel, M; Urquhart, R; Richardson, C; Mariz, S; Tan, M H; Long-term effects of pioglitazone and metformin on insulin sensitivity in patients with Type 2 diabetes mellitus.; Diabetic medicine : a journal of the British Diabetic Association; 2005; vol. 22 (no. 8); 1101-6

401.1. Study details

Secondary publication of another included study- see primary study for details	See report 1.1

402. Rosenstock, 2019

Bibliographic Reference	Rosenstock, J.; Allison, D.; Birkenfeld, A. L.; Blicher, T. M.; Deenadayalan, S.; Jacobsen, J. B.; Serusclat, P.; Violante, R.; Watada, H.; Davies, M.; Effect of additional oral semaglutide vs sitagliptin on glycated hemoglobin in adults with type 2 diabetes uncontrolled with metformin alone or with sulfonylurea: the PIONEER 3 randomized clinical trial; JAMA; 2019; vol. 321 (no. 15); 1466-1480

402.1. 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	PIONEER 3 [NCT02607865]
Study type	Randomised controlled trial (RCT)
Study location	206 sites in 14 countries [Argentina, Brazil, France, Germany, Israel, Japan, Mexico, Romania, Russian Federation, South Africa, Turkey, Ukraine, United Kingdom, United States of America]
Study setting	NA
Study dates	Between February 2016 and March 2018
Sources of funding	Novo Nordisk
Inclusion criteria	Adult patients diagnosed as having type 2 diabetes, with HbA1c levels of 7.0% to 10.5% and taking a stable dosage of metformin with or without sulfonylurea.

Exclusion criteria	• Treatment with any medication for diabetes or obesity 90 days or less before screening (other than metformin, sulfonylurea, or short-term insulin [≤14 days in total]) • History of pancreatitis, renal impairment, and proliferative retinopathy or maculopathy requiring acute treatment
Recruitment / selection of participants	NR
Intervention(s)	• Oral semaglutide 3 mg/d • Oral semaglutide 7 mg/d • Oral semaglutide 14 mg/d [Oral semaglutide treatment was initiated with the 3-mg/d dosage, then escalated to 7 mg/d after 4 weeks and 14 mg/d after a further 4 weeks, until the randomized dosage was achieved.]
Cointervention	Participants received background metformin with or without sulfonylurea, maintained at the stable, pretrial dosage. Intensification of existing background glucose-lowering medication and/or initiation of new glucose-lowering medication was prescribed as an add-on to randomized treatment for patients with persistent or unacceptable hyperglycemia, based on predefined fasting plasma glucose and/or HbA1c criteria. Participants were instructed to administer trial products in the morning, in a fasting state, with up to half a glass of water (approximately 120 mL) at least 30 minutes before having breakfast or taking any other oral medication (including background glucose-lowering medication).
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear Exclusion criteria for NYHA class IV but no other information.
Strata 2: People with atherosclerotic cardiovascular disease	People without atherosclerotic cardiovascular diseases Exclusion criteria for myocardial infarction, stroke, hospitalisation for unstable angina and/or TIA within the past 180 days, planned coronary, carotid or peripheral artery revascularisation.
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear Renal impairment by eGFR but no other information

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	NA
Comparator	Sitagliptin was initiated and maintained at 100 mg/d
Number of participants	2463 patients were screened, with 1864 randomized to semaglutide, 3 mg/d (n = 466), 7 mg/d (n = 466), or 14 mg/d (n = 465); or to sitagliptin (n = 467). The trial was completed by 94.3% of patients (1758/1864). The percentages of patients completing treatment without use of rescue medication were 52.1% (243/466), 64.6% (301/466), 72% (335/465), and 60.6% (283/467) in the semaglutide 3-mg/d, 7-mg/d, and 14-mg/d and the sitagliptin groups, respectively.
Duration of follow-up	Weeks 26, 52 and 78

Indirectness	Directly applicable
Method of analysis	ITT Treatment policy estimand evaluates the treatment effect for all randomized patients regardless of trial product discontinuation or use of rescue medication. Effect was estimated by a pattern mixture model using multiple imputation to handle missing data, both the imputation and the analysis were based on analysis of covariance models with region and background medication as factors and baseline value as a covariate. Not stated/unclear The trial product estimand evaluates the treatment effect for all randomized patients under the assumption that all patients continued taking trial product for the entire planned duration of the trial and did not use rescue medication. This estimand aims at reflecting the effect of oral semaglutide compared with sitagliptin without the confounding effect of trial product discontinuation or use of rescue medication.
Additional comments	NA

402.2. Study arms

402.2.1. Semaglutide 3 mg/d (N = 466)

402.2.2. Semaglutide 7 mg/d (N = 466)

402.2.3. Semaglutide 14 mg/d (N = 465)

402.2.4. Sitagliptin 100 mg/d (N = 467)

402.3. Characteristics

402.3.1. Arm-level characteristics

Characteristic	Semaglutide 3 mg/d (N = 466)	Semaglutide 7 mg/d (N = 466)	Semaglutide 14 mg/d (N = 465)	Sitagliptin 100 mg/d (N = 467)
% Male Sample size	n = 254 ; % = 54.5	n = 245 ; % = 52.7	n = 247 ; % = 53.1	n = 238 ; % = 51
Mean age (SD) Mean (SD)	58 (10)	58 (10)	57 (10)	58 (10)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
White Sample size	n = 344 ; % = 73.8	n = 330 ; % = 71	n = 317 ; % = 68.2	n = 333 ; % = 71.3
Black of African American Sample size	n = 38 ; % = 8.2	n = 38 ; % = 8.2	n = 45 ; % = 9.7	n = 39 ; % = 8.4
Asian Sample size	n = 56 ; % = 12	n = 69 ; % = 14.8	n = 61 ; % = 13.1	n = 59 ; % = 12.6
American Indian or Alaska Native Sample size	n = 4 ; % = 0.9	n = 3 ; % = 0.6	n = 5 ; % = 1.1	n = 6 ; % = 1.3
Native Hawaiian or other Pacific Islander Sample size	n = 1 ; % = 0.2	n = 0 ; % = 0	n = 0 ; % = 0	n = 0 ; % = 0
Other Sample size	n = 13 ; % = 2.8	n = 11 ; % = 2.4	n = 20 ; % = 4.3	n = 12 ; % = 2.6
Hispanic or Latino Sample size	n = 76 ; % = 16.3	n = 77 ; % = 16.6	n = 75 ; % = 16.1	n = 93 ; % = 19.9
Comorbidities Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
Hypertension Sample size	n = 348 ; % = 74.7	n = 328 ; % = 70.5	n = 357 ; % = 76.8	n = 339 ; % = 72.6

Characteristic	Semaglutide 3 mg/d (N = 466)	Semaglutide 7 mg/d (N = 466)	Semaglutide 14 mg/d (N = 465)	Sitagliptin 100 mg/d (N = 467)
Dyslipidemia Sample size	n = 134 ; % = 28.8	n = 132 ; % = 28.4	n = 136 ; % = 29.2	n = 141 ; % = 30.2
Obesity Sample size	n = 125 ; % = 26.8	n = 142 ; % = 30.5	n = 119 ; % = 25.6	n = 133 ; % = 28.5
Diabetic neuropathy Sample size	n = 127 ; % = 27.3	n = 102 ; % = 21.9	n = 115 ; % = 24.7	n = 129 ; % = 27.6
Hyperlipidemia Sample size	n = 104 ; % = 22.3	n = 99 ; % = 21.3	n = 94 ; % = 20.2	n = 102 ; % = 21.8
Gallbladder disease Sample size	n = 75 ; % = 16.1	n = 66 ; % = 14.2	n = 84 ; % = 18.1	n = 85 ; % = 18.2
Ischemic heart disease Sample size	n = 73 ; % = 15.7	n = 76 ; % = 16.3	n = 77 ; % = 16.6	n = 81 ; % = 17.3
Diabetic retinopathy Sample size	n = 73 ; % = 15.7	n = 73 ; % = 15.7	n = 74 ; % = 15.9	n = 81 ; % = 17.3
Osteoarthritis Sample size	n = 67 ; % = 14.4	n = 61 ; % = 13.1	n = 74 ; % = 15.9	n = 59 ; % = 12.6
Hepatic steatosis Sample size	n = 55 ; % = 11.8	n = 47 ; % = 10.1	n = 56 ; % = 12	n = 55 ; % = 11.8
Cholecystectomy Sample size	n = 51 ; % = 10.9	n = 49 ; % = 10.5	n = 52 ; % = 11.2	n = 46 ; % = 9.9
Cataract Sample size	n = 45 ; % = 9.7	n = 46 ; % = 9.9	n = 54 ; % = 11.6	n = 45 ; % = 9.6
Diabetic nephropathy Sample size	n = 46 ; % = 9.9	n = 43 ; % = 9.2	n = 52 ; % = 11.2	n = 40 ; % = 8.6
Depression Sample size	n = 37 ; % = 7.9	n = 47 ; % = 10.1	n = 36 ; % = 7.7	n = 32 ; % = 6.9
Presence of frailty Nominal	NR	NR	NR	NR

Characteristic	Semaglutide 3 mg/d (N = 466)	Semaglutide 7 mg/d (N = 466)	Semaglutide 14 mg/d (N = 465)	Sitagliptin 100 mg/d (N = 467)
Time since type 2 diabetes diagnosed Mean (SD)	8.4 (6.1)	8.3 (5.8)	8.7 (6.1)	8.8 (6)
Cardiovascular risk factors Nominal	NR	NR	NR	NR
Smoking status Nominal	NR	NR	NR	NR
Alcohol consumption Nominal	NR	NR	NR	NR
Presence of severe mental illness Nominal	NR	NR	NR	NR
People with significant cognitive impairment Nominal	NR	NR	NR	NR
People with a learning disability Nominal	NR	NR	NR	NR
BMI (kg/m2) Mean (SD)	32.6 (6.7)	32.6 (6.4)	32.3 (6.3)	32.5 (6.2)
Number of people with obesity Nominal	NR	NR	NR	NR
Other antidiabetic medication used Mean (SD)	NA (NA)	NA (NA)	NA (NA)	NA (NA)
Metformin Mean (SD)	466 (100)	465 (100)	465 (100)	467 (100)
Sulfonylurea - Glimepiride	93 (47.2)	218 (46.9)	220 (47.3)	219 (46.9)

Characteristic	Semaglutide 3 mg/d (N = 466)	Semaglutide 7 mg/d (N = 466)	Semaglutide 14 mg/d (N = 465)	Sitagliptin 100 mg/d (N = 467)
Mean (SD)				
Sulfonylurea - Gliclazide Mean (SD)	47 (10.1)	59 (12.7)	51 (11)	53 (11.3)
Sulfonylurea - Glibenclamide Mean (SD)	46 (9.9)	41 (8.8)	36 (7.7)	46 (9.9)
Sulfonylrea - Glipizide Mean (SD)	33 (7.1)	30 (6.5)	26 (5.6)	23 (4.9)
Sulfonylurea - Gliquidone Mean (SD)	1 (0.2)	0 (*empty data*)	0 (0)	0 (*empty data*)
Blood pressure-lowering medication used Nominal	NR	NR	NR	NR
Statins/lipid-lowering medication used Nominal	NR	NR	NR	NR
Other treatment being received Nominal	NR	NR	NR	NR

1

2

403. Rosenstock, 2006

Bibliographic Reference	Rosenstock, J.; Brazg, R.; Andryuk, P. J.; Lu, K.; Stein, P.; Efficacy and safety of the dipeptidyl peptidase-4 inhibitor sitagliptin added to ongoing pioglitazone therapy in patients with type 2 diabetes: a 24-week, multicenter, randomized, double-blind, placebo-controlled, parallel-group study; Clin Ther; 2006; vol. 28 (no. 10); 1556-68

403.1. 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	Sitagliptin Protocol #19 [NCT00086502]
Study type	Randomised controlled trial (RCT)
Study location	Multinational study
Study setting	NR
Study dates	NR
Sources of funding	Merck & Co., Inc.
Inclusion criteria	Men and women, aged >18 years, with type 2 diabetes whether they were already taking an oral antihyperglycemic agent (OHA) or not
Exclusion criteria	• History of type 1 diabetes or ketoacidosis • Had been treated with insulin within 8 weeks of the screening visit • Had moderate renal dysfunction (creatinine clearance [CrCl] <45 mL/min or age- and sex-adjusted serum creatinine levels consistent with this CrC1)

	• History of hypersensitivity, intolerance, or a contraindication to the use of TZDs
Recruitment / selection of participants	At the screening visit, patients began a diet/exercise program that continued throughout the study period. Patients who were already taking a stable dose of pioglitazone (30 or 45 mg/d) and had a glycosylated hemoglobin (HbA1c) value ≥7% and ≤10% entered a 2-week, single-blind, placebo run-in period. Patients who were not taking an OHA, were taking monotherapy with another OHA, or were taking dual OHA therapy entered a pioglitazone monotherapy run-in period. Other OHAs were discontinued on entry to the run-in period, and pioglitazone was initiated and titrated upward as appropriate. Once they had achieved a stable pioglitazone dose (30 or 45 mg/d), patients entered a stable-dose period lasting up to 14 weeks. Patients with inadequate glycaemic control (HbA1c ≥7% and ≤10%) after the stable dose pioglitazone monotherapy period entered a 2-week, single-blind, placebo run-in period.
Intervention(s)	Sitagliptin 100 mg once daily
Cointervention	Stable dose of pioglitazone therapy. During the treatment period, patients not meeting specific progressive glycaemic goals (fasting plasma glucose [FPG] >270 mg/dL between randomization [day 1] and week 6; FPG >240 mg/dL after week 6 through week 12; or FPG >200 mg/dL after week 12 through week 24) were given rescue therapy (metformin) through the end of the study. Patients who were given metformin rescue therapy remained in the study to generate additional safety experience with the combination of sitagliptin and pioglitazone.
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	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
Population subgroups	NA
Comparator	Placebo
Number of participants	928 participants were screened and 353 were randomised. Of 175 participants were allocated to sitagliptin, 26 discontinued and 149 completed. Of 178 participants allocated to placebo, 20 discontinued and 158 completed.
Duration of follow-up	24 weeks
Indirectness	Directly applicable
Method of analysis	Other

	Report states that efficacy analyses were performed on the all-patients-treated (APT) population, which is all randomised participants who received ≥1 dose of study drug and had both baseline and ≥1 postbaseline measurements. HbA1C was analysed using an ANCOVA model with missing data imputed using the last-observation-carried forward. Data were treated as missing after the initiation of metformin rescue therapy in the efficacy analyses. Safety and tolerability analyses were performed on the all-patients-as-treated (APaT) population which included randomised patients who received ≥1 dose of the study drug. Weight change data were excluded after initiation of rescue therapy.
Additional comments	NA

403.2. Study arms

403.2.1. Sitagliptin (N = 175)

403.2.2. Placebo (N = 178)

403.3. Characteristics

403.3.1. Arm-level characteristics

Characteristic	Sitagliptin (N = 175)	Placebo (N = 178)
% Male Sample size	n = 93 ; % = 53.1	n = 103 ; % = 57.9
Mean age (SD) Mean (SD)	55.6 (10.4)	56.9 (11.1)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA
White Sample size	n = 127 ; % = 72.6	n = 129 ; % = 72.5
Hispanic	n = 21 ; % = 12	n = 22 ; % = 12.4

Characteristic	Sitagliptin (N = 175)	Placebo (N = 178)
Sample size		
Black Sample size	n = 11 ; % = 6.3	n = 12 ; % = 6.7
Asian Sample size	n = 10 ; % = 5.7	n = 5 ; % = 2.8
Other Sample size	n = 6 ; % = 3.4	n = 10 ; % = 5.6
Comorbidities Sample size	n = NA ; % = NA	n = NA ; % = NA
Metabolic syndrome Met NCEP ATP-III criteria Sample size	n = 92 ; % = 52.6	n = 90 ; % = 50.6
Presence of frailty Nominal	NR	NR
Time since type 2 diabetes diagnosed (years) Mean (SD)	6.1 (5.4)	6.1 (5.7)
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
BMI (kg/m2) Mean (SD)	32 (5.2)	31 (5)

Characteristic	Sitagliptin (N = 175)	Placebo (N = 178)
Number of people with obesity Nominal	NR	NR
Other antidiabetic medication used Sample size	n = NA ; % = NA	n = NA ; % = NA
OHA monotherapy at screening Sample size	n = 109 ; % = 62.3	n = 103 ; % = 58.2
Dual therapy with a TZD at screening Sample size	n = 52 ; % = 29.7	n = 54 ; % = 30.5
None Sample size	n = 14 ; % = 8	n = 20 ; % = 11.3
TZD use at screening Sample size	n = 89 ; % = 50.9	n = 84 ; % = 47.2
Blood pressure-lowering medication used Nominal	NR	NR
Statins/lipid-lowering medication used Nominal	NR	NR
Other treatment being received Nominal	NR	NR

1

2

404. Rosenstock, 2018

Bibliographic Reference	Rosenstock, J.; Buse, J. B.; Azeem, R.; Prabhakar, P.; Kjems, L.; Huang, H.; Baron, M. A.; Efficacy and Safety of ITCA 650, a Novel Drug-Device GLP-1 Receptor Agonist, in Type 2 Diabetes Uncontrolled With Oral Antidiabetes Drugs: the FREEDOM-1 Trial; Diabetes Care; 2018; vol. 41 (no. 2); 333-340

404.1. 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	FREEDOM-1 trial [NCT01455857]
Study type	Randomised controlled trial (RCT)
Study location	126 clinical sites in the U.S.
Study setting	NR
Study dates	NR
Sources of funding	Intarcia Therapeutics
Inclusion criteria	• Participants with type 2 diabetes receiving stable (≥3 months) treatment with diet and exercise alone or with metformin (≥1,500 mg/day), sulfonylureas (SUs) (greater than or equal to half maximal dose), or pioglitazone ≥30 mg/day monotherapy or in any combinations • Aged 18 to 80 years • Had an HbA1c ≥7.5% and ≤10%, fasting plasma glucose (FPG) ≤270 mg/dL, BMI ≥25 to ≤45 kg/m2, and serum calcitonin <50 ng/L at screening

Exclusion criteria	• Previously received a GLP-1 RA • Took dipeptidyl inhibitors, meglitinides, sodium-glucose cotransporter 2 inhibitors, or insulin (except short-term treatment) within 3 months of screening) • eGFR <60 mL/min per 1.73 m2
Recruitment / selection of participants	There was a 4-week screening period
Intervention(s)	• 40 mcg/day subcutaneous exenatide delivered by ITCA 650 (exenatide in osmotic mini-pump) • 60 mcg/day subcutaneous exenatide delivered by ITCA 650 (exenatide in osmotic mini-pump) [Treatment was initiated with subdermal placement in the abdominal wall of either the 20 mcg/day dose of ITCA 650 or a matching placebo mini-pump. These were removed and replaced with the allocated treatment dose at week 13.]
Cointervention	Participants maintained their baseline dose of background medication throughout the study. SUs could be down-titrated to avoid or treat hypoglycaemia. Participants with unacceptable hypoglycaemia were expected to receive additional antidiabetes treatment and continue in the study. Criteria for rescue therapy became more stringent as the study progressed beyond week 13.
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 Excluded if they had an eGFR <60 - but no other information
Strata 4: People with type 2 diabetes mellitus and	Not stated/unclear

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 Exclusion criteria: eGFR <60 mL/min per 1.73 m2
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Population subgroups	NA
Comparator	Matching placebo mini-pump
Number of participants	460 participants were randomised and 441 (95.9%) were included in the mITT population. Study completion rates were 79.9%, 78.4%, and 80.4% in the placebo, ITCA 650 40 mg/ay, and ITCA 650 60 mg/day group, respectively.
Duration of follow-up	39 weeks
Indirectness	Directly applicable
Method of analysis	ITT Not explicitly stated - The safety population included all randomised participants who had a procedure started.

	Modified ITT Included all participants from the safety population who had a baseline and at least one postbaseline HbA1c value. Missing values were imputed using the last observation carried forward method with data post-rescue excluded. Each treatment group was compared with placebo based on an ANCOVA model with change in HbA1c at LOCF end point as the outcome variable, treatment, baseline HbA1c, and concomitant use of SUs as explanatory factors.
Additional comments	NA

404.2. Study arms

404.2.1. Exenatide 40 mcg/day (N = 147)

404.2.2. Exenatide 60 mcg/day (N = 151)

404.2.3. Placebo (N = 143)

404.3. Characteristics

404.3.1. Arm-level characteristics

Characteristic	Exenatide 40 mcg/day (N = 147)	Exenatide 60 mcg/day (N = 151)	Placebo (N = 143)
Mean age (SD) (years) Mean (SD)	55.5 (10.3)	54.7 (9.6)	54.7 (9.1)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
White Sample size	n = 129 ; % = 84.3	n = 125 ; % = 81.7	n = 126 ; % = 81.8
Black or African American Sample size	n = 20 ; % = 13.1	n = 21 ; % = 13.7	n = 23 ; % = 14.9

Characteristic	Exenatide 40 mcg/day (N = 147)	Exenatide 60 mcg/day (N = 151)	Placebo (N = 143)
Other Sample size	n = 4 ; % = 2.6	n = 7 ; % = 4.6	n = 5 ; % = 3.3
Hispanic or Latino Sample size	n = 56 ; % = 36.6	n = 47 ; % = 30.7	n = 59 ; % = 38.3
Comorbidities Nominal	NR	NR	NR
Presence of frailty Nominal	NR	NR	NR
Time since type 2 diabetes diagnosed (years) Mean (SD)	9.1 (6.2)	8.9 (6.9)	8.6 (6)
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
BMI (kg/m2) Mean (SD)	33.1 (5.1)	33.8 (5.2)	33.7 (5.5)
Number of people with obesity Nominal	NR	NR	NR

Characteristic	Exenatide 40 mcg/day (N = 147)	Exenatide 60 mcg/day (N = 151)	Placebo (N = 143)
Other antidiabetic medication used Sample size	n = 137 ; % = 89.5	n = 135 ; % = 88.2	n = 138 ; % = 89.6
Metformin monotherapy Sample size	n = 63 ; % = 41.2	n = 61 ; % = 39.9	n = 66 ; % = 42.9
SU monotherapy Sample size	n = 7 ; % = 4.6	n = 7 ; % = 4.6	n = 2 ; % = 1.3
metformin + SU Sample size	n = 61 ; % = 39.9	n = 65 ; % = 42.5	n = 64 ; % = 41.6
Metformin + SU + TZD Sample size	n = 4 ; % = 2.6	n = 1 ; % = 0.7	n = 6 ; % = 3.9
Blood pressure-lowering medication used Nominal	NR	NR	NR
Statins/lipid-lowering medication used Nominal	NR	NR	NR
Other treatment being received Nominal	NR	NR	NR
% Female Sample size	n = 64 ; % = 41.8	n = 62 ; % = 40.5	n = 62 ; % = 40.3

1

2

405. Rosenstock, 2016

Bibliographic Reference	Rosenstock, J.; Guerci, B.; Hanefeld, M.; Gentile, S.; Aronson, R.; Tinahones, F. J.; Roy-Duval, C.; Souhami, E.; Wardecki, M.; Ye, J.; Perfetti, R.; Heller, S.; Prandial options to advance basal insulin glargine therapy: Testing lixisenatide plus basal insulin versus insulin glulisine either as basal-plus or basal-bolus in type 2 diabetes: The GetGoal Duo-2 Trial; Diabetes Care; 2016; vol. 39 (no. 8); 1318-1328

405.1. 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 Duo-2 [NCT01768559]
Study type	Randomised controlled trial (RCT)
Study location	199 centres in 18 countries [Canada, Chile, Czech Republic, Estonia, France, Germany, Hungary, Italy, Latvia, Lithuania, Mexico, Poland, Romania, Russian Federation, Spain, Ukraine, United Kingdom, United States
Study setting	NR
Study dates	January 2013 to December 2014
Sources of funding	Sanofi
Inclusion criteria	• Adults with type 2 diabetes for at least 1 year and a BMI >20.0–40.0 kg/m2 • Patients on on basal insulin for at least 6 months at screening (stable dose ≥20 units/day for ≥2 months before screening, alone or combined with stable doses of 1–3 OADs (metformin [≥1.5

	mg/day or maximum tolerated dose], a DPP-4 inhibitor, an SU, or a glinide) • Patients receiving basal insulin alone or with metformin had to have HbA1c 7.5–10.0% at screening. Patients receiving basal insulin plus an SU and/or a DPP-4 inhibitor and/or a glinide had to have HbA1c 7.0–10.0% at screening
Exclusion criteria	• Clinically relevant history of gastrointestinal disease or a history of unexplained/chronic pancreatitis • Alanine/aspartate aminotransferase, amylase, or lipase levels more than three times the upper limit of normal or calcitonin levels >20 pg/mL
Recruitment / selection of participants	During a run-in phase, OADs other than metformin were discontinued, and insulin glargine was introduced (for patients previously on a different basal insulin) or continued as part of a once-daily regimen, and titrated every 3 days to achieve fasting self-monitored plasma glucose (SMPG) between 80 and 100 mg/dL while avoiding hypoglycaemia. After the run-in phase, if HbA1c remained between ≥7 and ≤9% and mean fasting plasma glucose (FPG) was ≤140 mg/dL, patients were randomized.
Intervention(s)	Lixisenatide 10 mcg once daily for 2 weeks followed by 20 mcg for the remainder of the study, injected 30-60 min before main meal
Cointervention	Insulin glargine with dose adjusted weekly to maintain a fasting daily SMPG between 80 and 100 mg/dL except during the 4 weeks after randomisation when a stable insulin dose was maintained.
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	Not stated/unclear

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	NA
Comparator	• Insulin glulisine once daily (basal-plus) • Insulin glulisine three times daily (basal-bolus)
Number of participants	894 patients were randomised. Of 298 participants allocated to lixisenatide QD + insulin glargine, 268 (98.9%) completed treatment, and 30 (10.1%) discontinued treatment. Of 298 participants allocated to insulin glulisine QD + insulin glargine, 281 (94.3%) participants completed treatment, and 17 (5.7%) discontinued treatment. Of 298 participants allocated to insulin glulisine TID + insulin glargine 285 (95.6%) completed treatment and 12 (4.0%) discontinued treatment.
Duration of follow-up	26 weeks
Indirectness	Directly applicable

Method of analysis	Modified ITT Defined as all randomised participants with at least one dose of study medication and a baseline assessment and at least one assessment after the baseline of any primary or secondary outcome. Participants were analysed int he treatment group to which they were randomised, irrespective of compliance with the study protocol. HbA1c and weight change were analysed using an ANCOVA model with treatment, week -1 strata of HbA1c (<8 or ≥8%), randomisation strata of metformin use, and country as fixed effects, and using the corresponding baseline value as a covariate. Missing data were imputed using the last observation carried forward method. Not stated/unclear The safety analysis was conducted on the safety population (all randomised participants who received at least one dose of study medication regardless of the amount of treatment administered)
Additional comments	NA

405.2. Study arms

405.2.1. Lixisenatide (N = 298)

Comparator	• Insulin glulisine once daily (basal-plus) • Insulin glulisine tree times daily (basal-bolus)	• Insulin glulisine once daily (basal-plus) • Insulin glulisine tree times daily (basal-bolus)

405.2.2. Insulin glulisine QD (N = 298)

Comparator	• Insulin glulisine once daily (basal-plus) • Insulin glulisine tree times daily (basal-bolus)	• Insulin glulisine once daily (basal-plus) • Insulin glulisine tree times daily (basal-bolus)

405.2.3. Insulin glulisine TID (N = 298)

Comparator	• Insulin glulisine once daily (basal-plus) • Insulin glulisine tree times daily (basal-bolus)	• Insulin glulisine once daily (basal-plus) • Insulin glulisine tree times daily (basal-bolus)

405.3. Characteristics

405.3.1. Arm-level characteristics

Characteristic	Lixisenatide (N = 298)	Insulin glulisine QD (N = 298)	Insulin glulisine TID (N = 298)
% Male Sample size	n = 138 ; % = 46.3	n = 135 ; % = 45.3	n = 132 ; % = 44.3
Mean age (SD) Mean (SD)	59.8 (8.6)	60.2 (8.6)	59.4 (9.5)
Ethnicity White Sample size	n = 276 ; % = 92.6	n = 280 ; % = 94	n = 272 ; % = 91.3
Comorbidities Nominal	NR	NR	NR
Presence of frailty Nominal	NR	NR	NR
Time since type 2 diabetes diagnosed (years) Mean (SD)	11.9 (6.4)	12.3 (6.8)	12.4 (6.8)
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

Characteristic	Lixisenatide (N = 298)	Insulin glulisine QD (N = 298)	Insulin glulisine TID (N = 298)
BMI (kg/m2) Mean (SD)	32.3 (4.6)	31.9 (4.4)	32.5 (4.6)
Number of people with obesity Nominal	NR	NR	NR
Other antidiabetic medication used Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
Metformin Sample size	n = 262 ; % = 87.9	n = 260 ; % = 87.2	n = 259 ; % = 86.9
SU Sample size	n = 141 ; % = 47.3	n = 129 ; % = 43.3	n = 142 ; % = 47.7
DPP-4 inhibitor Sample size	n = 37 ; % = 12.4	n = 29 ; % = 9.7	n = 42 ; % = 14.1
Blood pressure-lowering medication used Nominal	NR	NR	NR
Statins/lipid-lowering medication used Nominal	NR	NR	NR
Other treatment being received Nominal	NR	NR	NR
Daily basal insulin dose (units/day) Mean (SD)	NA (NA)	NA (NA)	NA (NA)
NPH insulin Mean (SD)	41 (20)	39 (18)	41 (20)
Insulin glargine Mean (SD)	42 (23)	41 (23)	40 (23)
Insulin detemir Mean (SD)	41 (30)	40 (25)	39 (22)

1

2

406. Rosenstock, 2014

Bibliographic Reference	Rosenstock, J.; Hanefeld, M.; Shamanna, P.; Min, K. W.; Boka, G.; Miossec, P.; Zhou, T.; Muehlen-Bartmer, I.; Ratner, R. E.; Beneficial effects of once-daily lixisenatide on overall and postprandial glycemic levels without significant excess of hypoglycemia in Type 2 diabetes inadequately controlled on a sulfonylurea with or without metformin (GetGoal-S); J Diabetes Complications; 2014; vol. 28 (no. 3); 386-392

406.1. Study details

Trial name / registration number	GetGoal-S / NCT00713830
Study type	Randomised controlled trial (RCT)
Study location	136 centres in 16 countries; Bulgaria, Czech Republic, Egypt, Germany, India, Israel, Japan, Korea, The Netherlands, Romania, Russia, Taiwan, Thailand, Tunisia, Turkey, and the United States
Study setting	No additional information
Study dates	NR
Sources of funding	Sanofi
Inclusion criteria	Male and female participants aged 20–79 years with T2DM currently receiving a SU with or without metformin and with an HbA1c level of 7–10%
Exclusion criteria	Use of oral or injectable glucose lowering agents other than a SU or metformin within 3 months prior to the time of screening; fasting plasma glucose at screening >250.0 mg/dL (>13.9 mmol/L); history of unexplained pancreatitis, chronic pancreatitis, pancreatectomy, stomach/gastric surgery, or inflammatory bowel disease; history of gastrointestinal disease with prolonged nausea and vomiting in the 6 months prior to study initiation; history of metabolic acidosis, including diabetic ketoacidosis, within 1 year prior to screening; history of myocardial infarction, stroke, or heart failure requiring hospitalization within the previous 6 months; uncontrolled/inadequately controlled hypertension at the time of screening, with a resting systolic blood pressure of >180 mmHg or diastolic blood pressure >95 mmHg; amylase and/or lipase >3 times or aspartate aminotransferase, alanine aminotransferase, or alkaline phosphatase >2 times the upper limit of the normal laboratory range; and end-stage renal disease (defined by serum creatinine clearance of <15 mL/min) and/or dialysis. In the case of treatment with metformin, patients with renal impairment (defined by creatinine of >1.4 mg/dL in women and >1.5 mg/dL in men)

Recruitment / selection of participants	No additional information
Intervention(s)	Lixisenatide (n=574) Patients received lixisenatide once-daily in a 2-step dose-increase regimen (10 µg once-daily for 1 week, 15 µg once-daily for 1 week, then 20 µg once-daily). Lixisenatide was administered subcutaneously within 1 hour before the morning meal. During the dose-increase period, and depending on how well the patient tolerated the titration, the investigator could maintain the achieved dose level for an additional week before attempting a dose increase, reduce the dose (back to 15 µg once-daily and then, if necessary, to 10 µg once-daily), or discontinue treatment. If the dose was not increased as initially planned, another attempt had to be made within the subsequent 4 weeks. If the patient could not reach or tolerate the target dose of 20 µg once-daily, the 15 µg or 10 µg daily dose was maintained.
Cointervention	Sulfonylurea ± metformin Patients continued on their established doses of SU and, when appropriate, of metformin. Only in the case of a screening that resulted in HbA1c >8% was the SU dose decreased by 25–50% at the randomization visit to prevent hypoglycemia. The SU dose was then gradually increased to the dose received at screening between Weeks 4 and 12, according to fasting SMPG measurements. Both treatment groups received lifestyle and dietary counselling at screening and then every 3 months thereafter
Strata 1: People with type 2 diabetes mellitus and heart failure	People without heart failure Exclusion criteria for history of heart failure requiring hospitalisation in the previous 6 months
Strata 2: People with atherosclerotic cardiovascular disease	People without atherosclerotic cardiovascular diseases Exclusion criteria for myocardial infarction and stroke in the previous 6 months
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear Exclusion criteria for end-stage renal disease and/or dialysis and for specific renal impairment values but not specifically for chronic kidney disease
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	
Comparator	Placebo (n=286) Patients received once-daily placebo administered subcutaneously within 1 hour before the morning meal. Patients continued on their established doses of SU and, when appropriate, of metformin. Only in the case of a screening that resulted in HbA1c >8% was the SU dose decreased by 25–50% at the randomization visit to prevent hypoglycemia. The SU dose was then gradually increased to the dose received at screening between Weeks 4 and 12, according to fasting SMPG measurements.
Number of participants	859

Duration of follow-up	24 weeks
Indirectness	NA
Method of analysis	Modified ITT
Additional comments	The primary efficacy endpoint was analysed using an analysis of covariance (ANCOVA) model, with treatment group, randomization strata and country as fixed factors, and baseline HbA1c as a covariate. Continuous secondary efficacy variables were also analysed by ANCOVA; categorical secondary efficacy variables were analysed using a Cochran–Mantel–Haenszel method stratified on randomization strata. The last observation carried forward (LOCF) procedure was used to handle missing assessments or early discontinuation during the double-blind treatment period The primary efficacy endpoint was the absolute change in HbA1c from baseline to Week 24 for the mITT population, which consisted of all randomized patients who received at least one dose of double blind investigational product and had both a baseline and at least one post-baseline assessment of any primary or secondary efficacy parameter

406.2. Study arms

406.2.1. Lixisenatide (N = 573)

Patients received once daily subcutaneous lixisenatide in a two dose increase regimen; 10ug once daily for 1 week, 15ug once daily for one week, then 20ug for the remaining 22 weeks of treatment (24 weeks in total).

406.2.2. Placebo (N = 286)

Patients received once daily subcutaneous placebo for 24 weeks

406.3. Characteristics

406.3.1. Arm-level characteristics

Characteristic	Lixisenatide (N = 573)	Placebo (N = 286)
% Male Lixisenatide n= 547, Placebo n= 285 Sample size	n = 284 ; % = 49.5	n = 150 ; % = 52.6

Characteristic	Lixisenatide (N = 573)	Placebo (N = 286)
Mean age (SD) (Years (mean, SD)) Lixisenatide n= 547, Placebo n= 285 Mean (SD)	57 (9.8)	57.8 (10.1)
Ethnicity Lixisenatide n= 547, Placebo n= 285 Sample size	n = NA ; % = NA	n = NA ; % = NA
Caucasian Sample size	n = 297 ; % = 51.7	n = 151 ; % = 53
Black Sample size	n = 17 ; % = 3	n = 9 ; % = 3.2
Asian Sample size	n = 260 ; % = 45.3	n = 125 ; % = 43.9
Time since type 2 diabetes diagnosed (Years (mean, SD)) Lixisenatide n= 547, Placebo n= 285 Mean (SD)	9.1 (6)	9.8 (6.2)
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
Other antidiabetic medication used Sample size	n = NA ; % = NA	n = NA ; % = NA
Sulfonylurea Lixisenatide n= 547, Placebo n= 285 Sample size	n = 573 ; % = 100	n = 285 ; % = 100

Characteristic	Lixisenatide (N = 573)	Placebo (N = 286)
Metformin Lixisenatide n= 547, Placebo n= 285 Sample size	n = 465 ; % = 85	n = 239 ; % = 84
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

1

2

407. Rosenstock, 2015

Bibliographic Reference	Rosenstock, J.; Hansen, L.; Zee, P.; Li, Y.; Cook, W.; Hirshberg, B.; Iqbal, N.; Dual add-on therapy in type 2 diabetes poorly controlled with metformin monotherapy: a randomized double-blind trial of saxagliptin plus dapagliflozin addition versus single addition of saxagliptin or dapagliflozin to metformin; Diabetes Care; 2015; vol. 38 (no. 3); 376-83

407.1. 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	NCT01606007
Study type	Randomised controlled trial (RCT)
Study location	Canada, Mexico, Poland, Puerto Rico, Republic of Korea, Romania, South Africa; United States
Study setting	NR
Study dates	5th June 2012 to 17 January 2014
Sources of funding	Bristol-Myers Squibb and AstraZeneca
Inclusion criteria	• ≥18 years with type 2 diabetes and inadequate glycaemic control, defined as HbA1c ≥8.0% and ≤12.0% at screening • Patients on stable metformin therapy (≥1,500 mg/day) for 8 weeks before screening • C-peptide concentrations ≥1.0 ng/mL • BMI ≤ 45.0 kg/m2
Exclusion criteria	• Pregnancy

	• Uncontrolled hypertension (systolic blood pressure≥160mmHg and diastolic blood pressure≥100 mmHg) • Fasting plasma glucose (FPG) ≥270 mg/dL during the 4-week lead-in period, cardiovascular disease within 3 months of screening • Congestive heart failure (New York Heart Association functional class IV) • Estimated glomerular filtration rate <60mL/min/1.73m2 or serum creatinine ≥1.5mg/dL in men or ≥1.4mg/dL in women, and significant hepatic disease • Any antidiabetic medication, other than metformin, for more than 14 days during the 12 weeks before screening
Recruitment / selection of participants	At the beginning of a 4-week lead-in period, participants who had been on stable metformin therapy for at least 8 weeks before screening were switched to the nearest metformin extended release dose (1,500-2,000 mg/day) for the lead-in period and for the duration of the 24-week treatment period.
Intervention(s)	Saxagliptin (5 mg/day) and dapagliflozin (10 mg/day)
Cointervention	Metformin (dose 1,500-2,000 mg/day)
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear Exclusion criteria for congestive heart failure (NYHA class IV) - not clear if this includes all people with heart failure
Strata 2: People with atherosclerotic cardiovascular disease	People without atherosclerotic cardiovascular diseases Exclusion criteria for cardiovascular disease within 3 months of screening
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear eGFR categories in exclusion criteria but no specific mention to 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	eGFR ≥30mL/min/1.73m2
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Population subgroups	NA
Comparator	• Saxagliptin (5 mg/day) + Placebo • Dapagliflozin (10 mg/day) + Placebo
Number of participants	1282 people were enrolled, and 534 were randomised treatment. Of 179 participants allocated to saxagliptin + dapagliflozin, 10 (5.6% did not complete) and 169 (94.4%) completed. Of 176 participants allocated to saxagliptin + placebo, 15 (8.5%) did not complete and 161 (91.5%) completed. Of 179 participants allocated to dapagliflozin + placebo, 19 (10.6%) did not complete and 160 (89.4%) completed.
Duration of follow-up	24 weeks
Indirectness	Directly applicable
Method of analysis	Not stated/unclear Efficacy analysis included all randomised participants who received at least one does of a study medication during the treatment period. HbA1c change was performed using a longitudinal repeated-measures analysis

	with terms for baseline value, treatment group, time, the interaction of baseline value and tim, including observations before rescue.
Additional comments	Open-label rescue medication, including insulin or other antidiabetic medications, except metformin, GLP-1 receptor agonists, and other DPP-4 inhibitors or SGLT2 inhibitors, was given to patients with FPG>270mg/dL up to week 6; FPG.240 mg/dL at weeks 6–12; or FPG>200 mg/dL at weeks 12–24.

407.2. Study arms

407.2.1. Dapagliflozin + Saxagliptin (N = 179)

407.2.2. Saxagliptin + Placebo (N = 176)

407.2.3. Dapagliflozin + Placebo (N = 179)

407.3. Characteristics

407.3.1. Arm-level characteristics

Characteristic	Dapagliflozin + Saxagliptin (N = 179)	Saxagliptin + Placebo (N = 176)	Dapagliflozin + Placebo (N = 179)
Mean age (SD) Mean (SD)	53 (10)	55 (10)	54 (10)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
White Sample size	n = 120 ; % = 67	n = 121 ; % = 69	n = 131 ; % = 73
African American Sample size	n = 22 ; % = 12	n = 22 ; % = 13	n = 16 ; % = 9
Asian Sample size	n = 12 ; % = 7	n = 11 ; % = 6	n = 10 ; % = 6
Other Sample size	n = 25 ; % = 14	n = 22 ; % = 13	n = 22 ; % = 12

Characteristic	Dapagliflozin + Saxagliptin (N = 179)	Saxagliptin + Placebo (N = 176)	Dapagliflozin + Placebo (N = 179)
Comorbidities Nominal	NR	NR	NR
Presence of frailty Nominal	NR	NR	NR
Time since type 2 diabetes diagnosed Mean (SD)	7.1 (5)	8.2 (5.5)	7.4 (5.4)
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
BMI Mean (SD)	31.8 (4.8)	31.8 (5.1)	31.5 (5.3)
Number of people with obesity Nominal	NR	NR	NR
Other antidiabetic medication used Nominal	NR	NR	NR

Characteristic	Dapagliflozin + Saxagliptin (N = 179)	Saxagliptin + Placebo (N = 176)	Dapagliflozin + Placebo (N = 179)
Blood pressure-lowering medication used Nominal	NR	NR	NR
Statins/lipid-lowering medication used Nominal	NR	NR	NR
Other treatment being received Nominal	NR	NR	NR

1

2

408. Rosenstock, 2014

Bibliographic Reference	Rosenstock, J.; Jelaska, A.; Frappin, G.; Salsali, A.; Kim, G.; Woerle, H. J.; Broedl, U. C.; Improved glucose control with weight loss, lower insulin doses, and no increased hypoglycemia with empagliflozin added to titrated multiple daily injections of insulin in obese inadequately controlled type 2 diabetes; Diabetes Care; 2014; vol. 37 (no. 7); 1815-1823

408.1. Study details

Trial name / registration number	EMPA-REG MDI / NCT01306214
Study type	Randomised controlled trial (RCT)
Study location	104 centres across 14 countries
Study setting	No additional information
Study dates	March 2011 to April 2013
Sources of funding	Boehringer Ingelheim and Eli Lilly. A number of authors are employees of Boehringer Ingelheim and others declare funding and honoraria from multiple pharmaceutical companies
Inclusion criteria	This study enrolled obese adults (BMI ≥30 and ≤45 kg/m2) with T2DM and insufficient glycemic control (HbA1c ≥7.5 to ≤10% at screening) despite diet and exercise counselling and treatment with MDI insulin (total daily dose >60 international units) alone or in combination with metformin (immediate or extended release, ≥1,500 mg/day, maximum tolerated dose, or maximum dose according to the local label).
Exclusion criteria	Exclusion criteria included uncontrolled hyperglycemia (glucose level >13.3 mmol/L after an overnight fast during the placebo run-in, confirmed by a second measurement); acute coronary syndrome, stroke, or transient ischemic attack within 3 months prior to consent; indication of liver disease; impaired renal function during screening or run-in (eGFR using the modification of diet and renal disease equation <60 mL/min/1.73 m2); gastrointestinal surgeries that induce malabsorption; history of cancer (except for basal cell carcinoma) within 5 years; disorders causing hemolysis or unstable erythrocytes; treatment with systemic steroids at time of consent; change in dosage of thyroid hormones within 6 weeks prior to consent; treatment with anti-obesity drugs or alcohol or drug abuse within 3 months of consent; and investigational drug intake within 30 days of intake of study drug.
Recruitment / selection of participants	No additional information

Intervention(s)	Empagliflozin 10 mg (n= 186) Empagliflozin 25 mg (n= 189) Patients received once daily empagliflozin 10 mg or 25 mg for 52 weeks
Cointervention	Insulin ± Metformin Patients received insulin with or without metformin for 52 weeks. For the first 18 weeks, the total daily dose of insulin was to remain within 10% of the prescribed dose at randomization. During the titrated treat-to-target period (weeks 19–40), insulin dose was to be adjusted to achieve a preprandial glucose target of <5.5 mmol/L and a postprandial glucose target of <7.8 mmol/L. Between weeks 41 and 52, the total daily dose of insulin was to remain within 10% of the insulin dose prescribed at week 40, except for adjustments for safety reasons. Metformin dose was to remain unchanged throughout the study.
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 for acute coronary syndrome, stroke or transient ischaemic attack within 3 months
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear Exclusion criteria by eGFR value but no specific mention of 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	People with obesity
Subgroup 5: eGFR category at baseline	Not stated/unclear
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Population subgroups	NA
Comparator	Placebo (n= 188) Patients received once daily placebo as an add-on to insulin with or without metformin for 52 weeks. For the first 18 weeks, the total daily dose of insulin was to remain within 10% of the prescribed dose at randomization. During the titrated treat-to-target period (weeks 19–40), insulin dose was to be adjusted to achieve a preprandial glucose target of <5.5 mmol/L and a postprandial glucose target of <7.8 mmol/L. Between weeks 41 and 52, the total daily dose of insulin was to remain within 10% of the insulin dose prescribed at week 40, except for adjustments for safety reasons. Metformin dose was to remain unchanged throughout the study.
Number of participants	563
Duration of follow-up	52 weeks
Indirectness	NA
Method of analysis	ITT

Additional comments	The primary efficacy analysis was performed on the full analysis set (FAS), which included patients treated with ≥1 dose of study drug who had a baseline HbA1c value. Secondary end points and changes in insulin dose corrected for body weight were analysed in the "PPS-completers-52" set, defined as patients in the FAS who were on treatment up to day 357 and did not have important protocol violations. Efficacy analyses of other end points were performed on the FAS at week 18 and in the PPS-completers-52 set at week 52. Safety analyses were performed on the treated set (patients treated with ≥1 dose of study drug). The primary end point was assessed using an ANCOVA model, with treatment, region, background antidiabetes therapy, and eGFR as fixed effects and baseline HbA1c as a linear covariate. Secondary end points, continuous exploratory end points, and changes in insulin dose corrected for body weight were analysed using the statistical model described for the primary end point, with the baseline value for the end point in question as an additional linear covariate. Categorical change in HbA1c was analysed using logistic regression including the same factors as covariates.

408.2. Study arms

408.2.1. Empagliflozin 10 mg (N = 186)

Patients received once daily empagliflozin 10mg as add on to insulin with or without metformin for 52 weeks

408.2.2. Empagliflozin 25 mg (N = 189)

Patients received once daily empagliflozin 25 mg as add on to insulin with or without metformin for 52 weeks

408.2.3. Placebo (N = 188)

Patients received once daily placebo as add on to insulin with or without metformin for 52 weeks

408.3. Characteristics

408.3.1. Arm-level characteristics

Characteristic	Empagliflozin 10 mg (N = 186)	Empagliflozin 25 mg (N = 189)	Placebo (N = 188)
% Male Sample size	n = 97 ; % = 52	n = 84 ; % = 44	n = 75 ; % = 40

Characteristic	Empagliflozin 10 mg (N = 186)	Empagliflozin 25 mg (N = 189)	Placebo (N = 188)
Mean age (SD) (Years (mean, SD)) Mean (SD)	56.7 (8.7)	58 (9.4)	55.3 (10.1)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
White Sample size	n = 175 ; % = 94	n = 182 ; % = 96	n = 174 ; % = 93
Black/African American Sample size	n = 7 ; % = 4	n = 4 ; % = 2	n = 8 ; % = 4
Other Sample size	n = 4 ; % = 2	n = 3 ; % = 2	n = 6 ; % = 3
Time since type 2 diabetes diagnosed (Years (mean, SD)) 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
Other antidiabetic medication used Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
Metformin and insulin Sample size	n = 128 ; % = 69	n = 137 ; % = 72	n = 135 ; % = 72

Characteristic	Empagliflozin 10 mg (N = 186)	Empagliflozin 25 mg (N = 189)	Placebo (N = 188)
Insulin only Sample size	n = 58 ; % = 31	n = 52 ; % = 28	n = 53 ; % = 28
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

1

2

409. Rosenstock, 2015

Bibliographic Reference	Rosenstock, J.; Jelaska, A.; Zeller, C.; Kim, G.; Broedl, U. C.; Woerle, H. J.; on behalf of the EMPA-REG BASALTM trial, investigators; Impact of empagliflozin added on to basal insulin in type 2 diabetes inadequately controlled on basal insulin: a 78-week randomized, double-blind, placebo-controlled trial; Diabetes Obes Metab; 2015; vol. 17 (no. 10); 936-48

409.1. 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	EMPA-REG BASAL [NCT01011868]
Study type	Randomised controlled trial (RCT)
Study location	97 centres in seven countries (Denmark, France, Ireland, Korea, Portugal, UK and USA)
Study setting	NR
Study dates	November 2009 to May 2012
Sources of funding	Boehringer Ingelheim and Eli Lilly and Company
Inclusion criteria	• Body mass index (BMI) ≤45 kg/m2 • Inadequately controlled type 2 diabetes [HbA1c >7 to ≤10%] despite treatment with basal glargine or detemir insulin (≥20 UI/day) or NPH insulin (≥14 IU/day; at a dose unchanged by >10% of baseline value for ≥12 weeks before randomisation) • With or without metformin and/or sulfonylurea use (unchanged for ≥12 weeks prior to randomisation

Exclusion criteria	• Uncontrolled hyperglycaemia [glucose level ≥13.3mmol/l (>240mg/dl) after an overnight fast or >22.2mmol/l (>400mg/dl) from a random assessment during placebo run-in] • Frequent hypoglycaemic events on basal insulin therapy • Myocardial infarction, stroke or transient ischaemic attack <3months before consent • Estimated glomerular filtration rate (eGFR) <30 ml/min/1.73 m2 • Bariatric surgery • Investigational drug intake within 2 months of consent • Treatment with anti-obesity drugs, any oral anti-diabetes medication (other than metformin or sulfonylurea), chronic short-acting insulin or glucagon-like peptide-1 receptor agonists within 3 months of consent
Recruitment / selection of participants	There was a 2-week open-label placebo run-in, after which, eligible participants were randomised.
Intervention(s)	• Once daily empagliflozin 10 mg • Once daily empagliflozin 25 mg
Cointervention	Basal insulin, with or without metformin and/or sulfonylureas
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 for people who had a myocardial infarction, stroke or TIA <3 months before consent
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	Not stated/unclear
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Population subgroups	NA
Comparator	Placebo
Number of participants	826 patients were screened and 494 patients were randomised. Of 170 participants allocated to placebo, 118 (69%) completed 78 weeks treatment, and 170 participants were included in the full analysis set. Of 169 participants allocated to 10 mg empagliflozin, 131 (78%) completed 78 weeks treatment and 169 were included in the full analysis set. Of 155 participants were assigned to 25 mg empagliflozin, 111 (72%) completed 78 weeks treatment and 155 were included in the full analysis set.
Duration of follow-up	78 weeks
Indirectness	Directly applicable
Method of analysis	Other Full analysis set completers (participants in the full analysis set who did not discontinue before week 78, had a treatment duration of ≥532 days, and had an on-treatment HbA1c value available at day 532 or later). Data were analysed using ANCOVA with treatment and region as fixed effects

	and baseline HbA1c as a linear covariate. Values after initiation of rescue therapy were set to missing and imputed using the last observation carried forward approach. Safety analyses were performed on the treated set (participants with ≥1 dose of study drug).
Additional comments	For the first 18weeks, patients were to remain on a fixed dose of basal insulin; during the subsequent 60 weeks, the insulin dose was to be adjusted at the discretion of the investigator for any confirmed fasting plasma glucose (FPG) level >6.1mmol/l (>110mg/dl). Metformin and/or sulfonylurea were to remain unchanged. Rescue therapy could be initiated during treatment if a patient had: a confirmed glucose level >22.2mmol/l (>400mg/dl) from a randomly performed measurement; or between weeks 1 and 12, a confirmed glucose level >13.3mmol/l (>240mg/dl) after an overnight fast; or between weeks 12 and 18, a confirmed glucose level >11.1mmol/l (>200mg/dl) after an overnight fast; or between weeks 18 and 78, a confirmed glucose level >10.0mmol/l (>180mg/dl) after an overnight fast or HbA1c >8.0% (>64mmol/mol). Changes in dose of metformin or sulfonylureas for ≥7 days or addition of a new antidiabetic agent for ≥7days were considered as rescue therapy. Changes in basal insulin use were not considered as rescue therapy for the efficacy analyses after week 18.

409.2. Study arms

409.2.1. Empagliflozin 25 mg (N = 155)

409.2.2. Empagliflozin 10 mg (N = 169)

409.2.3. Placebo (N = 170)

409.3. Characteristics

409.3.1. Arm-level characteristics

Characteristic	Empagliflozin 25 mg (N = 155)	Empagliflozin 10 mg (N = 169)	Placebo (N = 170)
% Male Sample size	n = 93 ; % = 60	n = 93 ; % = 55	n = 90 ; % = 53
Mean age (SD) Mean (SD)	59.9 (10.5)	58.6 (9.8)	58.1 (9.4)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
White Sample size	n = 111 ; % = 72	n = 119 ; % = 70	n = 113 ; % = 66
Asian Sample size	n = 28 ; % = 18	n = 37 ; % = 22	n = 33 ; % = 19
Black/African-American Sample size	n = 15 ; % = 10	n = 12 ; % = 7	n = 21 ; % = 12
Other Sample size	n = 1 ; % = 1	n = 1 ; % = 1	n = 3 ; % = 2
Comorbidities Nominal	NR	NR	NR
Presence of frailty Nominal	NR	NR	NR
Time since type 2 diabetes diagnosed Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
< 1 year Sample size	n = 1 ; % = 1	n = 0 ; % = 0	n = 4 ; % = 2
>1 to 5 years Sample size	n = 12 ; % = 8	n = 15 ; % = 9	n = 20 ; % = 12
5+ years Sample size	n = 142 ; % = 92	n = 154 ; % = 91	n = 146 ; % = 86

Characteristic	Empagliflozin 25 mg (N = 155)	Empagliflozin 10 mg (N = 169)	Placebo (N = 170)
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
BMI Mean (SD)	32.7 (5.9)	32.1 (5.8)	31.8 (6)
Number of people with obesity Nominal	NR	NR	NR
Other antidiabetic medication used Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
Insulin + metformin Sample size	n = 69 ; % = 45	n = 70 ; % = 41	n = 61 ; % = 36
Insulin + metformin + SU Sample size	n = 58 ; % = 37	n = 68 ; % = 40	n = 68 ; % = 40
Insulin only Sample size	n = 11 ; % = 7	n = 16 ; % = 9	n = 24 ; % = 14
Insulin + SU Sample size	n = 17 ; % = 100	n = 15 ; % = 9	n = 17 ; % = 10

Characteristic	Empagliflozin 25 mg (N = 155)	Empagliflozin 10 mg (N = 169)	Placebo (N = 170)
Blood pressure-lowering medication used Nominal	NR	NR	NR
Statins/lipid-lowering medication used Nominal	NR	NR	NR
Other treatment being received Nominal	NR	NR	NR
Basal insulin type Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
Glargine Sample size	n = 87 ; % = 56	n = 95 ; % = 56	n = 104 ; % = 61
Detemir Sample size	n = 31 ; % = 20	n = 36 ; % = 21	n = 28 ; % = 16
NPH Sample size	n = 22 ; % = 14	n = 24 ; % = 14	n = 23 ; % = 14
MIssing Sample size	n = 15 ; % = 10	n = 14 ; % = 8	n = 15 ; % = 9

1

2

410. Rosenstock, 2019

Bibliographic Reference	Rosenstock, J.; Perl, S.; Johnsson, E.; Garcia-Sanchez, R.; Jacob, S.; Triple therapy with low-dose dapagliflozin plus saxagliptin versus dual therapy with each monocomponent, all added to metformin, in uncontrolled type 2 diabetes; Diabetes Obes Metab; 2019; vol. 21 (no. 9); 2152-2162

410.1. 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	NCT02681094
Study type	Randomised controlled trial (RCT)
Study location	119 centres in Canada, the Czech Republic, Germany, Mexico, Russia, and the USA
Study setting	NR
Study dates	The first participant was enrolled on 26 February 2016 and the last participant completed the study on 15 July 2017
Sources of funding	AstraZeneca
Inclusion criteria	• Aged ≥18 years • Diagnosis of type 2 diabetes • Stable metformin dose (≥1500 mg/d) for ≥8 weeks before enrolment • Body mass index ≤ 45 kg/m2 • Fasting plasma glucose (FPG) ≤15 mmol/L (≤270 mg/dL) • HbA1c 7.5% to 10.0%

Exclusion criteria	• A cardiovascular event in the 3 months before enrolment • Moderate or severe impairment of renal function (estimated glomerular filtration rate [eGFR] of <60 mL/min/1.73 or serum creatinine ≥1.5 mg/dL for men, or ≥1.4 mg/dL for women]) • Presence or history of severe (New York Heart Association class III and IV) congestive heart failure • Unstable or acute congestive heart failure
Recruitment / selection of participants	NA
Intervention(s)	Dapagliflozin 5 mg plus saxagliptin 5 mg
Cointervention	Treatment was added on to the patient's existing metformin treatment. Participants were eligible for open-label rescue with dapagliflozin 10 mg/d plus saxagliptin 5 mg/d, or with insulin from week 6 of the study onwards. The criteria for rescue medication were as follows: week 6, FPG >15.0 mmol/L (270 mg/dL); weeks 6 to 12, FPG >13.3 mmol/L (240 mg/dL); weeks 12 to 24, FPG >11.1 mmol/L (200 mg/dL).
Strata 1: People with type 2 diabetes mellitus and heart failure	People without heart failure Exclusion criteria for the presence or history of severe congestive heart failure (NYHA class III-IV) and/or unstable or acute congestive heart failure
Strata 2: People with atherosclerotic cardiovascular disease	People without atherosclerotic cardiovascular diseases Exclusion criteria for a cardiovascular event in the 3 months before enrolment
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear Exclusion criteria for a moderate or severe impairment of renal function based on eGFR or creatinine but no clear mention of CKD
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	eGFR ≥30mL/min/1.73m2
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Population subgroups	NA
Comparator	• Dapagliflozin 5 mg plus saxagliptin placebo • Saxagliptin 5 mg plus dapagliflozin placebo
Number of participants	1085 participants were enrolled and 883 were randomised. Of 293 participants allocated to dapagliflozin + saxagliptin, 20 discontinued treatment and 273 completed the study. Of 294 participants allocated to dapagliflozin, 17 discontinued treatment and 276 completed the study. Of 296 participants allocated to saxagliptin, 12 discontinued treatment and 283 completed the study.
Duration of follow-up	24 weeks
Indirectness	Directly applicable
Method of analysis	ITT All safety analyses were performed on the safety analysis dataset, which consisted of participants who received at least one dose of study medication; safety data were summarized using descriptive statistics. Not stated/unclear

	All efficacy analyses were conducted on the full analysis set, which comprised all randomized patients who received at least one dose of study medication during the double-blind treatment period and who had a baseline HbA1c measurement. Unless specified, analyses included values before rescue or treatment discontinuation. Analysis of HbA1c and weight change were carried out using a longitudinal repeated measures model, adjusted for treatment, week, baseline HbA1c, treatment-by-week interaction, and baseline HbA1c-by-week interaction. Sensitivity analyses were conducted for the primary end point using data up until the date of rescue medication or treatment discontinuation.
Additional comments	NA

410.2. Study arms

410.2.1. Dapagliflozin + Saxagliptin (N = 293)

410.2.2. Dapagliflozin (N = 294)

410.2.3. Saxagliptin (N = 296)

410.3. Characteristics

410.3.1. Arm-level characteristics

Characteristic	Dapagliflozin + Saxagliptin (N = 293)	Dapagliflozin (N = 294)	Saxagliptin (N = 296)
% Male Sample size	n = 142 ; % = 49	n = 152 ; % = 52.6	n = 157 ; % = 54
Mean age (SD) (years) Mean (SD)	57.2 (10.7)	55.9 (10.9)	57 (9.9)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA

Characteristic	Dapagliflozin + Saxagliptin (N = 293)	Dapagliflozin (N = 294)	Saxagliptin (N = 296)
White Sample size	n = 265 ; % = 91.4	n = 257 ; % = 88.9	n = 258 ; % = 88.7
Black/African American Sample size	n = 10 ; % = 3.4	n = 17 ; % = 5.9	n = 24 ; % = 8.2
Asian Sample size	n = 9 ; % = 3.1	n = 9 ; % = 3.1	n = 6 ; % = 2.1
Native American/Alaskan native Sample size	n = 1 ; % = 0.3	n = 3 ; % = 1	n = 0 ; % = 0
Other Sample size	n = 5 ; % = 1.7	n = 3 ; % = 1	n = 3 ; % = 1
Comorbidities Nominal	NR	NR	NR
Presence of frailty Nominal	NR	NR	NR
Time since type 2 diabetes diagnosed (years) Mean (SD)	7.5 (6.3)	7.6 (6.3)	7.8 (5.8)
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

Characteristic	Dapagliflozin + Saxagliptin (N = 293)	Dapagliflozin (N = 294)	Saxagliptin (N = 296)
People with a learning disability Nominal	NR	NR	NR
BMI (kg/m2) Mean (SD)	31.5 (5.5)	31.8 (5.2)	32.4 (5.5)
Number of people with obesity Nominal	NR	NR	NR
Other antidiabetic medication used Nominal	NR	NR	NR
Blood pressure-lowering medication used Nominal	NR	NR	NR
Statins/lipid-lowering medication used Nominal	NR	NR	NR
Other treatment being received Nominal	NR	NR	NR

1

2

411. Rosenstock, 2009

Bibliographic Reference	Rosenstock, J.; Rendell, M. S.; Gross, J. L.; Fleck, P. R.; Wilson, C. A.; Mekki, Q.; Alogliptin added to insulin therapy in patients with type 2 diabetes reduces HbA(1C) without causing weight gain or increased hypoglycaemia; Diabetes Obes Metab; 2009; vol. 11 (no. 12); 1145-52

411.1. 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	NCT00286429
Study type	Randomised controlled trial (RCT)
Study location	110 sites in 130 countries
Study setting	NR
Study dates	NR
Sources of funding	Unclear, appears that the study could have been funded by Takeda Pharmaceuticals
Inclusion criteria	• Aged 18-80 years with inadequately controlled type 2 diabetes on chromic insulin therapy • HbA1c level of ≥8.0% and a body mass index (BMI) of 23–45 kg/m2 and to have received insulin, with or without concomitant metformin therapy, at a stable dose of ≥15 and ≤100 units per day (varying by ≤15%of the mean) for at least 8 weeks before randomization
Exclusion criteria	• History of laser treatment for proliferative diabetic retinopathy, coronary angioplasty, coronary stent placement, coronary bypass surgery or myocardial infarction within the previous 6 months.

	• New York Heart Association class III or IV heart failure, treated diabetic gastroparesis and cancer (other than squamous cell or basal cell carcinoma of the skin) that had not been in full remission for at least 5 years. • Use of additional antidiabetic agents (other than metformin), weight loss drugs or glucocorticoids was not allowed from 3 months before randomization through the end of treatment.
Recruitment / selection of participants	Patients eligible for screening entered a 4-week, single-blind, run-in stabilization period where they maintained existing insulin regimen and metformin regimen if applicable. During this period, participants received dietary and exercise counselling and instruction on maintaining records of blood glucose monitoring and learning to recognise and document hypoglycaemic events. After the run-in/stabilization period, eligible participants with an HbA1c ≥8.0% were randomised to treatment.
Intervention(s)	• Alogliptin 12.5 mg QD • Alogliptin 25 mg QD
Cointervention	Stable insulin therapy with or without metformin
Strata 1: People with type 2 diabetes mellitus and heart failure	People without heart failure Exclusion criteria for people with NYHA class III-IV heart failure, likely people with symptomatic heart failure excluded
Strata 2: People with atherosclerotic cardiovascular disease	People without atherosclerotic cardiovascular diseases Exclusion criteria for people with coronary angioplasty, coronary stent placement, coronary bypass surgery or myocardial infarction in the previous 6 months
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	Not stated/unclear
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Population subgroups	NA
Comparator	Placebo
Number of participants	477 patients were enrolled, and 390 patients were randomised. Of 130 participants allocated to placebo. 55 (42.4%) completed, 52 (40%) required hyperglycaemic rescue, and 23 (17.7%) discontinued. Of 131 participants allocated to 12.5 mg alogliptin, 83 (63.4%) completed, 27, (20.6%) required hyperglycaemic rescue, and 21 (16%) discontinued. Of 129 participants allocated to 25 mg alogliptin, 77 (59.7%) completed, 25 (19.4%) required hyperglycaemic rescue, and 27 (20.9%) discontinued.
Duration of follow-up	26 weeks
Indirectness	Directly applicable
Method of analysis	Other Efficacy analyses were performed using the full analysis set (FAS), which for any efficacy variable included all participants who took at least one

	dose of the study drug and had a baseline assessment and at least one post-baseline assessment of that variable. Safety analyses included all participant who tool at least one dose of double-blind study drug.
Additional comments	Participants were withdrawn from the study if they fulfilled any of the following hyperglycaemic rescue criteria: fasting plasma glucose (FPG) ≥16.65 mmol/l after 1 week of treatment but before week 4; FPG ≥15.27 mmol/l from week 4 to week 8; FPG ≥13.88 mmol/l from week 8 to week 12 or HbA1C ≥8.7% with a ≤0.5% decrease from baseline after week 12.

411.2. Study arms

411.2.1. Alogliptin 12.5 mg (N = 131)

411.2.2. Alogliptin 25 mg (N = 129)

411.2.3. Placebo (N = 130)

411.3. Characteristics

411.3.1. Arm-level characteristics

Characteristic	Alogliptin 12.5 mg (N = 131)	Alogliptin 25 mg (N = 129)	Placebo (N = 130)
% Male Sample size	n = 55 ; % = 42	n = 44 ; % = 34	n = 62 ; % = 48
Mean age (SD) Mean (SD)	55.4 (9.8)	55.9 (10.2)	55 (10.6)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
White Sample size	n = 81 ; % = 62	n = 85 ; % = 66	n = 89 ; % = 69
Black/African-American Sample size	n = 19 ; % = 15	n = 19 ; % = 15	n = 16 ; % = 12

Characteristic	Alogliptin 12.5 mg (N = 131)	Alogliptin 25 mg (N = 129)	Placebo (N = 130)
Asian Sample size	n = 16 ; % = 12	n = 15 ; % = 12	n = 15 ; % = 12
Other Sample size	n = 15 ; % = 12	n = 10 ; % = 8	n = 10 ; % = 8
Hispanic or Latino Sample size	n = 45 ; % = 34	n = 42 ; % = 33	n = 42 ; % = 32
Comorbidities Nominal	NR	NR	NR
Presence of frailty Nominal	NR	NR	NR
Time since type 2 diabetes diagnosed Mean (SD)	12.1 (7.2)	13.4 (6.3)	12.2 (7.1)
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
BMI (kg/m2) Mean (SD)	32.7 (5.5)	32.3 (5.6)	32.4 (5.6)

Characteristic	Alogliptin 12.5 mg (N = 131)	Alogliptin 25 mg (N = 129)	Placebo (N = 130)
Number of people with obesity Nominal	NR	NR	NR
Other antidiabetic medication used Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
Insulin only Sample size	n = 54 ; % = 41	n = 57 ; % = 44	n = 51 ; % = 39
Insulin + metformin Sample size	n = 77 ; % = 59	n = 72 ; % = 56	n = 79 ; % = 61
Blood pressure-lowering medication used Nominal	NR	NR	NR
Statins/lipid-lowering medication used Nominal	NR	NR	NR
Other treatment being received Nominal	NR	NR	NR

1

2

412. Rosenstock, 2012

Bibliographic Reference	Rosenstock, J.; Vico, M.; Wei, L.; Salsali, A.; List, J. F.; Effects of dapagliflozin, an SGLT2 inhibitor, on HbA(1c), body weight, and hypoglycemia risk in patients with type 2 diabetes inadequately controlled on pioglitazone monotherapy; Diabetes Care; 2012; vol. 35 (no. 7); 1473-8

412.1. Study details

Trial name / registration number	Study MB102030 / NCT00683878
Study type	Randomised controlled trial (RCT)
Study location	105 sites in Argentina, Canada, India, Mexico, Peru, Philippines, Taiwan, and United States
Study setting	No additional information
Study dates	29 July 2008 to 15 June 2010
Sources of funding	Bristol-Myers Squibb and AstraZeneca. Numerous authors declare funding and honoraria from multiple pharmaceutical companies
Inclusion criteria	T2DM Patients ≥18 years old having fasting C-peptide ≥1.0 ng/mL and BMI ≤45.0 kg/m2 entered group A or B of the trial. Group A patients had received ≥12 weeks of pioglitazone 30 or 45 mg/day and had HbA1c ≥7.0 and ≤10.5%. Group B patients were drug naïve for the previous 10 weeks with HbA1c ≥8.0 and ≤11.0% or had received pioglitazone 15 mg/day or any dose of rosiglitazone with HbA1c ≥8.0 and ≤11.0% or had received ≥8 weeks of metformin ≤1700 mg/day or sulfonylurea less than or equal to half the maximal dose with HbA1c ≥7.0 and ≤11.0%.
Exclusion criteria	Aspartate or alanine aminotransferases >2.5 times the upper limit of normal, total bilirubin >2.0 mg/dL, serum creatinine ≥2.0 mg/dL, urine albumin/creatinine ratio >1,800 mg/g, calculated creatinine clearance <50 mL/min, and congestive heart failure class III and IV Group B patients could not be on >1 oral antidiabetic medication.

Recruitment / selection of participants	No additional information
Intervention(s)	Dapagliflozin 5 mg (n= 141) Dapagliflozin 10 mg (n=140) Patients received dapagliflozin 5 mg or 10 mg orally every day for 48 weeks
Cointervention	Pioglitazone Patients received open label pioglitazone 30 or 45 mg/day for 48 weeks
Strata 1: People with type 2 diabetes mellitus and heart failure	People without heart failure Exclusion criteria for people with congestive heart failure class III and IV.
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 Exclusion criteria for creatinine, urine albumin/creatinine ratios and creatinine clearance but no specific mention of 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	NA
Comparator	Placebo (n=139) Patients received oral placebo for in addition to 30 or 45 mg / day pioglitazone for 48 weeks
Number of participants	420
Duration of follow-up	48 weeks
Indirectness	NA
Method of analysis	ITT
Additional comments	Little information regarding analysis reported however appears to be ITT analysis At week 48, analyses of change from baseline in HbA1c, FPG, PPG, and body weight were performed using longitudinal repeated-measures analysis over time including the fixed categorical effects of strata based on pre-enrolment antidiabetic therapy, treatment, week, and treatment by-week interaction as well as the continuous fixed covariates of baseline measurement and baseline measurement-by-week interaction.

412.2. Study arms

412.2.1. Dapagliflozin 5 mg (N = 141)

Patients receive 5 mg dapagliflozin daily in addition to pioglitazone daily for 48 weeks

412.2.2. Dapagliflozin 10 mg (N = 140)

Patients receive 10 mg dapagliflozin daily in addition to pioglitazone daily for 48 weeks

412.2.3. Placebo (N = 139)

Patients receive placebo daily in addition to pioglitazone daily for 48 weeks

412.3. Characteristics

412.3.1. Arm-level characteristics

Characteristic	Dapagliflozin 5 mg (N = 141)	Dapagliflozin 10 mg (N = 140)	Placebo (N = 139)
% Male Sample size	n = 78 ; % = 55.3	n = 59 ; % = 42.1	n = 71 ; % = 51.1
Mean age (SD) (Years (mean, SD)) Mean (SD)	53.2 (10.9)	53.8 (10.4)	53.5 (11.4)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
White Sample size	n = 102 ; % = 72.3	n = 101 ; % = 72.1	n = 102 ; % = 74.3
African-American Sample size	n = 9 ; % = 6.4	n = 7 ; % = 5	n = 6 ; % = 4.3
Asian Sample size	n = 26 ; % = 18.4	n = 21 ; % = 15	n = 24 ; % = 17.3
Other Sample size	n = 4 ; % = 2.8	n = 11 ; % = 7.9	n = 7 ; % = 5
Time since type 2 diabetes diagnosed Mean (SD)	5.64 (5.36)	5.75 (6.44)	5.07 (5.05)

Characteristic	Dapagliflozin 5 mg (N = 141)	Dapagliflozin 10 mg (N = 140)	Placebo (N = 139)
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
Other antidiabetic medication used Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
Pioglitazone Sample size	n = 141 ; % = 100	n = 140 ; % = 100	n = 139 ; % = 100
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

1

2

413. Rosenstock, 2019

Bibliographic Reference	Rosenstock, J; Kahn S, E; Johansen O, E; Zinman, B; Espeland M, A; Woerle H, J; Pfarr, E; Keller, A; Mattheus, M; Baanstra, D; Meinicke, T; George J, T; Von Eynatten, M; McGuire D, K; Marx, N; Effect of Linagliptin vs Glimepiride on Major Adverse Cardiovascular Outcomes in Patients with Type 2 Diabetes: The CAROLINA Randomized Clinical Trial; JAMA - Journal of the American Medical Association; 2019; vol. 322 (no. 12); 1155-1166

413.1. Study details

Secondary publication of another included study- see primary study for details	This is the parent record of the CAROLINA trial and all study details for this trial will be included in this record. Rosenstock 2019B.
Other publications associated with this study included in review	Marx, Nikolaus, Rosenstock, Julio, Kahn, Steven E et al. (2015) Design and baseline characteristics of the CARdiovascular Outcome Trial of LINAgliptin Versus Glimepiride in Type 2 Diabetes (CAROLINA R). Diabetes & vascular disease research 12(3): 164-74
Trial name / registration number	CAROLINA/ NCT01243424
Study type	Randomised controlled trial (RCT)
Study location	Study completed in 607 centres across 43 countries.
Study setting	Hospital and primary care setting
Study dates	November 2010 to December 2012 (final follow-up August 2018)
Sources of funding	Boehringer Institute and Eli Lilly and Company.
Inclusion criteria	Adults with a documented diagnosis of type 2 diabetes mellitus; insufficient glycaemic control (defined as HbA1c 6.5% - 8.5% while the person is treatment naïve [if intolerant or contra-indicated to first line anti-diabetic treatment] or treated with metformin monotherapy, alpha-glucosidase inhibitor monotherapy, or metformin + alpha-glucosidase inhibitor. If patient HbA1c was 6.5% to 7.5% while patient is treated with sulfonylurea monotherapy, glinide monotherapy, metformin + sulfonylurea, or metformin + glinide, sulfonylurea + alpha-glucosidase inhibitor, or glinide + alpha-

	glucosidase inhibitor); high risk of CV events, defined as (any one or more) previous vascular disease (defined as myocardial infarction more than 6 weeks prior to informed consent, documented coronary artery disease, percutaneous coronary intervention, coronary artery by-pass grafting, ischemic or haemorrhagic stroke, or peripheral occlusive arterial disease), evidence of vascular-related end-organ damage (defined as moderately impaired renal function with estimated glomerular filtration rate 30-59 mL/min/1.73 m2, random spot urinary albumin: creatinine ratio ≥30 micrograms/mg (≥3.4 mg/mmol) in two of three unrelated specimens in previous 12 months prior to the first visit, or proliferative retinopathy), age ≥ 70 years, or at least two CV risk factors (identified as type 2 diabetes duration more than 10 years, current SBP >140 mmHg, current daily cigarette smoking, or current LDL cholesterol ≥135 mg/dL); BMI ≤45 kg/m2 at first visit; Age ≥40 and ≤85 years at first visit; Signed and dated informed consent; Stable anti-diabetic background medication (unchanged daily dose) for at least 8 weeks prior to first visit.
Exclusion criteria	Type 1 diabetes mellitus; any history and/or concurrent treatment with other antidiabetic drugs prior to informed consent; treatment with anti-obesity drugs 3 months prior to informed consent; uncontrolled hypoglycaemia with glucose level >240 mg/dl after an overnight fast during placebo run-in and confirmed by a second measurement; active liver disease or impaired hepatic function; any previous (or planned within the next 12 months) bariatric surgery or intervention; pre-planned coronary artery re-vascularisation (percutaneous coronary intervention or coronary artery bypass graft) within next 6 months after first visit or any previous percutaneous coronary intervention and/or coronary artery bypass graft ≤ 6 weeks prior informed consent; known hypersensitivity or allergy to the intervention; inappropriateness of glimepiride treatment for renal safety issues or other issues according to local prescribing information; congestive heart failure of NYHA class III or IV; acute or chronic metabolic acidosis; hereditary galactose intolerance; alcohol or drug abuse within the 3 months prior to informed consent that would interfere with trial participation; current treatment with systemic corticosteroids at time of informed consent or pre-planned initiation of such therapy; change in dose of thyroid hormones with 6 weeks prior to informed consent; participation in another trial with an investigational drug given within 2 months prior to informed consent; pre-menopausal women (last menstruation ≤ 1 year prior to informed consent) who are nursing or are pregnant, or are of child-bearing potential and are not practicing an acceptable method of birth control); people considered unreliable by the investigator concerning the requirements for follow-up during the study and/or compliance with the study drug administration, has a life expectancy of <5 years for non-CV causes, or has cancer other than non-melanoma skin cancer within last 3 years, or has any other condition than mentioned, which in the opinion of the investigator, would not allow safe participation in the study; acute coronary syndrome ≤6 weeks prior to informed consent; stroke or TIA ≤3 months prior to informed consent.
Recruitment / selection of participants	Not specified.
Intervention(s)	Linagliptin (5 mg)

Strata 1: People with type 2 diabetes mellitus and heart failure	People without heart failure Around 5% of people had heart failure
Strata 2: People with atherosclerotic cardiovascular disease	Mixed population Around 40% of people
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 People were entered into the trial if they were of 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	eGFR ≥30mL/min/1.73m2 baseline characteristics show that only 0.5% were <30ml/min/1.73m2
Subgroup 6: Albuminuria category at baseline	Mixed population Majority <30mg/g, but a proportion have a value 30-300 (around 21%)
Population subgroups	Pre-specified subgroups for 3P-MACE outcome include: baseline age, sex, race, ethnicity, region, glycated haemoglobin, body mass index, blood pressure control, estimated glomerular filtration rate according to the Modification of Diet in Renal Disease equation, urine albumin-to-creatinine ratio, cardiovascular risk, duration of type 2 diabetes, use of glucose-lowering medication, use of lipid-lowering drugs, use of anti-hypertensive therapy, and use of antiplatelet drugs
Comparator	Glimepiride (1-4 mg)
Number of participants	6042 participants
Duration of follow-up	6.3 years (median)
Indirectness	None noted.
Method of analysis	Per protocol ITT
Additional comments	A 5-step hierarchical testing strategy was prespecified, in which each subsequent test would be performed in case of significant prior results. If noninferiority was achieved for the primary outcome, the subsequent tests were (1) superiority test of 3P-MACE, (2) superiority test of 4P-MACE, (3) superiority test of the second key secondary end point (ie, proportion of patients receiving treatment and maintaining HbA1c≤7.0% at the final visit who were without the need for rescue medication following the end of titration, did not have moderate/severe hypoglycaemic episodes, and did not have >2% weight gain), and (4) superiority test of the third key secondary end point (i.e., proportion of patients receiving treatment and maintaining HbA1c ≤7.0% at the final visit who were, from the end of titration, without the need for rescue medication and did not have >2%weight gain). Time-to-event outcomes were analysed using Cox proportional hazards model. Additional sensitivity analyses were completed using the Cox model.

413.2. Study arms

413.2.1. Linagliptin (N = 3023)

5 mg once-daily oral medication in addition to concomitant therapy (including glucose-lowering therapies, blood pressure-lowering medications, and select cardiovascular medications).

413.2.2. Glimepiride (N = 3010)

1 to 4 mg once-daily.

413.3. Characteristics

413.3.1. Arm-level characteristics

Characteristic	Linagliptin (N = 3023)	Glimepiride (N = 3010)
% Male Sample size	n = 1838 ; % = 60.8	n = 1781 ; % = 59.2
Mean age (SD) (years) Mean (SD)	63.9 (9.5)	64.2 (9.5)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA
Non-Hispanic/Latino Sample size	n = 2495 ; % = 82.8	n = 2487 ; % = 82.9
Hispanic/Latino Sample size	n = 519 ; % = 17.2	n = 513 ; % = 17.1
Comorbidities Sample size	n = NA ; % = NA	n = NA ; % = NA
Coronary artery disease Sample size	n = 968 ; % = 32.1	n = 937 ; % = 31.2
Cerebrovascular disease Sample size	n = 371 ; % = 12.3	n = 356 ; % = 11.9
Peripheral artery disease Sample size	n = 207 ; % = 6.9	n = 200 ; % = 6.7
Diabetic neuropathy Sample size	n = 515 ; % = 17.1	n = 495 ; % = 16.5

Characteristic	Linagliptin (N = 3023)	Glimepiride (N = 3010)
Diabetic nephropathy Sample size	n = 352 ; % = 11.7	n = 372 ; % = 12.4
Diabetic retinopathy Sample size	n = 212 ; % = 7	n = 236 ; % = 7.9
History of heart failure Sample size	n = 122 ; % = 4.1	n = 149 ; % = 5
Presence of frailty Sample size	n = NA ; % = NA	n = NA ; % = NA
Time since type 2 diabetes diagnosed (years) Median (IQR)	6.3 (3 to 11.1)	6.2 (2.9 to 10.9)
HbA1c Mean (SD)	NR (NR)	NR (NR)
Cardiovascular risk factors Sample size	n = NA ; % = NA	n = NA ; % = NA
History of hypertension Sample size	n = 2720 ; % = 90.2	n = 2698 ; % = 89.6
Vascular disease Sample size	n = 1051 ; % = 34.8	n = 1038 ; % = 34.5
Microvascular-related organ damage Sample size	n = 258 ; % = 8.5	n = 254 ; % = 8.4
Age at least 70 years Sample size	n = 566 ; % = 18.7	n = 592 ; % = 19.7
Multiple cardiovascular risk factors Sample size	n = 1132 ; % = 37.4	n = 1111 ; % = 36.9
Blood pressure (mmHg) n Linagliptin = 3014. n Glimipiride = 2998. Mean (SD)	NA (NA)	NA (NA)
Systolic Mean (SD)	136 (16)	136 (16)

Characteristic	Linagliptin (N = 3023)	Glimepiride (N = 3010)
Diastolic Mean (SD)	79 (10)	79 (9)
Heart rate (beats/min) n Linagliptin = 3014. n Glimipiride = 2998. Mean (SD)	71 (11)	71 (10)
Smoking status Sample size	n = NA ; % = NA	n = NA ; % = NA
Never smoker Sample size	n = 1365 ; % = 45	n = 1442 ; % = 48.1
Previous smoker Sample size	n = 1051 ; % = 34.9	n = 977 ; % = 32.6
Current smoker Sample size	n = 607 ; % = 20.1	n = 581 ; % = 19.4
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 Mean (SD)	NR (NR)	NR (NR)
BMI (kg/m2) n Linagliptin = 3012. n Glimipiride = 2982. Mean (SD)	30.2 (5.2)	30 (5.1)
Number of people with obesity Sample size	n = NA ; % = NA	n = NA ; % = NA
Cholesterol and lipid levels	NA (NA)	NA (NA)

Characteristic	Linagliptin (N = 3023)	Glimepiride (N = 3010)
Mean (SD)		
Cholesterol and lipid levels Median (IQR)	NA (NA to NA)	NA (NA to NA)
Total cholesterol n Linagliptin = 2893. n Glimipiride = 2866. Mean (SD)	177 (43)	177 (45)
Total cholesterol n Linagliptin = 2893. n Glimipiride = 2866. Median (IQR)	NA (NA to NA)	NA (NA to NA)
LDL cholesterol n Linagliptin = 2794. n Glimipiride = 2763. Mean (SD)	95 (35)	95 (36)
LDL cholesterol n Linagliptin = 2794. n Glimipiride = 2763. Median (IQR)	NA (NA to NA)	NA (NA to NA)
HDL cholesterol n Linagliptin = 2889. n Glimipiride = 2854. Mean (SD)	48 (13)	49 (13)
HDL cholesterol n Linagliptin = 2889. n Glimipiride = 2854. Median (IQR)	NA (NA to NA)	NA (NA to NA)
Triglycerides n Linagliptin = 2893. n Glimipiride = 2866. Mean (SD)	NA (NA)	NA (NA)
Triglycerides n Linagliptin = 2893. n Glimipiride = 2866. Median (IQR)	144 (106 to 200)	142 (105 to 196)
Albumin creatinine ratio n Linagliptin = 3007. n Glimipiride = 2988. Sample size	n = NA ; % = NA	n = NA ; % = NA
Albumin creatinine ratio n Linagliptin = 3007. n Glimipiride = 2988. Median (IQR)	9.7 (5.3 to 31.8)	9.7 (5.3 to 30.1)

Characteristic	Linagliptin (N = 3023)	Glimepiride (N = 3010)
<30 Sample size	n = 2228 ; % = 74.1	n = 2234 ; % = 74.8
<30 Median (IQR)	NA (NA to NA)	NA (NA to NA)
30-300 Sample size	n = 645 ; % = 21.4	n = 630 ; % = 21.1
30-300 Median (IQR)	NA (NA to NA)	NA (NA to NA)
>300 Sample size	n = 134 ; % = 4.4	n = 124 ; % = 4.1
>300 Median (IQR)	NA (NA to NA)	NA (NA to NA)
eGFR mL/min/1.73m2 n Linagliptin = 3011. n Glimipiride = 3000. Sample size	n = NA ; % = NA	n = NA ; % = NA
eGFR mL/min/1.73m2 n Linagliptin = 3011. n Glimipiride = 3000. Mean (SD)	76.5 (19.7)	77 (19.8)
≥90 Sample size	n = 693 ; % = 23	n = 722 ; % = 24.1
≥90 Mean (SD)	NA (NA)	NA (NA)
60-89 Sample size	n = 1726 ; % = 57.3	n = 1740 ; % = 58
60-89 Mean (SD)	NA (NA)	NA (NA)
30-59 Sample size	n = 576 ; % = 19.1	n = 525 ; % = 17.5
30-59 Mean (SD)	NA (NA)	NA (NA)

Characteristic	Linagliptin (N = 3023)	Glimepiride (N = 3010)
15-29 Sample size	n = 13 ; % = 0.4	n = 13 ; % = 0.4
15-29 Mean (SD)	NA (NA)	NA (NA)
< 15 Sample size	n = 3 ; % = 0.1	n = 0 ; % = 0
< 15 Mean (SD)	NA (NA)	NA (NA)
Other antidiabetic medication used n Linagliptin = 3014. n Glimipiride = 3000. Sample size	n = NA ; % = NA	n = NA ; % = NA
Metformin Sample size	n = 2510 ; % = 83.3	n = 2510 ; % = 83.7
Sulfonylurea Sample size	n = 869 ; % = 28.8	n = 846 ; % = 28.2
Alpha-glucosidase inhibitor Sample size	n = 97 ; % = 3.2	n = 92 ; % = 3.1
Glinide Sample size	n = 28 ; % = 0.9	n = 38 ; % = 1.3
0 glucose-lowering therapies used Sample size	n = 274 ; % = 9.1	n = 271 ; % = 9.1
1 glucose-lowering therapy used Sample size	n = 1984 ; % = 65.8	n = 1982 ; % = 66.1
2 glucose-lowering therapies used Sample size	n = 736 ; % = 24.4	n = 725 ; % = 24.2
3 glucose-lowering therapies used Sample size	n = 20 ; % = 0.7	n = 21 ; % = 0.7
Blood pressure-lowering medication used n Linagliptin = 3014. n Glimipiride = 3000. Sample size	n = NA ; % = NA	n = NA ; % = NA

Characteristic	Linagliptin (N = 3023)	Glimepiride (N = 3010)
ACE inhibitors Sample size	n = 1330 ; % = 44.1	n = 1342 ; % = 44.7
ARBs Sample size	n = 956 ; % = 31.7	n = 928 ; % = 30.9
Beta-blockers Sample size	n = 1193 ; % = 39.6	n = 1159 ; % = 38.6
Calcium-channel antagonists Sample size	n = 891 ; % = 29.6	n = 885 ; % = 29.5
Diuretics Sample size	n = 1099 ; % = 36.5	n = 1137 ; % = 37.9
Statins/lipid-lowering medication used Sample size	n = 1913 ; % = 63.5	n = 1987 ; % = 66.2
Other treatment being received Sample size	n = NA ; % = NA	n = NA ; % = NA
Acetylsalicylic acid Sample size	n = 1410 ; % = 46.8	n = 1413 ; % = 47.1

1

2

414. Rosenstock, 2016

Bibliographic Reference	Rosenstock, Julio; Aronson, Ronnie; Grunberger, George; Hanefeld, Markolf; Piatti, PierMarco; Serusclat, Pierre; Cheng, Xi; Zhou, Tianyue; Niemoeller, Elisabeth; Souhami, Elisabeth; Davies, Melanie; Benefits of LixiLan, a Titratable Fixed-Ratio Combination of Insulin Glargine Plus Lixisenatide, Versus Insulin Glargine and Lixisenatide Monocomponents in Type 2 Diabetes Inadequately Controlled on Oral Agents: The LixiLan-O Randomized Trial.; Diabetes care; 2016; vol. 39 (no. 11); 2026-2035

414.1. Study details

Secondary publication of another included study- see primary study for details	NA
Other publications associated with this study included in review	Gautier 2021
Trial name / registration number	LixiLan-O [NCT02058147]
Study type	Randomised controlled trial (RCT)
Study location	240 centres in 23 countries (Australia, Belgium, Canada, Chile, Czech Republic, Denmark, Estonia, France, Germany, Hungary, Italy, Latvia, Lithuania, Mexico, Poland, Romania, Russian Federation, South Africa, Spain, Sweden, Ukraine, United Kingdom, United States)
Study setting	NR
Study dates	12 February 2014 to 17 June 2015
Sources of funding	Sanofi
Inclusion criteria	People (aged ≥18 years) with type 2 diabetes diagnosed at least 1 year before screening with inadequate glycaemic control despite being treated for at least 3 months with metformin with or without a second oral glucose-lowering therapy. Inadequate glycaemic control was defined as HbA1c ≥7.5% and

	≤10.0% for patients treated with metformin alone and ≥7.0% and ≤9.0% for those previously treated with metformin and a second oral glucose-lowering therapy, namely a sulfonylurea, glinide, sodium glucose cotransporter 2, or dipeptidyl peptidase 4 inhibitor.
Exclusion criteria	• Use of an oral agent other than sulfonylurea, glinide, sodium-glucose cotransporter 2, or dipeptidyl peptidase 4 inhibitor during the 3 months before screening • Previous treatment with insulin (except short-term treatment due to intercurrent illness, including gestational diabetes mellitus) • Previous discontinuation of a GLP-1 RA due to safety, tolerability, or lack of efficacy • Amylase and/or lipase more than three times the upper limit of normal or calcitonin ≥20 pg/mL (5.9 pmol/L)
Recruitment / selection of participants	Participants entered a 4-week run-in phase where those receiving metformin plus another oral glucose-lowering therapy at screening were required to stop the second oral agent at the start of the run-in. For all participants, the dose of metformin was titrated to at least 2,000 mg/day or the maximum tolerated dose, which had to be ≥1,500 mg/day. At the end of the run-in phase, participants with HbA1c ≥7.0% and ≤10.0% and an FPG ≤250 mg/dL were randomised.
Intervention(s)	iGlarLixi administered once daily using a pen injector. There were two pen injectors, initially pen A was used, which delivered treatment in a 2:1 ratio of 2 units insulin glargine: 1 mcg lixisenatide. Pen A was used for doses 10 units/5 mcg to 40 units/20 ug. When participants required doses greater than 40 units/20 mcg, they were switched to pen B. Pen B delivered treatment in a 3:1 ratio of 3 units insulin glargine: 1 mcg lixisenatide and delivered corresponding doses from 30/10 mcg to 60 units/20 mcg. Treatment was titrated once a week to reach and maintain a self-measured FPG of 80 to 100 mg/dL while avoiding hypoglycaemia. Treatment was self-administered once daily 0 to 60 min before breakfast.
Cointervention	Metformin at least 2,000 mg/day or the maximum tolerated dose, which had to be ≥1,500 mg/day.
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	Not stated/unclear Not an inclusion/exclusion criteria. No information in baseline characteristics.

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	NA
Comparator	• Insulin glargine was supplied in a prefilled disposable pen injector (100 units/mL), which can deliver doses from 1 to 80 units in steps of 1 unit. The maximum once-daily dose was 60 units. Injection time was at the discretion of participants and investigators and remained at the about the same time throughout treatment. The initial daily dose of insulin glargine during the first week of treatment was 10 units and was titrated once a week to reach and maintain a self-measured FPG of 80 to 100 mg/dL while avoiding hypoglycaemia.

	• Lixisenatide was supplied in a disposable pre-filled pen containing 50 mcg/mL lixisenatide for the starting dose of 10 mcg for the first 2 weeks. For the remainder of the study, the maintenance dose of 20 mcg was provided with an injector pen that contained 100 mcg/mL lixisenatide. Lixisenatide was self-administered once daily, 0 to 60 minutes before breakfast or the evening meal at the discretion of participants and investigators but remained at about the same time throughout the treatment.
Number of participants	2457 people were screened, 1479 entered the run-in, and 1170 were randomised. Of 469 participants allocated to lixisenatide/insulin glargine, 93.8% completed treatment and 6.2% discontinued. Of 467 participants allocated to insulin glargine, 94.2% completed treatment and 5.8% discontinued treatment. Of 234 participants allocated to lixisenatide, 87.6% completed treatment, and 12% discontinued.
Duration of follow-up	30 weeks
Indirectness	Directly applicable
Method of analysis	Modified ITT Described as all randomly assigned participants who had a baseline assessment and at least one post-baseline assessment of any primary or secondary efficacy variables. The change in HbA1c was analysed by a mixed-effect model with repeated measures. Other efficacy endpoints were analysed by mixed-effect model with repeated measured or ANCOVA. Other The safety population was defined as all randomised participants who received at least one dose of study treatment regardless of the amount administered. Participants were analysed for safety according to the treatment received rather than the group to which they were assigned.
Additional comments	NA

414.2. Study arms

414.2.1. Lixisenatide/Insulin glargine (N = 469)

414.2.2. Lixisenatide (N = 234)

414.2.3. Insulin glargine (N = 467)

414.3. Characteristics

414.3.1. Arm-level characteristics

Characteristic	Lixisenatide/Insulin glargine (N = 469)	Lixisenatide (N = 234)	Insulin glargine (N = 467)
% Male Sample size	n = 222 ; % = 47.3	n = 133 ; % = 56.8	n = 237 ; % = 50.7
Mean age (SD) Mean (SD)	58.2 (9.5)	58.7 (8.7)	58.3 (9.4)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
Caucasian Sample size	n = 417 ; % = 88.9	n = 216 ; % = 92.3	n = 421 ; % = 90.1
Black Sample size	n = 33 ; % = 7	n = 12 ; % = 5.1	n = 33 ; % = 7.1
Asian/Oriental Sample size	n = 8 ; % = 1.7	n = 3 ; % = 1.3	n = 7 ; % = 1.5
Other Sample size	n = 11 ; % = 2.3	n = 3 ; % = 1.3	n = 6 ; % = 1.3
Hispanic Sample size	n = 85 ; % = 18.1	n = 51 ; % = 21.8	n = 87 ; % = 18.6
Non-Hispanic Sample size	n = 384 ; % = 81.9	n = 183 ; % = 78.2	n = 380 ; % = 81.4
Comorbidities Nominal	NR	NR	NR
Presence of frailty Nominal	NR	NR	NR

Characteristic	Lixisenatide/Insulin glargine (N = 469)	Lixisenatide (N = 234)	Insulin glargine (N = 467)
Time since type 2 diabetes diagnosed Mean (SD)	8.9 (5.5)	8.9 (6.3)	8.7 (5.6)
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
BMI Mean (SD)	31.6 (4.4)	32 (4.4)	31.7 (4.5)
Number of people with obesity Participants with BMI >= 30 kg/m2 Sample size	% = 62.9	% = 67.9	% = 61.7
Other antidiabetic medication used Sample size	% = 58.4	% = 56.8	% = 57.8
Sulfonylurea Sample size	% = 55.2	% = 52.6	% = 53.3
Glinide	% = 0.6	% = 2.1	% = 2.1

Characteristic	Lixisenatide/Insulin glargine (N = 469)	Lixisenatide (N = 234)	Insulin glargine (N = 467)
Sample size			
SGLT2 inhibitor Sample size	% = 0.4	% = 0	% = 0.4
DPP-4 inhibitor Sample size	% = 2.6	% = 2.1	% = 2.4
Blood pressure-lowering medication used Nominal	NR	NR	NR
Statins/lipid-lowering medication used Nominal	NR	NR	NR
Other treatment being received Nominal	NR	NR	NR

1

2

415. Rosenstock, 2016

Bibliographic Reference	Rosenstock, Julio; Diamant, Michaela; Aroda, Vanita R; Silvestre, Louise; Souhami, Elisabeth; Zhou, Tianyue; Perfetti, Riccardo; Fonseca, Vivian; Efficacy and Safety of LixiLan, a Titratable Fixed-Ratio Combination of Lixisenatide and Insulin Glargine, Versus Insulin Glargine in Type 2 Diabetes Inadequately Controlled on Metformin Monotherapy: The LixiLan Proof-of-Concept Randomized Trial.; Diabetes care; 2016; vol. 39 (no. 9); 1579-86

415.1. 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	LixiLan PoC [NCT01476475]
Study type	Randomised controlled trial (RCT)
Study location	67 centres in 13 countries (Chile, Czech Republic, Germany, Denmark, France, Hungary, Lithuania, Mexico, Poland, Romania, Slovakia, Sweden, and the U.S.).
Study setting	NR
Study dates	21 November 2011 to 17 December 2012
Sources of funding	Sanofi
Inclusion criteria	• Adults with type 2 diabetes diagnosed ≥1 year before the screening visit • HbA1c ≥7% to ≤10% • Screening FPG ≤13.9 mmol/L • Treatment with metformin at a stable dose of ≥1.5 g/day for ≥3 months before the screening visit

Exclusion criteria	• Treatment with glucose-lowering agent(s) other than metformin during the 3 months before the screening visit • Any use of insulin within the last 6 months before screening • Use of insulin 6 months before screening except for episode(s) of short-term treatment caused by intercurrent illness
Recruitment / selection of participants	There was an up-to 2-week screening period.
Intervention(s)	LixiLan (combined lixisenatide and insulin glargine) was initiated at 10 units of Gla100 and 5 mcg lixisenatide. Titration was based on plasma glucose levels. The dose of lixisenatide followed the Gla-100 dose according to the 2 units/1mcg fixed ratio. The maximum daily dose was 60 units Gla-100/30 mcg lixisenatide. Treatment was administered in the morning within 1 hour before breakfast. LixiLan was supplied as a sterile aqueous solution for subcutaneous injection in 3 mL cartridges that were used in a reusable self-injector pen.
Cointervention	Participants continued to receive metformin unless there was a safety issue.
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	Not stated/unclear
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Population subgroups	NA
Comparator	Gla-100 (insulin glargine) at an initial daily dose of 10 units. Titration of Gla-100 was based on plasma glucose levels, and there was no upper limit for titration. Treatment was administered in the morning within 1 hour before breakfast, and was supplied as a sterile, aqueous solution in a Lantus SoloSTAR pen.
Number of participants	520 patients were screened and 323 participants were randomised. Of 161 participants allocated to LixiLan, 150 completed the 24-week treatment period and 11 did not complete the study treatment period. Of 162 participants allocated to Gla-100, 159 completed the treatment period and 3 did not complete the study.
Duration of follow-up	24 weeks
Indirectness	Directly applicable
Method of analysis	Modified ITT Comprised all participants who were randomised to treatment who received one dose or more of the study drug and had both a baseline and one or more postbaseline assessments of the primary or secondary

	endpoint, irrespective of compliance with the study protocol and procedures. Efficacy was analysed using an ANCOVA model. Missing endpoint values were imputed from the last available on-treatment value using the last observation carried forward. The safety population comprised all participants who were randomised to treatment and who received 1 dose or more of the study drug.
Additional comments	One participant in the Insulin arm and no participants in the Lixisenatide + Insulin arm required rescue therapy.

415.2. Study arms

415.2.1. Lixisentatide + Insulin glargine (N = 161)

415.2.2. Insulin glargine (N = 162)

415.3. Characteristics

415.3.1. Arm-level characteristics

Characteristic	Lixisentatide + Insulin glargine (N = 161)	Insulin glargine (N = 162)
% Male Sample size	n = 80 ; % = 49.7	n = 85 ; % = 52.5
Mean age (SD) Sample size	n = 56.9 ; % = 9.5	n = 56.6 ; % = 9.4
Ethnicity Nominal	NR	NR
Comorbidities Nominal	NR	NR
Presence of frailty Nominal	NR	NR
Time since type 2 diabetes diagnosed Mean (SD)	4.1 (3.6)	4.3 (3.9)

Characteristic	Lixisentatide + Insulin glargine (N = 161)	Insulin glargine (N = 162)
Cardiovascular risk factors Nominal	NR	NR
Blood pressure Nominal	NR	NR
Heart rate 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
BMI (kg/m2) Mean (SD)	32.2 (4.8)	32 (4.4)
Number of people with obesity Nominal	NR	NR
Other antidiabetic medication used (mg/day) Metformin dose Mean (SD)	2076 (441)	2094 (416)
Blood pressure-lowering medication used Nominal	NR	NR
Statins/lipid-lowering medication used Nominal	NR	NR

Characteristic	Lixisentatide + Insulin glargine (N = 161)	Insulin glargine (N = 162)
Other treatment being received Nominal	NR	NR

1

2

416. Rosenstock, 2023

Bibliographic Reference	Rosenstock, Julio; Frias, Juan P; Rodbard, Helena W; Tofe, Santiago; Sears, Emmalee; Huh, Ruth; Fernandez Lando, Laura; Patel, Hiren; Tirzepatide vs Insulin Lispro Added to Basal Insulin in Type 2 Diabetes: The SURPASS-6 Randomized Clinical Trial.; JAMA; 2023; vol. 330 (no. 17); 1631-1640

416.1. 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	SURPASS-6 / NCT04537923
Study type	Randomised controlled trial (RCT)
Study location	Globally - 135 centres in Argentina, Belgium, Brazil, Czech Republic, Germany, Greece, Hungary, Italy, Mexico, Romania, Russia, Slovakia, Spain, Turkey, and the US
Study setting	Medical research centres and hospitals
Study dates	Between October 19, 2020, and November 1, 2022
Sources of funding	Eli Lilly and Company
Inclusion criteria	adults (male or female) 18 years or older with type 2 diabetes inadequately controlled with basal insulin (insulin NPH, insulin glargine, insulin detemir, or insulin degludec), with or without any combination of up to 2 of the following oral glucose-lowering medications: metformin of at least 1500 mg per day, sulfonylurea, or dipeptidyl peptidase-4 inhibitors; have a BMI ≥23 kg/m2 and ≤45 kg/m2 at Visit 1; Have an HbA1c ≥7.5% (58 mmol/mol) to ≤11% (97 mmol/mol), at Visit 1 and an HbA1c ≥7.5% (58 mmol/mol) to ≤11% (97 mmol/mol), at Visit 5 (pre-randomization), for those participants that need insulin glargine (U100) optimization; Are of stable weight (±5%)

	90 days or more prior to Visit 1 and agree to not initiate a diet and/or exercise program during the study with the intent of reducing body weight other than the lifestyle and dietary measures for diabetes treatment;
Exclusion criteria	diagnosis of type 1 diabetes, history of pancreatitis, proliferative diabetic retinopathy, diabetic macular edema, non-proliferative diabetic retinopathy that required immediate treatment, severe hypoglycemia and/or hypoglycemia unawareness; an estimated glomerular filtration rate (eGFR) less than 30 mL/min/1.73 m2 (or less than 45 mL/min/1.73 m2 for participants receiving metformin); Are chronically taking drugs that directly affect GI motility, or have a known clinically significant gastric emptying abnormality, such as severe diabetic gastroparesis or gastric outlet obstruction, or have undergone or plan to undergo weight loss procedure during the study; history of diabetic ketoacidosis or hyperosmolar state/coma during 6 months prior to Visit 1; have acute MI, stroke or hospitalization due to congestive heart failure within 2 months prior to Visit 1; New York Heart Association Functional Classification III and IV congestive heart failure; acute or chronic hepatitis, signs and symptoms of any other liver disease other than NAFLD, or ALT level >3.0 times the upper limit of the reference range; uncontrolled endocrine abnormality; history of medullary thyroid carcinoma or multiple endocrine neoplasia syndrome type 2; serum calcitonin level of 35 ng/L or more; Known or suspected hypersensitivity to trial intervention(s) or related products; evidence of a significant, active autoimmune abnormality; had a transplanted organ or awaiting; history of an active or untreated malignancy or are in remission from a clinically significant malignancy for less than 5 years; any hematological condition that may interfere with HbA1c measurement; Female participants who are pregnant or breast feeding; Prior/Concomitant Therapy with any glucose-lowering agent other than stated in the inclusion criteria 2 in a period of 90 days prior to Visit 1 and use of any other glucose lowering medication except insulin glargine (U100) and metformin (≥1500 mg/day), between Visit 2 and randomization (Visit 6); treated with prescription drugs that promote weight loss within 90 days prior to Visit 1; currently enrolled in any other clinical study involving an investigational product; Have previously completed or discontinued from this study or any other study investigating tirzepatide
Recruitment / selection of participants	NA
Intervention(s)	Participants were randomized to receive subcutaneous injection of once-weekly tirzepatide (5 mg, 10 mg, or 15 mg). Tirzepatide was initiated at 2.5 mg once weekly with the dose increased by 2.5 mg every 4 weeks until the randomized dose was achieved and maintained until 52 weeks
Cointervention	Metformin
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
Subgroup 6: Albuminuria category at baseline	Not stated/unclear

Population subgroups	NA
Comparator	Insulin lispro (100 IU/mL). Participants were randomized to receive subcutaneous injection thrice-daily prandial insulin lispro (100 IU/mL) for 52 weeks, followed by a 4-week safety follow-up period. Insulin lispro was initiated at 4 IU prior to the 3 largest meals of the day. Doses were adjusted twice weekly until week 24 and at least once weekly after week 24 to achieve a pre-lunch, pre-dinner, and bedtime blood glucose target of 100 to 125 mg/dL following a standardized titration algorithm
Number of participants	1,424
Duration of follow-up	52 weeks
Indirectness	NA
Method of analysis	Modified ITT

416.2. Study arms

416.2.1. Tirzepatide (N = 717)

Participants were randomized to receive subcutaneous injection of once-weekly Tirzepatide (5 mg, 10 mg, or 15 mg) for 52 weeks, followed by a 4-week safety follow-up period

416.2.2. insulin lispro (N = 708)

Participants were randomized to receive subcutaneous injection thrice-daily prandial insulin lispro (100 IU/mL) for 52 weeks, followed by a 4-week safety follow-up period

416.3. Characteristics

416.3.1. Arm-level characteristics

Characteristic	Tirzepatide (N = 717)	insulin lispro (N = 708)
% Male Sample size	n = 291 ; % = 40.6	n = 312 ; % = 44.1

Characteristic	Tirzepatide (N = 717)	insulin lispro (N = 708)
Mean age (SD) Mean (SD)	58.6 (9.8)	59 (9.7)
American Indian or Alaska Native Sample size	n = 1 ; % = 0.1	n = 2 ; % = 0.3
Asian Sample size	n = 4 ; % = 0.6	n = 4 ; % = 0.6
Black or African American Sample size	n = 31 ; % = 4.3	n = 26 ; % = 3.7
Multiple Sample size	n = 7 ; % = 1	n = 8 ; % = 1.1
Hispanic or Latino Sample size	n = 674 ; % = 94	n = 668 ; % = 94.4
Time since type 2 diabetes diagnosed (years) Mean (SD)	13.6 (7.2)	14 (7.4)
HbA1c (%) Mean (SD)	8.8 (0.99)	8.8 (0.96)
Weight (kg) Mean (SD)	90.7 (18.5)	90.3 (17.7)
BMI (kg/m2) Mean (SD)	33.3 (5.4)	33 (5.2)
eGFR mL/min/1.73m2 Mean (SD)	89.3 (19.6)	88.8 (18.8)
Metformin Sample size	n = 598 ; % = 83.4	n = 606 ; % = 85.6

1

2

417. Rosenstock, 2018

Bibliographic Reference	Rosenstock, Julio; Frias, Juan; Pall, Denes; Charbonnel, Bernard; Pascu, Raluca; Saur, Didier; Darekar, Amanda; Huyck, Susan; Shi, Harry; Lauring, Brett; Terra, Steven G; Effect of ertugliflozin on glucose control, body weight, blood pressure and bone density in type 2 diabetes mellitus inadequately controlled on metformin monotherapy (VERTIS MET).; Diabetes, obesity & metabolism; 2018; vol. 20 (no. 3); 520-529

417.1. Study details

Other publications associated with this study included in review	
Trial name / registration number	VERTIS MET / NCT02033889
Study type	Randomised controlled trial (RCT)
Study location	North America, South America, Europe, Asia, South Africa, Australia, New Zealand
Study setting	No additional information
Study dates	Not recorded
Sources of funding	Study funded by Pfizer. Numerous authors declare funding and honoraria from multiple pharmaceutical companies
Inclusion criteria	Men and women aged ≥18 years with T2DM (diagnosed in accordance with American Diabetes Association guidelines) inadequately controlled (HbA1c, 7.0–10.5%) on metformin monotherapy (≥1500 mg/day for ≥8 weeks) and with BMI 18.0–40.0 kg/m2.
Exclusion criteria	Diagnosis of type 1 diabetes mellitus, history of ketoacidosis, eGFR <55 mL/min/1.73 m2 according to the 4-variable modification of diet in renal disease equation at screening, <80% compliance (based on pill count) with the placebo run-in medication, documented history of osteoporosis or gender specific BMD T-score of less than –2.5 at any skeletal site assessed at screening, or any illness that could impact BMD assessment. Participants who had undergone bariatric surgery were also ineligible. Those who had received prior therapeutic agents that could confound BMD assessment or affect bone turnover were also excluded.

Recruitment / selection of participants	No additional information
Intervention(s)	Ertugliflozin 5 mg (n=207) Once daily 5 mg dose of ertugliflozin Ertugliflozin 15 mg (n=205) Once daily 5 mg dose of ertugliflozin
Cointervention	Metformin: The median metformin dose at baseline was 2000 mg/day in all groups.
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 Excluded "estimated glomerular filtration rate (eGFR) <55 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
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=209) Patients received daily oral placebo for 28 weeks
Number of participants	621
Duration of follow-up	28 weeks
Indirectness	No additional information
Method of analysis	Modified ITT
Additional comments	Efficacy analyses comprised all randomized participants who received ≥1 dose of study medication. For endpoints that used a longitudinal data analysis (LDA) model, at least one measurement (baseline or postbaseline) was required. An ordered testing procedure (HbA1c, FPG, body weight, HbA1c <7.0%, SBP, DBP) was used to control the family-wise type 1 error rate at the 0.05 level across all key efficacy endpoints. For each endpoint, the 15-mg dose was tested vs placebo first, followed by the 5-mg dose vs placebo.

1

417.2. Study arms

417.2.1. Empagliflozin 5 mg (N = 207)

Once daily 5 mg dose added to metformin for 26 weeks

417.2.2. Empagliflozin 15 mg (N = 205)

Once daily 15 mg dose added to metformin for 26 weeks

417.2.3. Placebo (N = 209)

Once daily added to metformin for 26 weeks

417.3. Characteristics

417.3.1. Arm-level characteristics

Characteristic	Empagliflozin 5 mg (N = 207)	Empagliflozin 15 mg (N = 205)	Placebo (N = 209)
% Male Sample size	n = 97 ; % = 46.9	n = 93 ; % = 45.4	n = 98 ; % = 46.9
Mean age (SD) (Years (mean, SD)) Mean (SD)	56.6 (8.1)	56.9 (9.4)	56.5 (8.7)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
Asian Sample size	n = 34 ; % = 16.4	n = 35 ; % = 17.1	n = 31 ; % = 14.8
Black or African American Sample size	n = 22 ; % = 10.6	n = 23 ; % = 11.2	n = 19 ; % = 9.1
Multiple Sample size	n = 17 ; % = 8.2	n = 14 ; % = 6.8	n = 15 ; % = 7.2
White Sample size	n = 134 ; % = 64.7	n = 133 ; % = 64.9	n = 144 ; % = 68.9

Characteristic	Empagliflozin 5 mg (N = 207)	Empagliflozin 15 mg (N = 205)	Placebo (N = 209)
Time since type 2 diabetes diagnosed (Years (mean, SD)) Mean (SD)	7.9 (6.1)	8.1 (5.5)	8 (6.3)
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
Other antidiabetic medication used Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
Metformin Background therapy at screening Sample size	n = 207 ; % = 100	n = 204 ; % = 99.5	n = 209 ; % = 100
DPP-4 inhibitors Background therapy at screening Sample size	n = 6 ; % = 2.9	n = 8 ; % = 3.9	n = 7 ; % = 3.3
Other blood glucose lowering agents Background therapy at screening Sample size	n = 3 ; % = 1.4	n = 2 ; % = 1	n = 0 ; % = 0
Sulphonamides, urea derivatives Background therapy at screening Sample size	n = 57 ; % = 27.5	n = 45 ; % = 22	n = 62 ; % = 29.7

1

1

418. Rosenstock, 2018

Bibliographic Reference	Rosenstock, Julio; Perkovic, Vlado; Alexander John, H; Cooper Mark, E; Marx, Nikolaus; Pencina Michael, J; Toto Robert, D; Wanner, Christoph; Zinman, Bernard; Baanstra, David; Pfarr, Egon; Mattheus, Michaela; Broedl Uli, C; Woerle, Hans-Juergen; George Jyothis, T; von Eynatten, Maximilian; McGuire Darren, K; CARMELINA, R; investigators; Rationale, design, and baseline characteristics of the CArdiovascular safety and Renal Microvascular outcomE study with LINAgliptin (CARMELINA R): a randomized, double-blind, placebo-controlled clinical trial in patients with type 2 diabetes and high cardio-renal risk.; Cardiovascular diabetology; 2018; vol. 17 (no. 1); 39

418.1. Study details

Secondary publication of another included study- see primary study for details	This study is a part of the CARMELINA trial. For the full data extraction please see the primary study. Rosenstock, Julio, Perkovic, Vlado, Johansen Odd, Erik et al. (2019) Effect of Linagliptin vs Placebo on Major Cardiovascular Events in Adults With Type 2 Diabetes and High Cardiovascular and Renal Risk: The CARMELINA Randomized Clinical Trial. JAMA 321(1): 69-79
Other publications associated with this study included in review	McGuire Darren, K, Alexander John, H, Johansen Odd, Erik et al. (2019) Linagliptin Effects on Heart Failure and Related Outcomes in Individuals With Type 2 Diabetes Mellitus at High Cardiovascular and Renal Risk in CARMELINA. Circulation 139(3): 351-361 Perkovic, V, Toto, R, Cooper M, E et al. (2020) Effects of linagliptin on cardiovascular and kidney outcomes in people with normal and reduced kidney function: Secondary analysis of the carmelina randomized trial. Diabetes Care 43(8): 1803-1812
Trial name / registration number	CARMELINA. ClinicalTrials.gov = NCT01897531

419. Rosenstock, 2019

Bibliographic Reference	Rosenstock, Julio; Perkovic, Vlado; Johansen Odd, Erik; Cooper Mark, E; Kahn Steven, E; Marx, Nikolaus; Alexander John, H; Pencina, Michael; Toto Robert, D; Wanner, Christoph; Zinman, Bernard; Woerle Hans, Juergen; Baanstra, David; Pfarr, Egon; Schnaidt, Sven; Meinicke, Thomas; George Jyothis, T; von Eynatten, Maximilian; McGuire Darren, K; CARMELINA, Investigators; Effect of Linagliptin vs Placebo on Major Cardiovascular Events in Adults With Type 2 Diabetes and High Cardiovascular and Renal Risk: The CARMELINA Randomized Clinical Trial.; JAMA; 2019; vol. 321 (no. 1); 69-79

419.1. Study details

Secondary publication of another included study- see primary study for details	This is the primary study for the CARMELINA study. All outcomes regarding the primary cohort will be reported here. Rosenstock 2019A.
Other publications associated with this study included in review	Rosenstock, Julio, Perkovic, Vlado, Alexander John, H et al. (2018) Rationale, design, and baseline characteristics of the CArdiovascular safety and Renal Microvascular outcomE study with LINAgliptin (CARMELINA R): a randomized, double-blind, placebo-controlled clinical trial in patients with type 2 diabetes and high cardio-renal risk. Cardiovascular diabetology 17(1): 39 McGuire Darren, K, Alexander John, H, Johansen Odd, Erik et al. (2019) Linagliptin Effects on Heart Failure and Related Outcomes in Individuals With Type 2 Diabetes Mellitus at High Cardiovascular and Renal Risk in CARMELINA. Circulation 139(3): 351-361 Perkovic, V, Toto, R, Cooper M, E et al. (2020) Effects of linagliptin on cardiovascular and kidney outcomes in people with normal and reduced kidney function: Secondary analysis of the carmelina randomized trial. Diabetes Care 43(8): 1803-1812
Trial name / registration number	CARMELINA ClinicalTrials.gov = NCT01897531
Study type	Randomised controlled trial (RCT)
Study location	27 countries (not specified)

Study setting	605 clinic sites (no further information)
Study dates	August 2013 to August 2016. Final follow-up occurred on January 18, 2018
Sources of funding	Study was sponsored by Boehringer Ingelheim and Eli Lilly.
Inclusion criteria	People with type 2 diabetes aged at least 18 years with glycated hemoglobin A1c (HbA1c) 6.5-10.0% (48-86mmol/mol) and body-mass index (BMI) no more than 45kg/m2; high risk of vascular events based on established history of cardiovascular disease and the presence of markers of chronic kidney disease (either albuminuria, and confirmed history of myocardial infarction or advanced coronary artery disease or high-risk single-vessel coronary artery disease or history of ischaemic or haemorrhagic stroke or presence of carotid artery disease or presence of peripheral artery disease and evidence of impaired renal function); drug naive or receiving any glucose-lowering therapy except glucagon-like peptide-1 receptor agonists, DPP-4 inhibitors and/or sodium-glucose co-transporter 2 inhibitors. Those already receiving glucose-lowering therapy had to be on the same dose for at least 8 weeks prior to randomisation.
Exclusion criteria	Type 1 diabetes mellitus; treatment for more than 7 consecutive days with GLP-1 receptor agonists, other DPP-4 inhibitors or SGLT-2 inhibitors; acute coronary syndrome in the 2 months prior to screening; people who had a stroke or transient ischaemic attack in the 3 months before screening, those scheduled to have percutaneous coronary intervention or coronary artery bypass graft surgery or had had PCI and/or CABG in the 2 months before screening; people with end stage kidney disease (eGFR <15mL/min/1.73m2 and/or receipt of maintenance dialysis); premenopausal women who were pregnant, nursing or not practicing birth control; people with active liver disease or impaired hepatic function (serum levels of ALT, AST, ALP equal to or greater than three times the upper limit of normal); those with prior or planned bariatric surgery; known hypersensitivity or allergy to the investigational products or its excipients; participation in another trial ongoing or within 2 months prior to visit 1; any previous or current alcohol or drug abuse that would interfere with trial participation; people considered unreliable by the investigation; life expectancy less than 5 years for non-cardiovascular causes; cancer other than non-melanoma skin cancer within the last 3 years; other condition mentioned which in the opinion of the investigation would not allow safe participation in the study.
Recruitment / selection of participants	Recruited from 407 clinics in 27 countries. No additional information.
Intervention(s)	Linagliptin N=3499 Linagliptin 5mg once daily initially for 12 weeks, then 24 week periods until the study end, median end follow up of 2.2 years.
Cointervention	Concomitant therapy: Majority received at least 1 background glucose-lowering therapy in addition to the new therapy, as well as a large number of people receiving antihypertensive medication, aspirin and statins (see characteristics table).

Strata 1: People with type 2 diabetes mellitus and heart failure	Mixed population Around 27% of people had heart failure
Strata 2: People with atherosclerotic cardiovascular disease	Mixed population Around 57% of people had established CVD
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Mixed population 74% had prevalent kidney disease (defined as eGFR <60 mL/min/1.73 m2 and/or UACR >300 mg/g creatinine). Not based on prior CKD diagnosis, but was study-classified as kidney disease and was based on more than one measurement, so taken as per agreed approach.
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	eGFR ≥30mL/min/1.73m2 baseline characteristics show that 15.2% were <30ml/min/1.73m2 (cut-off in protocol 20%)
Subgroup 6: Albuminuria category at baseline	Mixed population The median is 162, but the individual values are reported and is a range between all of the categories.
Population subgroups	No additional information.
Comparator	Placebo N=3492 Placebo once daily initially for 12 weeks, then 24 weeks periods until the study end, median end follow up of 2.2 years.
Number of participants	6991
Duration of follow-up	Median follow up 2.2 years
Indirectness	No additional information
Method of analysis	Per protocol ITT Other
Additional comments	Hazard ratio with 95% CI outlined based on cox regression analysis based on patients treated with at least 1 dose of study drug; Adverse event assessments were conducted using descriptive statistics. Protocol amendment (via steering group) in 2016 based on emerging evidence that a primary outcome definition based on 3-point MACE was preferred by regulators and consistent with other CV outcome trials - the original protocol included hospitalization for unstable angina pectoris in the primary outcome (a 4-point MACE). Assessment of outcome change - Death due to renal failure: The eGFR criterion was changed from the original decrease of at least 50% in eGFR in accord with National Kidney Foundation and the US Food and Drug Administration (FDA) recommendations. Use of the originally planned decrease of at least 50% in eGFR in the kidney composite was evaluated as a tertiary outcome.

419.2. Study arms

419.2.1. Linagliptin (N = 3499)

Linagliptin 5mg once daily initially for 12 weeks, then 24 week periods until the study end, median end follow up of 2.2 years. Concomitant therapy: Majority received at

least 1 background glucose-lowering therapy in addition to the new therapy, as well as a large number of people receiving antihypertensive medication, aspirin and statins (see characteristics table).

419.2.2. Placebo (N = 3492)

Placebo once daily initially for 12 weeks, then 24 weeks periods until the study end, median end follow up of 2.2 years. Concomitant therapy: Majority received at least 1 background glucose-lowering therapy in addition to the new therapy, as well as a large number of people receiving antihypertensive medication, aspirin and statins (see characteristics table).

419.3. Characteristics

419.3.1. Arm-level characteristics

Characteristic	Linagliptin (N = 3499)	Placebo (N = 3492)
% Male Sample size	n = 2148 ; % = 61.5	n = 2242 ; % = 64.3
Mean age (SD) (years) Mean (SD)	66.1 (9.1)	65.6 (9.1)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA
White Sample size	n = 2827 ; % = 80.9	n = 2769 ; % = 79.5
Asian Sample size	n = 307 ; % = 8.8	n = 333 ; % = 9.6
Black/African American Sample size	n = 194 ; % = 5.6	n = 217 ; % = 6.2
Other Sample size	n = 166 ; % = 4.8	n = 166 ; % = 4.8
Comorbidities Sample size	n = NA ; % = NA	n = NA ; % = NA
History of heart failure Sample size	n = 952 ; % = 27.2	n = 921 ; % = 26.4

Characteristic	Linagliptin (N = 3499)	Placebo (N = 3492)
Ischaemic heart disease Sample size	n = 2029 ; % = 58.1	n = 2052 ; % = 58.9
History of hypertension Sample size	n = 3171 ; % = 90.8	n = 3178 ; % = 91.2
Atrial fibrillation Sample size	n = 319 ; % = 9.1	n = 354 ; % = 10.2
Presence of frailty Sample size	n = NR ; % = NR	n = NR ; % = NR
Time since type 2 diabetes diagnosed (years) Mean (SD)	15 (9.6)	14.5 (9.3)
HbA1c (%) Mean (SD)	7.9 (1)	8 (1)
Cardiovascular risk factors Sample size	n = NA ; % = NA	n = NA ; % = NA
Blood pressure (mmHg) Mean (SD)	NA (NA)	NA (NA)
Systolic blood pressure Mean (SD)	140.4 (17.7)	140.6 (18)
Diastolic blood pressure Mean (SD)	77.8 (10.5)	77.9 (10.4)
Heart rate (/min) Mean (SD)	69.8 (12.2)	69.8 (12.3)
Smoking status Sample size	n = NA ; % = NA	n = NA ; % = NA
Never smoker Sample size	n = 1897 ; % = 54.3	n = 1856 ; % = 53.3
Ex-smoker Sample size	n = 1231 ; % = 35.2	n = 1276 ; % = 36.6
Current smoker	n = 362 ; % = 10.4	n = 350 ; % = 10

Characteristic	Linagliptin (N = 3499)	Placebo (N = 3492)
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
Weight Mean (SD)	NR (NR)	NR (NR)
BMI (kg/m2) Mean (SD)	31.4 (5.3)	31.3 (5.4)
Number of people with obesity Sample size	n = NR ; % = NR	n = NR ; % = NR
Cholesterol and lipid levels (mg/dL) Mean (SD)	NA (NA)	NA (NA)
Total cholesterol Mean (SD)	173 (49)	171 (47)
LDL cholesterol Mean (SD)	92 (40)	91 (39)
HDL cholesterol Mean (SD)	45 (13)	44 (13)
Triglycerides Mean (SD)	190 (135)	187 (130)
Albumin creatinine ratio (mg/g) Sample size	n = NA ; % = NA	n = NA ; % = NA
Median <30 Sample size	n = 696 ; % = 20	n = 696 ; % = 20

Characteristic	Linagliptin (N = 3499)	Placebo (N = 3492)
Median 30-300 Sample size	n = 1463 ; % = 41.9	n = 1431 ; % = 41.1
Median >300 Sample size	n = 1333 ; % = 38.2	n = 1357 ; % = 38.9
eGFR mL/min/1.73m2 Sample size	n = NA ; % = NA	n = NA ; % = NA
eGFR mL/min/1.73m2 Mean (SD)	54.7 (25.1)	54.5 (24.9)
≥90 Sample size	n = 363 ; % = 10.4	n = 365 ; % = 10.5
≥90 Mean (SD)	NA (NA)	NA (NA)
≥60 Sample size	n = 1294 ; % = 37	n = 1337 ; % = 38.4
≥60 Mean (SD)	NA (NA)	NA (NA)
≥45 to <60 Sample size	n = 690 ; % = 19.7	n = 658 ; % = 18.9
≥45 to <60 Mean (SD)	NA (NA)	NA (NA)
≥30 to <45 Sample size	n = 994 ; % = 28.4	n = 944 ; % = 27.1
≥30 to <45 Mean (SD)	NA (NA)	NA (NA)
<30 Sample size	n = 516 ; % = 14.8	n = 546 ; % = 15.7
<30 Mean (SD)	NA (NA)	NA (NA)
Other antidiabetic medication used	n = NA ; % = NA	n = NA ; % = NA

Characteristic	Linagliptin (N = 3499)	Placebo (N = 3492)
Sample size		
Metformin Sample size	n = 1881 ; % = 53.8	n = 1927 ; % = 55.3
Sulfonylurea Sample size	n = 1102 ; % = 31.5	n = 1140 ; % = 32.7
Insulin Sample size	n = 2056 ; % = 58.8	n = 1995 ; % = 57.2
ACE inhibitors Sample size	n = 2860 ; % = 81.9	n = 2798 ; % = 80.3
Beta-blockers Sample size	n = 2080 ; % = 59.5	n = 2073 ; % = 59.5
Diuretics Sample size	n = 1982 ; % = 54.1	n = 1936 ; % = 55.6
Calcium antagonists Sample size	n = 1433 ; % = 41	n = 1446 ; % = 41.5
Aspirin Sample size	n = 2166 ; % = 62	n = 2178 ; % = 62.5
Statins Sample size	n = 2495 ; % = 71.4	n = 2523 ; % = 72.4
Blood pressure-lowering medication used See other antidiabetic medication used for details Sample size	n = NA ; % = NA	n = NA ; % = NA
Statins/lipid-lowering medication used See other antidiabetic medication used for details Sample size	n = NA ; % = NA	n = NA ; % = NA
Other treatment being received See other antidiabetic medication used for details Sample size	n = NA ; % = NA	n = NA ; % = NA
Number of background glucose-lowering therapies Sample size	n = NA ; % = NA	n = NA ; % = NA

Characteristic	Linagliptin (N = 3499)	Placebo (N = 3492)
n = 1 Sample size	n = 1756 ; % = 50.3	n = 1769 ; % = 50.8
n = 2 Sample size	n = 1424 ; % = 40.8	n = 1420 ; % = 40.7
n = 3 Sample size	n = 192 ; % = 5.5	n = 180 ; % = 5.2
n = ≥4 Sample size	n = 6 ; % = 0.2	n = 7 ; % = 0.2

1

2

420. Rosenstock, 2013

Bibliographic Reference	Rosenstock, Julio; Raccah, Denis; Koranyi, Laszlo; Maffei, Laura; Boka, Gabor; Miossec, Patrick; Gerich, John E; Efficacy and safety of lixisenatide once daily versus exenatide twice daily in type 2 diabetes inadequately controlled on metformin: a 24-week, randomized, open-label, active-controlled study (GetGoal-X).; Diabetes care; 2013; vol. 36 (no. 10); 2945-51

420.1. Study details

Secondary publication of another included study- see primary study for details	N/A
Other publications associated with this study included in review	
Trial name / registration number	NCT00707031
Study location	122 centres in 18 countries: Argentina, Austria, Brazil, Colombia, Denmark, Finland, Germany, Greece, Hungary, Italy, the Netherlands, Norway, Poland, Puerto Rico, Russian Federation, Spain, Sweden, United States of America.
Study setting	No further information
Study dates	June 2008 to November 2010
Sources of funding	The study was funded by Sanofi (manufacturers of lixisenatide)
Inclusion criteria	• Men and women aged 21-84 years with type 2 diabetes receiving ≥1.5g/day metformin and with Hba1c 7-10% (between 53 and 86 mmol/mol)
Exclusion criteria	• Use of oral or injectable glucose-lowering agents other than metformin within 3 months prior to screening • FPG at screening > 13.9 mmol/L (250 mg/dL)

	• History of unexplained pancreatitis, chronic pancreatitis, pancreatectomy, stomach/gastric surgery or inflammatory bowel disease • History of metabolic ketoacidosis, including diabetic ketoacidosis, within 1 year prior to screening • History of myocardial infarction, stroke or heart failure requiring hospitalisation within 6 months • Clinically relevant history of gastrointestinal disease, with prolonged nausea and vomiting during the previous 6 months.
Recruitment / selection of participants	No further information
Intervention(s)	Lixisenatide initiated at 10 µg once daily for 1 week, increased to15 µg once daily for 1 week, and then increased to 20 µg once daily. Treatments were administered within 1 hour before the morning meal.
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear People who were hospitalised for heart failure within previous 6 months were excluded. No information about events before the 6 months and no information reported in baseline characteristics.
Strata 2: People with atherosclerotic cardiovascular disease	Not stated/unclear People who had a stroke or myocardial infarction within the past 6 months were excluded. No information about stroke or MI prior to the 6 months and no information in the baseline characteristics. No information about angina, peripheral arterial disease or revascularisation procedures.
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear No information in the inclusion/exclusion criteria or baseline characteristics.
Strata 4: People with type 2 diabetes	Not stated/unclear No information

mellitus and high cardiovascular risk	
Subgroup 1: People with moderate or severe frailty	Not stated/unclear No information in inclusion/exclusion criteria or baseline characteristics
Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear Baseline characteristics report mean duration of diabetes; age of onset not reported and not specified in the inclusion/exclusion criteria.
Subgroup 3: People with non-alcoholic fatty liver disease	Not stated/unclear
Subgroup 4: People with obesity	Not stated/unclear Obesity not an inclusion/exclusion criteria. Number of people with obesity not reported in baseline characteristics (only mean BMI).
Subgroup 5: eGFR category at baseline	Not stated/unclear
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Comparator	Exenatide initiated at 5 µg twice daily for 4 weeks and increased to 10 µg twice daily. Treatments were administered within 1 hour before the morning and evening meals.
Number of participants	N = 639
Duration of follow-up	24 weeks

Method of analysis	Modified ITT Modified ITT population comprised all randomised participants who received at least one dose of open-label study drug and had both a baseline assessment and at least one post-baseline assessment for any primary or secondary efficacity outcome. Other Safety population comprised all randomised participants who received at least one dose of study drug.
Additional comments	

420.2. Study arms

420.2.1. Lixisenatide (N = 318)

Lixisenatide 20 µg once daily

420.2.2. Exenatide (N = 316)

Exenatide 10 µg twice daily.

420.3. Characteristics

420.3.1. Arm-level characteristics

Characteristic	Lixisenatide (N = 318)	Exenatide (N = 316)
% Male Sample size	n = 151 ; % = 47.5	n = 187 ; % = 59.2
Mean age (SD) (years) Mean (SD)	57.3 (9.2)	57.6 (10.7)
Ethnicity Race Sample size	n = NA ; % = NA	n = NA ; % = NA
Causasian Sample size	n = 296 ; % = 93.1	n = 292 ; % = 92.4

Characteristic	Lixisenatide (N = 318)	Exenatide (N = 316)
Black Sample size	n = 8 ; % = 2.5	n = 10 ; % = 3.2
Asian Sample size	n = 3 ; % = 0.9	n = 4 ; % = 1.3
Other race Sample size	n = 11 ; % = 3.5	n = 10 ; % = 3.2
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)	57.3 (9.2)	57.6 (10.7)
HbA1c (%) Mean (SD)	8.03 (0.8)	8.02 (0.8)
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
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

Characteristic	Lixisenatide (N = 318)	Exenatide (N = 316)
People with a learning disability Sample size	n = NR ; % = NR	n = NR ; % = NR
Weight (kg) Mean (SD)	94 (19.6)	96.1 (22.5)
BMI (kg/m²) Mean (SD)	33.7 (6.3)	33.5 (6.5)
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 (mg) Daily metformin dose Mean (SD)	2020 (459)	2058 (453)
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

1

2

421. Roussel, 2019

Bibliographic Reference	Roussel, R.; Duran-Garcia, S.; Zhang, Y.; Shah, S.; Darmiento, C.; Shankar, R. R.; Golm, G. T.; Lam, R. L. H.; O'Neill, E. A.; Gantz, I.; Kaufman, K. D.; Engel, S. S. R. T. Y. Journal article; Double-blind, randomized clinical trial comparing the efficacy and safety of continuing or discontinuing the dipeptidyl peptidase-4 inhibitor sitagliptin when initiating insulin glargine therapy in patients with type 2 diabetes: the CompoSIT-I Study; Diab Obes Metab; 2019; vol. 21 (no. 4); 781-790

421.1. Study details

Trial name / registration number	CompoSIT-I / NCT02738879
Study type	Randomised controlled trial (RCT)
Study location	149 sites in 22 countries
Study setting	No additional information
Study dates	NR
Sources of funding	Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc. The lead author declares support from multiple pharmaceutical companies and numerous authors are employees of Merck Sharp & Dohme Corp
Inclusion criteria	Male and female individuals , aged ≥18 years, with type 2 diabetes and on a stable regimen (>12 weeks) of metformin (≥1500 mg/d) in dual or triple combination therapy with a DP inhibitor (maximum labelled dose) and/or a sulphonylurea. Metformin could be immediate-release, extended-release or part of a fixed-dose combination. Patients on dual combination therapy with metformin and a DPP-4 inhibitor or metformin and a sulphonylurea were required to have an HbA1c concentration ≥58 mmol/mol and ≤97 mmol/mol (≥7.5% and ≤11.0%). Patients on triple combination therapy (metformin, DPP-4 inhibitor and a sulphonylurea) were required to have an HbA1c concentration ≥53 mmol/mol and ≤86 mmol/mol (≥7.0% and ≤10.0%). At randomization, eligible patients were required to have a fasting finger-stick glucose level >7.2 mmol/L and <15.0 mmol/L.
Exclusion criteria	Patients were excluded from the study if they had type 1 diabetes, a history of ketoacidosis, active liver disease, significant cardiovascular disease, a history of malignancy or haematological disorders, if they had been treated with any AHAs other than those specified in the inclusion criteria within 12 weeks prior to screening, or if they had a history of two or more episodes of hypoglycaemia resulting in seizure, coma or loss of consciousness, or recurrent (≥3 times per week) episodes of hypoglycaemia within 8 weeks prior to screening. Laboratory exclusion criteria included estimated glomerular filtration rate <60 mL/min/1.73 m2 (calculated by the Modification of Diet in Renal Disease formula), serum alanine aminotransferase or aspartate aminotransferase levels >2 times

	the upper limit of normal, haemoglobin <110 g/L (men) or <100 g/L (female), triglycerides >6.8 mmol/L or thyroid-stimulating hormone outside the central laboratory normal range.
Recruitment / selection of participants	No additional information
Intervention(s)	Sitagliptin (n=373) Patients received 100 mg /day sitagliptin for 30 weeks
Cointervention	Insulin glargine; All participants initiated insulin glargine on the evening of the day of randomization with a starting dose of 10 units. Participants were instructed to administer their insulin in the evening at the same time every day. Participants were instructed to titrate insulin throughout the entire study period, based on their pre-breakfast fasting BG level using an algorithm that targeted a fasting value of 4.0 to 5.6 mmol/L. If, on 3 consecutive days the fasting BG was >5.6 mmol/L but ≤7.8 mmol/L, the insulin dose was increased by 2 units; if fasting BG was >7.8 mmol/L, the insulin dose was increased by 4 units. If the fasting BG was ≤3.9 mmol/L, the insulin dose was reduced by 4 units after consultation with the investigator. Metformin; Patients receive co-administration with sitagliptin of either metformin immediate release or extended release
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear Exclusion criteria for significant cardiovascular disease but no other information
Strata 2: People with atherosclerotic cardiovascular disease	Not stated/unclear Exclusion criteria for significant cardiovascular disease but no other information
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear
Strata 4: People with type 2	Not stated/unclear

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
Population subgroups	NA
Comparator	Placebo (n=370) Patients received daily placebo for 30 weeks Insulin glargine; All participants initiated insulin glargine on the evening of the day of randomization with a starting dose of 10 units. Participants were instructed to administer their insulin in the evening at the same time every day. Participants were instructed to titrate insulin throughout the entire study period, based on their pre-breakfast fasting BG level using an algorithm that targeted a fasting value of 4.0 to 5.6 mmol/L. If, on 3 consecutive days the fasting BG was >5.6 mmol/L but ≤7.8 mmol/L, the insulin dose was

	increased by 2 units; if fasting BG was >7.8 mmol/L, the insulin dose was increased by 4 units. If the fasting BG was ≤3.9 mmol/L, the insulin dose was reduced by 4 units after consultation with the investigator. Metformin; Patients receive co-administration with sitagliptin of either metformin immediate release or extended release
Number of participants	746
Duration of follow-up	30 weeks
Indirectness	NA
Method of analysis	ACA
Additional comments	The population for all efficacy endpoints included all randomized participants who received at least one dose of study treatment and, with the exception of the endpoint of hypoglycaemia, who had at least one measurement of the respective endpoint. Safety analyses included all randomized and treated participants.

421.2. Study arms

421.2.1. Sitagliptin (N = 373)

Patients received a daily dose of 100 mg sitagliptin for 30 weeks

421.2.2. Placebo (N = 370)

Patients received daily placebo for 30 weeks

421.3. Characteristics

421.3.1. Arm-level characteristics

Characteristic	Sitagliptin (N = 373)	Placebo (N = 370)
% Male Sample size	n = 170 ; % = 45.6	n = 190 ; % = 51.4

Characteristic	Sitagliptin (N = 373)	Placebo (N = 370)
Mean age (SD) (Years (mean, SD)) Mean (SD)	58.6 (9.5)	58.1 (9.7)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA
White Sample size	n = 258 ; % = 69.2	n = 270 ; % = 73
Asian Sample size	n = 42 ; % = 11.3	n = 36 ; % = 9.7
Multiple Sample size	n = 34 ; % = 9.1	n = 34 ; % = 9.2
American-Indian/Alaska Native Sample size	n = 19 ; % = 5.1	n = 17 ; % = 4.6
Black or African American Sample size	n = 12 ; % = 3.2	n = 12 ; % = 3.2
Native Hawaiian or other Pacific Islander Sample size	n = 6 ; % = 1.6	n = 1 ; % = 0.3
Missing Sample size	n = 2 ; % = 0.5	n = 0 ; % = 0
Not Hispanic or Latino Sample size	n = 247 ; % = 66.2	n = 239 ; % = 64.6
Hispanic or Latino Sample size	n = 122 ; % = 32.7	n = 129 ; % = 34.9
Not reported Sample size	n = 4 ; % = 1.1	n = 2 ; % = 0.5
Time since type 2 diabetes diagnosed (Years (mean, SD)) Mean (SD)	10.4 (6.8)	11.1 (6.9)
Smoking status Sample size	n = NR ; % = NR	n = NR ; % = NR

Characteristic	Sitagliptin (N = 373)	Placebo (N = 370)
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
Other antidiabetic medication used Sample size	n = NA ; % = NA	n = NA ; % = NA
Metformin + DPP4 inhibitor Sample size	n = 184 ; % = 49.3	n = 182 ; % = 49.2
Metformin + DPP-4 inhibitor + Sulfonylurea Sample size	n = 87 ; % = 23.3	n = 86 ; % = 23.2
Metformin + Sulfonylurea Sample size	n = 102 ; % = 27.3	n = 102 ; % = 27.6
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

1

2

422. Russell-Jones, 2009

Bibliographic Reference	Russell-Jones, D.; Vaag, A.; Schmitz, O.; Sethi, B. K.; Lalic, N.; Antic, S.; Zdravkovic, M.; Ravn, G. M.; Simó, R.; Liraglutide vs insulin glargine and placebo in combination with metformin and sulfonylurea therapy in type 2 diabetes mellitus (LEAD-5 met+SU): a randomised controlled trial; Diabetologia; 2009; vol. 52 (no. 10); 2046-55

422.1. 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	LEAD-5 met+SU/NCT00331851
Study type	Randomised controlled trial (RCT) Double-blind (liraglutide and placebo) and open-label (insulin glargine, metformin, and glimepiride) parallel group RCT
Study location	International (107 sites in 17 countries: Argentina, Austria, Brazil, Denmark, Finland, France, India, Italy, Netherlands, Philippines, Poland, Russian Federation, Serbia, Slovakia, South Africa, Spain, UK)
Study setting	Outpatient
Study dates	05/2006 to 04/2007
Sources of funding	Funded by Novo Nordisk A/S
Inclusion criteria	• Aged 18-80 years old • Type 2 diabetes diagnosis • Treated with oral glucose-lowering therapy for at least 3 months before screening • HbA1c level 7.5–10% if on oral glucose-lowering monotherapy or 7–10% if on combination therapy

	• BMI≤45kg/m2
Exclusion criteria	• Used insulin within 3 months prior to the trial (except for short-term treatment for intercurrent illness • Impaired hepatic or renal function • Clinically significant cardiovascular disease • Proliferative retinopathy or maculopathy • Hypertension (≥180/100 mmHg) • Cancer • Pregnancy • Experienced recurrent hypoglycaemia or hypoglycaemia unawareness • Seropositive for hepatitis B antigen or hepatitis C antibody • Used any drugs except for oral glucose-lowering drugs that could affect blood glucose level
Recruitment / selection of participants	Participants recruited from 107 sites in 17 countries. After 6-week run-in period in which participants were put on metformin and glimepiride combination therapy (3 week forced dose escalation, then 3 week maintenance period). Participants already on metformin 2 mg and sulphonylurea therapy allowed to proceed directly to maintenance period. Dose escalation of metformin and glimepiride increased by up to 2g/day and 4mg/day respectively. Participants randomised if inclusion criteria met, had received at least 3-wk glimepiride 4 mg daily and metformin 2 g daily, and had FPG 7.5-12.8 mmol/L after 6-wk run in period. Randomisation used telephone or web-based randomisation system and stratified according to baseline oral glucose lowering mono- or combination therapy.
Intervention(s)	• Liraglutide 1.8 mg daily Subcutaneous injection of liraglutide 1.8 mg daily for 26 weeks, in addition to metformin and glimepiride. Injection could be abdomen, thigh or upper arm using NovoFine 30G disposable needle (Novo Nordisk) at any time of day. Participants encouraged to inject liraglutide during same time period every day. After randomisation, participants in liraglutide group underwent 2-wk dose escalation period (0.6 mg daily, increased weekly by 0.6 mg, to 1.8 mg daily by end of second week, fixed thereafter for 24 weeks).
Cointervention	• Metformin 1 mg twice daily + glimepiride 4 mg daily All participants received open-label metformin and glimepiride for 26 weeks. Glimepiride could be reduced to 2 mg after randomisation if adverse events and hypoglycaemia.
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear Exclusion criteria for clinically significant cardiovascular disease but no explicit mention
Strata 2: People with	Not stated/unclear

atherosclerotic cardiovascular disease	Exclusion criteria for clinically significant cardiovascular disease but no explicit mention
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear Exclusion criteria for impaired renal function but no explicit mention
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 • Insulin glargine Double-blind placebo for liraglutide, with injections matched volume of liraglutide during 2-wk escalation period, for 26 weeks. Open-label insulin glargine 100 IU/ml injected once daily (OptiSet; Sanofi-Aventis) at any time of day (but at same time of day) and titrated using version of AT-LANTUS dosing algorithm. Starting dose numerically equivalent to highest FPG mmol/L over previous 7 days (e.g. if PFG 10 mmol/L then insulin dose was 10 IU). In first 8 weeks, participant dose titrated twice weekly based on self-measured FPG (aiming for FPG≤5.5 mmol/L). After 8 weeks, frequency of monitoring and titration at investigator discretion, but at minimum dose adjusted at 12 and 18 week visits. Investigators reviewed doses and could change them at their discretion.
Number of participants	N=581
Duration of follow-up	26 weeks
Indirectness	None
Method of analysis	Modified ITT mITT analysis (all randomised participants exposed to at least one dose of study drug) for all outcomes. mITT LOCF analysis for HbA1c outcome.
Additional comments	

422.2. Study arms

422.2.1. Liraglutide 1.8 mg daily (N = 232)

Subcutaneous injection of liraglutide 1.8 mg daily for 26 weeks, in addition to metformin 1 g twice daily and glimepiride 4 mg daily.

422.2.2. Placebo (N = 115)

Subcutaneous placebo to liraglutide injection for 26 weeks, in addition to metformin 1 g twice daily and glimepiride 4 mg daily.

422.2.3. Insulin glargine (N = 234)

Open-label insulin glargine titrated for 26 weeks, in addition to metformin 1 g twice daily and glimepiride 4 mg daily.

422.3. Characteristics

422.3.1. Arm-level characteristics

Characteristic	Liraglutide 1.8 mg daily (N = 232)	Placebo (N = 115)	Insulin glargine (N = 234)
% Male Sample size	n = 132 ; % = 57	n = 58 ; % = 51	n = 93 ; % = 40
Mean age (SD) (years) Mean (SD)	57.6 (9.5)	57.5 (9.6)	57.5 (10.5)
Ethnicity Nominal	NR	NR	NR
Comorbidities Nominal	NR	NR	NR
Presence of frailty Nominal	NR	NR	NR
Time since type 2 diabetes diagnosed (years) Mean (SD)	9.2 (5.8)	9.4 (6.2)	9.7 (6.4)
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

Characteristic	Liraglutide 1.8 mg daily (N = 232)	Placebo (N = 115)	Insulin glargine (N = 234)
People with a learning disability Nominal	NR	NR	NR
Number of people with obesity Nominal	NR	NR	NR
Other antidiabetic medication used Previous use of oral glucose-lowering drugs Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
Oral glucose-lowering monotherapy only Sample size	n = 14 ; % = 6	n = 6 ; % = 5	n = 12 ; % = 5
Oral glucose-lowering combination therapy Sample size	n = 218 ; % = 94	n = 109 ; % = 95	n = 222 ; % = 95
Blood pressure-lowering medication used Nominal	NR	NR	NR
Statins/lipid-lowering medication used Nominal	NR	NR	NR
Other treatment being received Nominal	NR	NR	NR

1

2

423. Sarraju, 2021

Bibliographic Reference	Sarraju, Ashish; Li, JingWei; Cannon, Christopher P; Chang, Tara I; Agarwal, Rajiv; Bakris, George; Charytan, David M; de Zeeuw, Dick; Greene, Tom; Heerspink, Hiddo J L; Levin, Adeera; Neal, Bruce; Pollock, Carol; Wheeler, David C; Yavin, Yshai; Zhang, Hong; Zinman, Bernard; Perkovic, Vlado; Jardine, Meg; Mahaffey, Kenneth W; Effects of canagliflozin on cardiovascular, renal, and safety outcomes in participants with type 2 diabetes and chronic kidney disease according to history of heart failure: Results from the CREDENCE trial.; American heart journal; 2021; vol. 233; 141-148

423.1. Study details

Secondary publication of another included study- see primary study for details	CREDENCE trial. Perkovic, V., Jardine, M. J., Neal, B. et al. (2019) Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. N Engl J Med 380(24): 2295-2306
Other publications associated with this study included in review	Jardine, Meg J, Mahaffey, Kenneth W, Neal, Bruce et al. (2017) The Canagliflozin and Renal Endpoints in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) Study Rationale, Design, and Baseline Characteristics. American journal of nephrology 46(6): 462-472
Trial name / registration number	CREDENCE trial. NCT02065791
Study type	Randomised controlled trial (RCT)
Study location	Multiple countries: USA, Argentina, Australia, Brazil, Bulgaria, Canada, Chile, China, Colombia, Czechia, France, Germany, Guatemala, Hungary, India, Japan, Korea, Lithuania, Malaysia, Mexico, New Zealand, Philippines, Poland, Puerto Rico, Romania, Russia, Serbia, Slovakia, South Africa, Spain, Taiwan, Ukraine, UAE, UK.
Study setting	Unspecified clinical setting
Study dates	February 17, 2014 - October 30, 2018
Sources of funding	Janssen Research & Development, LLC
Inclusion criteria	• Type 2 diabetes mellitus with a hemoglobin A1c (HbA1c) greater than or equal to (>=) 6.5 percent (%) and less than or equal to (<=) 12.0%, with an estimated glomerular filtration rate (eGFR) of >= 30

	millilitre (mL)/minute (min)/1.73meter (m)^2 and less than (<) 90 mL/min/1.73 m^2 • Participants need to be on a stable maximum tolerated labeled daily dose of an angiotensin-converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB) for at least 4 weeks prior to randomization • Must have a urine albumin to creatinine ratio (UACR) of greater than (>) 300 milligram (mg)/gram (g) and <= 5000 mg/g
Exclusion criteria	• History of diabetic ketoacidosis or type 1 diabetes mellitus • History of hereditary glucose-galactose malabsorption or primary renal glucosuria • Renal disease that required treatment with immunosuppressive therapy • Known significant liver disease • Current or history of New York Heart Association (NYHA) Class IV heart failure • Blood potassium level >5.5 millimole (mmol)/litre (L) during Screening
Recruitment / selection of participants	Participants from CREDENCE trial, no further details provided.
Intervention(s)	Drug: Canagliflozin One 100 mg over-encapsulated tablet orally once daily
Cointervention	angiotensin-converting enzyme inhibitor or angiotensin receptor blocker
Strata 1: People with type 2 diabetes mellitus and heart failure	People without heart failure 15% with heart failure. Data for this group available if needed (large sample size, so might be useful)
Strata 2: People with atherosclerotic cardiovascular disease	Mixed population
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	People with 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	eGFR ≥30mL/min/1.73m2
Subgroup 6: Albuminuria category at baseline	A3 (ACR >300mg/g or >30mgmmol)
Comparator	Placebo: One matching placebo capsule orally (by mouth) once daily
Number of participants	A total of 4401 participants were randomized, with 2199 and 2202 participants assigned to placebo and canagliflozin 100 milligrams (mg), respectively
Duration of follow-up	Up to 66 months
Indirectness	None
Method of analysis	ITT

Additional comments	Data extracted for all participants, including those with heart failure (15%). Data on just participants without HF is also available.

423.2. Study arms

423.2.1. Canagliflozin (N = 2202)

Participants received canagliflozin 100 milligram (mg) orally once daily.

423.2.2. Placebo (N = 2199)

Participants received matching placebo orally once daily

423.3. Characteristics

423.3.1. Arm-level characteristics

Characteristic	Canagliflozin (N = 2202)	Placebo (N = 2199)
% Male Nominal	65.4	66.7
Mean age (SD) Mean (SD)	62.9 (9.17)	63.2 (9.23)
Asian % Nominal	19.3	20.6
Black % Nominal	5.1	5.1
Hispanic/Latino Nominal	25.7	25.2
White % Nominal	41.3	40.1
Other Nominal	8.6	9

424. Sathyanarayana, 2011

Bibliographic Reference	Sathyanarayana, Padma; Jogi, Medhavi; Muthupillai, Raja; Krishnamurthy, Ramkumar; Samson, Susan L; Bajaj, Mandeep; Effects of combined exenatide and pioglitazone therapy on hepatic fat content in type 2 diabetes.; Obesity (Silver Spring, Md.); 2011; vol. 19 (no. 12); 2310-5

424.1. 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	US
Study setting	Hospital
Study dates	No additional information.
Sources of funding	Amylin Pharmaceuticals and Eli-Lilly supported the research through grants.
Inclusion criteria	Age = 30–70 years, stable body weight (±2 lbs) for at least 3 months before study, fasting plasma glucose (FPG) = 126–260mg/ dl. All patients were in good general health, without evidence of cardiac, hepatic, renal, or other chronic diseases as determined by history, physical examination, screening blood tests, and urinalysis.
Exclusion criteria	Patients with ALT or aspartate aminotransferase greater than 2.5 times upper limit of normal were excluded from the study. No subjects participated in any heavy exercise, and no subjects were taking any medications known to affect glucose metabolism.

Recruitment / selection of participants	Patients on metformin with uncontrolled type 2 diabetes were recruited and randomised 1:1 to pioglitazone 45 mg daily or pioglitazone 45 mg daily in combination with exenatide (10 µg subcutaneously twice daily).
Intervention(s)	Pioglitazone 45 mg daily + exenatide (10 µg twice daily) Administered orally and subcutaneously
Cointervention	Metformin
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear "All patients were in good general health, without evidence of cardiac, hepatic, renal, or other chronic diseases as determined by history, physical examination, screening blood tests, and urinalysis." No further information about heart failure.
Strata 2: People with atherosclerotic cardiovascular disease	Not stated/unclear "All patients were in good general health, without evidence of cardiac, hepatic, renal, or other chronic diseases as determined by history, physical examination, screening blood tests, and urinalysis." No further information about CVD.
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear "All patients were in good general health, without evidence of cardiac, hepatic, renal, or other chronic diseases as determined by history, physical examination, screening blood tests, and urinalysis." No further information about 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	People without non-alcoholic 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	Pioglitazone 45 mg daily Administered orally
Number of participants	N=21
Duration of follow-up	12-month
Indirectness	Two patients in each treatment group were not on metformin therapy at the time of randomisation or during the entire study period.
Method of analysis	ITT Not stated/unclear
Additional comments	Although not specifically stated, the results imply that an ITT approach was taken for analysis where all patients randomised were included in the analysis.

424.2. Study arms

424.2.1. Pioglitazone 30 - 45 mg daily + Exenatide 10 µg twice daily (N = 11)

Administered orally and subcutaneously

424.2.2. Pioglitazone 30 mg - 45 mg daily (N = 10)

Administered orally

424.3. Characteristics

424.3.1. Study-level characteristics

Characteristic	Study (N = 21)
Mean age (SD) (years) Mean (SD)	52 (3)

424.3.2. Arm-level characteristics

Characteristic	Pioglitazone 30 - 45 mg daily + Exenatide 10 µg twice daily (N = 11)	Pioglitazone 30 mg - 45 mg daily (N = 10)
% Male Nominal	NR	NR
Ethnicity Nominal	NR	NR
Presence of frailty Nominal	NR	NR
Time since type 2 diabetes diagnosed 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

Characteristic	Pioglitazone 30 - 45 mg daily + Exenatide 10 µg twice daily (N = 11)	Pioglitazone 30 mg - 45 mg daily (N = 10)
People with a learning disability Nominal	NR	NR
Number of people with obesity Nominal	NR	NR
Metformin No of events	n = 9 ; % = 82	n = 8 ; % = 80

1

2

425. Savvidou, 2016

Bibliographic Reference	Savvidou, Savvoula; Karatzidou, Kyparissia; Tsakiri, Kalliopi; Gagalis, Asterios; Hytiroglou, Prodromos; Goulis, John; Circulating adiponectin levels in type 2 diabetes mellitus patients with or without non-alcoholic fatty liver disease: Results of a small, open-label, randomized controlled intervention trial in a subgroup receiving short-term exenatide.; Diabetes research and clinical practice; 2016; vol. 113; 125-34

425.1. Study details

Trial name / registration number	NA
Study type	Randomised controlled trial (RCT)
Study location	Medical Center of Diabetes Mellitus in ‘‘Papageorgiou’’ University Hospital of Thessaloniki, Greece
Study setting	No additional information
Study dates	January 2010 to December 2012
Sources of funding	None
Inclusion criteria	– Age above 18 years old, – Prior treatment with >20 Units per day of glargine insulin plus metformin for at least the past 6 months, – Suboptimal glucose control with HbA1c > 8.0% (>64 mmol/ mol), – Refused history of previous administration of thiazolidinediones, GLP-1 receptor agonists or dipeptidyl peptidase-4 (DDP-4) inhibitors, – Denied alcohol consumption in excess 120 g per week,
Exclusion criteria	– Severe comorbid conditions including end-stage renal disease, recent cardiovascular events, chronic heart failure, hypo- or hyperthyroidism, history of acute or chronic pancreatitis, – Written willing to participate
Recruitment / selection of participants	No additional information
Intervention(s)	Exenatide (n=55)

	Exenatide was supplied through subcutaneous injections in the upper arm, thigh or abdomen with prefilled pens of 5 ug twice daily for the first 4 weeks and 1u mg (forced titration) twice daily thereafter for the study duration of 6 months. Patients were self-injected within 60 min before morning and evening meals. None of the patients received special recommendations on diet and exercise.
Cointervention	Metformin All patients received optimally titrated metformin
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
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	People without 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	People without non-alcoholic fatty liver disease

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	Insulin (n=55) Patients received short-acting insulin three times daily prior to the meals according to self monitoring of glucose levels and self-titrations
Number of participants	110
Duration of follow-up	6 months
Indirectness	NA
Method of analysis	Per protocol
Additional comments	Statistical analysis poorly described but appears to be per protocol

425.2. Study arms

425.2.1. Exenatide (N = 55)

Patients received Exenatide via subcutaneous injections with prefilled pens of 5 ug twice daily for the first 4 weeks followed by 10 ug twice daily thereafter.

425.2.2. Insulin (N = 55)

Patients received short-acting insulin three times daily for 6 months

425.3. Characteristics

425.3.1. Arm-level characteristics

Characteristic	Exenatide (N = 55)	Insulin (N = 55)
% Male Exenatide n = 55, Insulin n = 48 Sample size	n = 25 ; % = 45.5	n = 16 ; % = 33
Mean age (SD) (Years (mean, SD)) Exenatide n = 55, Insulin n = 48 Mean (SD)	62.2 (7.2)	63.7 (7.1)
Ethnicity Exenatide n = 55, Insulin n = 48 Sample size	n = NA ; % = NA	n = NA ; % = NA
White (Caucasian) Sample size	n = 55 ; % = 100	n = 48 ; % = 100
Time since type 2 diabetes diagnosed (Years (mean, SD)) Exenatide n = 55, Insulin n = 48 Mean (SD)	NR (NR)	NR (NR)
Presence of severe mental illness Exenatide n = 55, Insulin n = 48 Sample size	n = NR ; % = NR	n = NR ; % = NR
People with significant cognitive impairment Exenatide n = 55, Insulin n = 48 Sample size	n = NR ; % = NR	n = NR ; % = NR
People with a learning disability Exenatide n = 55, Insulin n = 48 Sample size	n = NR ; % = NR	n = NR ; % = NR
Other antidiabetic medication used Exenatide n = 55, Insulin n = 48 Sample size	n = NA ; % = NA	n = NA ; % = NA
Metformin Sample size	n = 55 ; % = 100	n = 48 ; % = 100

Characteristic	Exenatide (N = 55)	Insulin (N = 55)
Blood pressure-lowering medication used Exenatide n = 55, Insulin n = 48 Sample size	n = NR ; % = NR	n = NR ; % = NR
Statins/lipid-lowering medication used Exenatide n = 55, Insulin n = 48 Sample size	n = NR ; % = NR	n = NR ; % = NR
Other treatment being received Exenatide n = 55, Insulin n = 48 Sample size	n = NR ; % = NR	n = NR ; % = NR

1

2

426. Schernthaner, 2015

Bibliographic Reference	Schernthaner, G.; Duran-Garcia, S.; Hanefeld, M.; Langslet, G.; Niskanen, L.; Ostgren, C. J.; Malvolti, E.; Hardy, E.; Efficacy and tolerability of saxagliptin compared with glimepiride in elderly patients with type 2 diabetes: A randomized, controlled study (GENERATION); Diabetes Obes Metab; 2015; vol. 17 (no. 7); 630-638

426.1. 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	GENERATION [NCT0100660]
Study type	Randomised controlled trial (RCT)
Study location	152 sites in 12 European countries and Mexico
Study setting	NR
Study dates	Between October 2009 and June 2012
Sources of funding	AstraZeneca and Bristol-Myers Squibb
Inclusion criteria	• T2D aged≥65 years • On stable metformin monotherapy at any dose for ≥8 weeks before enrolment and had an HbA1c concentration of 7.0–9.0%,
Exclusion criteria	• Type 1 diabetes mellitus • Treatment with any anti-hyperglycaemic therapy other than metformin monotherapy<8weeks before enrolment • Treatment with systemic glucocorticoids (except for replacement therapy) or cytochrome P450 3A4 inducers • History of ketoacidosis or hyperosmolar non-ketonic coma

	• History of haemoglobinopathies • Renal impairment (creatinine clearance<60 ml/min) • Cognitive function problems • Alcohol or illegal drug abuse for ≤12months before enrolment • History of hypersensitivity or contraindication to the study drugs
Recruitment / selection of participants	There was a 2-week screening period, a 2 week enrolment period, a 2-week single-blinded (to patients only) placebo lead-in period, and a 52-week double-blinded treatment period. Patients were randomised after the lead-in period.
Intervention(s)	• Saxagliptin 5 mg/day and placebo • Glimepiride ≤6 mg and placebo [During the titration period, glimepiride or placebo was up titrated every 3 weeks in 1- or 2 mg increments to the optimum dose (fasting plasma glucose ≤6.1 mmol/l) up to 6 mg/day.]
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. Baseline characteristics table reports history of vascular disease (coronary artery disease, previous MI, cardiovascular accident and table angina) but unclear if these are mutually exclusive..
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear CKD not an inclusion/exclusion criteria. People with renal impairment (creatinine clearance<60ml/min) were excluded. 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 There was a posthoc analysis regarding eGFR, however, as this was a post hoc analysis, this was not eligible for inclusion in the review.
Population subgroups	NA
Comparator	NA
Number of participants	957 participants were enrolled and 720 participants were randomised. 360 participants were allocated to saxagliptin + metformin, 71 participants discontinued (19.7%), and 289 participants (80.3% completed 52 weeks treatment period. 360 participants were allocated to glimepiride + metformin, 75 participants discontinued (20.8%), and 285 participants (79.2%) completed the 52-week treatment period.
Duration of follow-up	52 weeks
Indirectness	Directly applicable
Method of analysis	Not stated/unclear Participants with non-missing baseline and ≥1 post-baseline efficacy data for ≥1 variable. Continuous endpoints were analysed using an analysis of covariance model, with treatment group and age as fixed effects and baseline value of the endpoint as a covariate.
Additional comments	NA

1

426.2. Study arms

426.2.1. Saxaglitpin (N = 360)

426.2.2. Glimepiride (N = 360)

426.3. Characteristics

426.3.1. Arm-level characteristics

Characteristic	Saxagliptin (N = 360)	Glimepiride (N = 360)
% Male Sample size	n = 217 ; % = 60.3	n = 228 ; % = 63.3
Mean age (SD) Mean (SD)	72.5 (5.7)	72.7 (5.4)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA
White Sample size	n = 352 ; % = 97.8	n = 355 ; % = 98.6
Other Sample size	n = 8 ; % = 2.2	n = 5 ; % = 1.4
Comorbidities Sample size	n = NA ; % = NA	n = NA ; % = NA
Musculoskeletal and connective tissue disorders Sample size	n = 120 ; % = 33.3	n = 121 ; % = 33.6
Gastrointestinal disorders Sample size	n = 85 ; % = 23.6	n = 82 ; % = 22.8
Reproductive system and breast disorders Sample size	n = 52 ; % = 14.4	n = 60 ; % = 16.7
Neoplasm Sample size	n = 53 ; % = 14.7	n = 49 ; % = 13.6

Characteristic	Saxagliptin (N = 360)	Glimepiride (N = 360)
Hypertension Sample size	n = 276 ; % = 76.7	n = 279 ; % = 77.5
Coronary artery disease Sample size	n = 31 ; % = 8.6	n = 36 ; % = 10
previous myocardial infarction Sample size	n = 34 ; % = 9.4	n = 20 ; % = 5.6
Cardiovascular accident Sample size	n = 19 ; % = 5.3	n = 21 ; % = 5.8
Stable angina Sample size	n = 17 ; % = 4.7	n = 21 ; % = 5.8
History of lipid disorder Sample size	n = 220 ; % = 61.1	n = 213 ; % = 59.2
Presence of frailty Nominal	NA	NA
Time since type 2 diabetes diagnosed Mean (SD)	7.6 (6.4)	7.6 (6)
Cardiovascular risk factors Nominal	NA	NA
Smoking status Nominal	NA	NA
Alcohol consumption Nominal	NA	NA
Presence of severe mental illness Nominal	NA	NA
People with significant cognitive impairment Nominal	NA	NA
People with a learning disability Nominal	NA	NA
BMI	29.9 (5)	29.3 (4.7)

Characteristic	Saxagliptin (N = 360)	Glimepiride (N = 360)
Mean (SD)		
Number of people with obesity >= 30 kg/m2 Sample size	n = 161 ; % = 44.7	n = 156 ; % = 43.3
Other antidiabetic medication used (mg) Metformin use Mean (SD)	1647 (705)	1572 (671)
Blood pressure-lowering medication used Nominal	NR	NR
Statins/lipid-lowering medication used Nominal	NR	NR
Other treatment being received Nominal	NR	NR

1

2

427. Schernthaner, 2013

Bibliographic Reference	Schernthaner, G.; Gross, J. L.; Rosenstock, J.; Guarisco, M.; Fu, M.; Yee, J.; Kawaguchi, M.; Canovatchel, W.; Meininger, G.; Canagliflozin compared with sitagliptin for patients with type 2 diabetes who do not have adequate glycemic control with metformin plus sulfonylurea: A 52-week randomized trial; Diabetes Care; 2013; vol. 36 (no. 9); 2508-2515

427.1. 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	CANTATA-D2 [NCT01137812]
Study type	Randomised controlled trial (RCT)
Study location	140 centres in 17 countries
Study setting	NR
Study dates	30 June 2010 to 9 March 2012
Sources of funding	Janssen Global Services, LLC.
Inclusion criteria	Type 2 diabetes using stable metformin and sulfonylurea therapy
Exclusion criteria	• Repeated fasting plasma glucose (FPG) or fasting self-monitored blood glucose measurements ≥16.7 mmol/L (300mg/dL), or both, during the pre-treatment phase • History of type 1 diabetes, cardiovascular disease, or uncontrolled hypertension

	• Treatment with either a PPAR agonist, ongoing insulin therapy, another SGLT2 inhibitor, or any other AHA (other than metformin and a sulfonylurea) within 12 weeks before screening • Estimated glomerular filtration rate < 55 mL/min/1.73 m2 (or 60 mL/min/1.73 m2 if based on restriction of metformin use in the metformin local label) • Serum creatinine ≥124 umol/L (men) and ≥115 umol/L (women).
Recruitment / selection of participants	• Participants using a combination of metformin and sulfonylurea at maximal or near-maximal doses (metformin ≥2,000 mg/day [or ≥1,500 mg/day if unable to tolerate a higher dose] and sulfonylurea at half-maximal labelled dose or more), who had HbA1c ≥7.0% and ≤10.5%, directly entered a 2-week single-blind placebo run-in before randomisation • All other participants underwent an antihyperglycemic agent adjustment period of up to 12 week (including an 8-week dose-stable period) to use maximally or near-maximally effective doses of metformin and sulfonylurea agent. These participants then entered the 2-week single-blind placebo run-in period if they had an HbA1c ≥7.0% and ≤10.5%.
Intervention(s)	• Canagliflozin 300 mg orally once daily • Sitagliptin 100 mg orally once daily
Cointervention	• Participants received intervention in addition to existing metformin and sulfonylurea
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear History of cardiovascular disease is an exclusion criterion; no further description provided. No information in baseline characteristics.
Strata 2: People with atherosclerotic cardiovascular disease	Not stated/unclear History of cardiovascular disease is an exclusion criterion; no further description provided. No information in baseline characteristics.
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear CKD no an inclusion/exclusion criteria. No information in baseline characteristics.
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	eGFR ≥30mL/min/1.73m2
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Population subgroups	NA
Comparator	NA
Number of participants	1,672 participants were assessed for eligibility, 916 were excluded, and 756 were randomised. 378 participants were allocated to sitagliptin, of these 168 did not complete the study, and 210 completed the study. 378 participants were allocated to canagliflozin, of these, 123 did not complete the study, and 254 completed the study.
Duration of follow-up	52 weeks
Indirectness	Directly applicable

Method of analysis	Per protocol Defined as participants completing the 52-week study and without protocol deviations that could impact the efficacy assessment Modified ITT Extracted data - Defined as all randomised participants who received one or more doses of the study drug. A last observation carried forward approach was used to impute missing data at the endpoint.
Additional comments	Participants were discontinued from the trial if they did not meet prespecified glycaemic criteria (FPG: Day 1 to week 6 >15 mmol/L [270 mg/dL], week 6 to week 12 >13.3 mmol/L [240 mg/dL] and week 12 to 26 12 >11.1 mmol/L [200 mg/dL]; HbA1c>8.0% after week 26). Participants were also discontinued if serum creatinine was ≥133 umol/L for men or ≥124 umol/L for women, eGFR was <50 mL/min/1.73 m2 or constituted contraindications to metformin use in the country of investigational site.

427.2. Study arms

427.2.1. Canagliflozin (N = 378)

427.2.2. Sitagliptin (N = 378)

427.3. Characteristics

427.3.1. Arm-level characteristics

Characteristic	Canagliflozin (N = 378)	Sitagliptin (N = 378)
% Male Sample size	n = 207 ; % = 54.9	n = 215 ; % = 56.9
Mean age (SD) Mean (SD)	56.6 (9.6)	56.7 (9.3)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA
White Sample size	n = 245 ; % = 65	n = 240 ; % = 63.5

Characteristic	Canagliflozin (N = 378)	Sitagliptin (N = 378)
Black or African American Sample size	n = 43 ; % = 11.4	n = 45 ; % = 11.9
Asian Sample size	n = 67 ; % = 17.8	n = 65 ; % = 17.2
Other Sample size	n = 22 ; % = 5.8	n = 28 ; % = 7.4
Hispanic or Latino Sample size	n = 79 ; % = 21	n = 80 ; % = 21.2
Not hispanic or latino Sample size	n = 298 ; % = 79	n = 296 ; % = 78.3
Other Sample size	n = 0 ; % = 0	n = 2 ; % = 0.5
Comorbidities Nominal	NR	NR
Presence of frailty Nominal	NR	NR
Time since type 2 diabetes diagnosed Mean (SD)	9.4 (6.1)	9.7 (6.3)
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

Characteristic	Canagliflozin (N = 378)	Sitagliptin (N = 378)
People with a learning disability Nominal	NR	NR
Weight Mean (SD)	87.4 (23.2)	89.1 (23.2)
BMI Mean (SD)	31.5 (6.9)	31.7 (6.9)
Number of people with obesity Nominal	NR	NR
Other antidiabetic medication used Sample size	n = NA ; % = NA	n = NA ; % = NA
Glipizide Sample size	n = 47 ; % = 12	n = 40 ; % = 11
Glipizide extended release Sample size	n = 16 ; % = 4	n = 18 ; % = 5
Glyburide/glibenclamide Sample size	n = 128 ; % = 34	n = 133 ; % = 35
Glimepiride Sample size	n = 121 ; % = 32	n = 106 ; % = 28
Gliclazide Sample size	n = 26 ; % = 7	n = 30 ; % = 8
Gliclazide modified release Sample size	n = 37 ; % = 10	n = 50 ; % = 13
Glyburide micronized Sample size	n = 2 ; % = 1	n = 0 ; % = 0
Tolazamide Sample size	n = 0 ; % = 0	n = 1 ; % = 0.26
Statins/lipid-lowering medication used Nominal	NR	NR
Other treatment being received	NR	NR

Characteristic	Canagliflozin (N = 378)	Sitagliptin (N = 378)
Nominal		

1

2

428. Scirica Benjamin, 2013

Bibliographic Reference	Scirica Benjamin, M; Bhatt Deepak, L; Braunwald, Eugene; Steg P, Gabriel; Davidson, Jaime; Hirshberg, Boaz; Ohman, Peter; Frederich, Robert; Wiviott Stephen, D; Hoffman Elaine, B; Cavender Matthew, A; Udell Jacob, A; Desai Nihar, R; Mosenzon, Ofri; McGuire Darren, K; Ray Kausik, K; Leiter Lawrence, A; Raz, Itamar; SAVOR-TIMI 53 Steering Committee, and; Investigators; Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus.; The New England journal of medicine; 2013; vol. 369 (no. 14); 1317-26

428.1. Study details

Secondary publication of another included study- see primary study for details	Parent study SAVOR-TIMI 53
Other publications associated with this study included in review	Mosenzon et al (2017) Effect of Saxagliptin on Renal Outcomes in the SAVOR-TIMI 53 Trial. Diabetes care; 2017; vol. 40 (no. 1); 69-76
Trial name / registration number	SAVOR-TIMI ClinicalTrials.gov no. NCT01107886
Study type	Randomised controlled trial (RCT)
Study location	Multicentre study - 788 sites in 26 countries (Argentina, Australia, Brazil, Canada, Chile, China, Czech Republic, France, Germany, Hong Kong, Hungary, India, Israel, Italy, Mexico, Netherlands, Peru, Poland, Russian Federation, South Africa, Spain, Sweden, Taiwan, Thailand, UK, USA)
Study setting	Multicentre study - 788 sites in 26 countries. No additional information.
Study dates	Participants randomised from May 2010 to December 2011.
Sources of funding	AstraZeneca and Bristol-Myers Squibb.
Inclusion criteria	1. Provision of informed consent before any study specific procedures 2. Age ≥40 years 3. Diagnosed with T2DM based on the current American Diabetes Association guidelines

	4. HbA1c ≥6.5% (based on the last measured and documented laboratory measurement in the previous 6 months) 5. High risk for a CV event defined as having either established CV disease and/or multiple risk factors: Established CV disease • Ischemic heart disease, and/or • Peripheral vascular disease (eg, intermittent claudication), and/or • Ischemic stroke Multiple risk factors • Patient must be at least 55 years old (male) or 60 years old (female) and have at least 1 additional risk factor (treated or nontreated) from the following: • Dyslipidemia (based on the last measured and documented laboratory measurement in the previous 6 months and defined as at least 1 of the following): ◦ High level of low-density lipoprotein cholesterol (LDL-C), defined as N130 mg/dL (N 3.36 mmol/L) regardless of lipid-lowering therapy ◦ Low level of high-density lipoprotein cholesterol (HDL-C), defined as b40 mg/dL (b1.04 mmol/L) for men or b50 mg/dL (b1.30 mmol/L) for women • Hypertension, as confirmed at the enrolment visit ◦ BP N140/N90 mm Hg, or ◦ BP N130/N80 mm Hg on BP-lowering agent • Currently smoking, as confirmed at the enrolment visit 6. Women of childbearing potential must take precautions to avoid pregnancy throughout the study and for 4 weeks after intake of the last dose. Men participating in the study should also take precautions not to father a child while participating in the study and for 4 weeks after intake of the last dose.
Exclusion criteria	1. Any conditions that, in the opinion of the investigator, may render the patient unable to complete the study including non-CV disease (eg, active malignancy, cardiomyopathy, cirrhosis, or chronic lung disease) with a likely fatal outcome within 5 years 2. Current or previous (within 6 months) treatment with an incretin-based therapy such as DPP-4 inhibitors and/or GLP-1 mimetics 3. Acute vascular (cardiac or stroke) event b2 months before randomization 4. Initiation of chronic dialysis and/or renal transplant and/or a serum creatinine N6.0 mg/dL 5. Pregnant or breast-feeding patients 6. History of human immunodeficiency virus 7. Patients being treated for severe autoimmune diseases such as lupus 8. Any patient currently receiving long-term (N30 consecutive days) treatment with an oral steroid 9. Patients with • Body mass index N50 kg/m2 • Last measured HbA1c ≥12% • Sustained BP N180/100 mm Hg • LDL-C N250 mg/dL (N6.48 mmol/L) (based on the last measured and documented laboratory

	measurement in the previous 6 months) regardless of lipid-lowering therapy • Triglycerides N1,000 mg/dL (N11.3 mmol/L) (based on the last measured and documented laboratory measurement in the previous 6 months) • HDL-C b25 mg/dL (b0.64 mmol/L) (based on the last measured and documented laboratory measurement in the previous 6 months) • Known liver function tests N3 times upper limit of normal (ULN) (based on the last measured and documented laboratory measurement in the previous 6 months) 10. Involvement in the planning and/or conduct of the study (applies to both AstraZeneca and Bristol-- Myers Squibb or representative staff and/or staff at the study site) 11. Previous randomization in the present study 12. Participation in another clinical study with an investigational product and/or intervention within 30 days before visit 1 13. Individuals at risk for poor protocol or medication compliance
Recruitment / selection of participants	No additional information
Intervention(s)	Saxagliptin at dose of 5mg daily or 2.5mg daily in patients with an estimated GFR<=50ml per minute. Administered until follow-up (median 2.1 years) Concomitant treatment: All other therapy for the management of the patient's diabetes and cardiovascular disease — including adding, discontinuing, or changing the dose of concomitant antihyperglycemic drugs — was at the discretion of the responsible physician. Concomitant use of other DPP-4 inhibitors or glucagon-like peptide 1 agonists was not allowed.
Strata 1: People with type 2 diabetes mellitus and heart failure	People without heart failure 12.8 % of both arms had prior heart failure at baseline
Strata 2: People with atherosclerotic cardiovascular disease	Mixed population 78.4 % Saxagliptin group and 78.7 % placebo group had established atherosclerotic disease at baseline
Strata 3: People with type 2 diabetes	Not stated/unclear

mellitus and chronic kidney disease	
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	People at higher risk of developing cardiovascular disease Participants had T2DM and either a history of established cardiovascular disease or multiple risk factors for vascular disease. To meet the criteria for established cardiovascular disease, patients had to be at least 40 years old and have a history of a clinical event associated with atherosclerosis involving the coronary, cerebrovascular, or peripheral vascular system. To meet the criteria for the multiple risk factors, patients had to be at least 55 years of age (men) or 60 years of age (women) with at least one of the following additional risk factors: dyslipidemia, hypertension, or active smoking.
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 53.7 % of Saxagliptin group and 53.4 % of placebo group BMI ≥30 (not split by ethnic group)
Subgroup 5: eGFR category at baseline	eGFR ≥30mL/min/1.73m2 baseline characteristics show that only 2% were <30ml/min/1.73m2
Subgroup 6: Albuminuria category at baseline	Mixed population Saxagliptin group: 61.5% <3.4; 28.0% 3.4-33.9; 10.5% >33.9 Placebo group: 61.6% <3.4; 28.2% 3.4-33.9; 10.3% >33.9
Population subgroups	Within study subgroup analyses reported: Atherosclerosis (established, multiple risk factors) Estimated GFR (>50, 30-50, <30)

	Sex (Male, female) Race (White, Black, Asian, Other) Age (<75 Y, ≥75 Y) Region (North America, Europe, Latin America, Asia) BMI (≥30, <30) Prior heart failure (Y, N) Duration of diabetes (<5 Y, 5 to <10 Y, 10 to >15 Y, 15 to <20 Y, ≥20 Y) Baseline glycated hemoglobin (<7%, 7-<8%, 8-<9%, ≥9%) Baseline insulin (Y, N) Baseline sulfonyl urea, (Y, N) Baseline metformin (Y, N) Baseline thiazolidinedione (Y, N) Baseline microalbumin: creatinine ration (<30, 30-300, >300) Ethnicity (Hispanic, non-Hispanic) Weight (≥80kg, <80kg) Prior hypertension (Y, N) Current smoker (Y, N) Baseline aspirin (Y, N) Baseline statin (Y, N) Baseline ACEi/ARB (Y, N) Baseline CCB (Y, N) Baseline Diuretic (Y, N)
Comparator	Matching placebo
Number of participants	16492

Duration of follow-up	Median 2.1 years (IQR 1.8 to 2.3)
Indirectness	No concerns
Method of analysis	ITT Modified ITT conducted as a sensitivity analysis (including events that occurred within 30 days after last dose of study medication.
Additional comments	Notes for appraisal: 202 participants in Saxagliptin arm and 214 participants in placebo arm non-completers (3%). Of these 15 and 13 lost to FUP respectively. Remaining non-completers withdrew consent. This info is reported only in Consort diagram in supplementary data. Numbers of non-completers not presented by outcomes (so limits assessment of attrition bias).

428.2. Study arms

428.2.1. Saxagliptin (N = 8280)

Saxagliptin at dose of 5mg daily or 2.5mg daily in patients with an estimated GFR<=50ml per minute

428.2.2. Placebo (N = 8212)

Matching placebo

428.3. Characteristics

428.3.1. Arm-level characteristics

Characteristic	Saxagliptin (N = 8280)	Placebo (N = 8212)
% Male Sample size	n = 5512 ; % = 66.6	n = 5525 ; % = 67.3
Mean age (SD) Sample size	n = NA ; % = NA	n = NA ; % = NA
Mean age (SD) Mean (SD)	65.1 (8.5)	65 (8.6)

Characteristic	Saxagliptin (N = 8280)	Placebo (N = 8212)
75 years and older Sample size	n = 1169 ; % = 14.1	n = 1161 ; % = 14.1
75 years and older Mean (SD)	NA (NA)	NA (NA)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA
White race Self-reported Sample size	n = 6241 ; % = 75.4	n = 6166 ; % = 75.1
Hispanic ethnic group Self-reported Sample size	n = 1778 ; % = 21.5	n = 1763 ; % = 21.5
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) Median (IQR)	10.3 (5.2 to 16.7)	10.3 (5.3 to 16.6)
HbA1c (%) Mean (SD)	8 (1.4)	8 (1.4)
Cardiovascular risk factors Sample size	n = NA ; % = NA	n = NA ; % = NA
Established atherosclerotic disease Sample size	n = 6494 ; % = 78.4	n = 6465 ; % = 78.7
Hypertension Sample size	n = 6725 ; % = 81.2	n = 6767 ; % = 82.4
Dyslipidemia Sample size	n = 5895 ; % = 71.2	n = 5844 ; % = 71.2
Prior myocardial infarction Sample size	n = 3147 ; % = 38	n = 3090 ; % = 37.6

Characteristic	Saxagliptin (N = 8280)	Placebo (N = 8212)
Prior heart failure Sample size	n = 1056 ; % = 12.8	n = 1049 ; % = 12.8
Prior coronary revascularisation Sample size	n = 3566 ; % = 43.1	n = 3557 ; % = 43.3
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
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)	87.7 (18.7)	88.1 (19.4)
BMI Mean (SD)	31.1 (5.5)	31.2 (5.7)
Number of people with obesity Reported as BMI 30 and over - not adjusted for ethnicity Sample size	n = 4446 ; % = 53.7	n = 4370 ; % = 53.4
Cholesterol and lipid levels Mean (SD)	NR (NR)	NR (NR)

Characteristic	Saxagliptin (N = 8280)	Placebo (N = 8212)
Albumin creatinine ratio (albumin mg, creatinine mm) n=7916 saxagliptin, n=7844 placebo Sample size	n = NA ; % = NA	n = NA ; % = NA
Albumin creatinine ratio (albumin mg, creatinine mm) n=7916 saxagliptin, n=7844 placebo Median (IQR)	1.8 (0.7 to 7.5)	1.9 (0.7 to 7.9)
below 3.4 Sample size	n = 4867 ; % = 61.5	n = 4829 ; % = 61.6
below 3.4 Median (IQR)	NA (NA to NA)	NA (NA to NA)
3.4 to 33.9 Sample size	n = 2217 ; % = 28	n = 2209 ; % = 28.2
3.4 to 33.9 Median (IQR)	NA (NA to NA)	NA (NA to NA)
>33.9 Sample size	n = 832 ; % = 10.5	n = 806 ; % = 10.3
>33.9 Median (IQR)	NA (NA to NA)	NA (NA to NA)
eGFR mL/min/1.73m2 (ml/min) Sample size	n = NA ; % = NA	n = NA ; % = NA
eGFR mL/min/1.73m2 (ml/min) Mean (SD)	72.5 (22.6)	72.7 (22.6)
<30 ml/min Sample size	n = 172 ; % = 2.1	n = 164 ; % = 2
<30 ml/min Mean (SD)	NA (NA)	NA (NA)
30 to 50 ml/min Sample size	n = 1122 ; % = 13.6	n = 1118 ; % = 13.6

Characteristic	Saxagliptin (N = 8280)	Placebo (N = 8212)
30 to 50 ml/min Mean (SD)	NA (NA)	NA (NA)
> 50 ml/min Sample size	n = 6986 ; % = 84.4	n = 6930 ; % = 84.4
> 50 ml/min Mean (SD)	NA (NA)	NA (NA)
Other antidiabetic medication used Sample size	n = NA ; % = NA	n = NA ; % = NA
Metformin Sample size	n = 5789 ; % = 69.9	n = 5684 ; % = 69.2
Sulfonylureas Sample size	n = 3352 ; % = 40.5	n = 3281 ; % = 40
Thiazolidinediones Sample size	n = 513 ; % = 6.2	n = 465 ; % = 5.7
Insulin Sample size	n = 3448 ; % = 41.6	n = 3384 ; % = 41.2
Other antihyperglycemic medications Sample size	n = 52 ; % = 0.6	n = 50 ; % = 0.6
None Sample size	n = 343 ; % = 4.1	n = 392 ; % = 4.8
Blood pressure-lowering medication used Sample size	n = NA ; % = NA	n = NA ; % = NA
Angiotensin-converting enzyme inhibitor Sample size	n = 4435 ; % = 53.6	n = 4505 ; % = 54.9
Angiotensin receptor blockers Sample size	n = 2332 ; % = 28.2	n = 2263 ; % = 27.6
Statins/lipid-lowering medication used Sample size	n = NA ; % = NA	n = NA ; % = NA
Aspirin	n = 6249 ; % = 75.5	n = 6155 ; % = 75

Characteristic	Saxagliptin (N = 8280)	Placebo (N = 8212)
Sample size		
Statin Sample size	n = 6482 ; % = 78.3	n = 6435 ; % = 78.4
Beta blockers Sample size	n = 5101 ; % = 61.6	n = 5061 ; % = 61.6
Other treatment being received Sample size	n = NA ; % = NA	n = NA ; % = NA

1

2

429. Scott, 2018

Bibliographic Reference	Scott, R.; Morgan, J.; Zimmer, Z.; Lam, R. L. H.; O'Neill, E. A.; Kaufman, K. D.; Engel, S. S.; Raji, A.; A randomized clinical trial of the efficacy and safety of sitagliptin compared with dapagliflozin in patients with type 2 diabetes mellitus and mild renal insufficiency: the CompoSIT-R study; Diab Obes Metab; 2018; vol. 20 (no. 12); 2876-2884

429.1. 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	CompoSIT-R [NCT02532855]
Study type	Randomised controlled trial (RCT)
Study location	185 sites in 24 countries [United States, Argentina, Australia, Brazil, Canada, Colombia, Estonia, Finland, Germany, Hungary, Ireland, Latvia, Lithuania, Mexico, New Zealand, Norway, Peru, Puerto Rico, Romania, Russia, South Africa, South Korea, Spain, United Kingdom]
Study setting	NR
Study dates	October 21, 2015 to October 10, 2017
Sources of funding	Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA.
Inclusion criteria	• Male or female • ≥25 years of age • Type 2 diabetes and mild renal insufficiency (eGFR ≥60 and <90 mL/min/1.73m2, calculated by the Chronic Kidney Disease Epidemiology Collaboration [CKD-epi] serum creatinine • Participants on a stable dose of metformin (≥1500 mg/d) alone or in combination with a sulfonylurea (SU) (at a dose of ≥50% of the

	maximum labelled dose in the country of the investigational site) for ≥8 weeks • HbA1c ≥7.0% and ≤9.5% at screening • Fasting finger-stick glucose >6.1 mmol/L and <14.4 mmol/L at randomization
Exclusion criteria	• Type 1 diabetes • A history of ketoacidosis, active liver disease, significant cardiovascular disease, malignancy or haematological disorders, if they were at high risk for volume depletion, hypotension and/or electrolyte imbalances • Previously treated with any AHAs other than metformin or, if on dual therapy, metformin in combination with an SU, within 12 weeks prior to screening • Serum alanine aminotransferase or aspartate aminotransferase levels >2 times the upper limit of normal (ULN) • Haemoglobin <120 g/L (male) or <110 g/L (female) • Triglycerides >6.8 mmol/L • Thyroid-stimulating hormone outside the central laboratory normal range.
Recruitment / selection of participants	There was a 2-week screening period and a 2-week single-blind placebo run-in. 2770 participants were screened and 641 were randomised.
Intervention(s)	• Sitagliptin 100 mg/d and placebo matching dapagliflozin. • Dapagliflozin and placebo matching sitagliptin. Dapagliflozin was initiated at 5 mg and titrated up to 10 mg at week 4 unless the participant was unable to tolerate up-titration to 10 mg.
Cointervention	All participants remained on their stable regimen of background anti-hyperglycaemic agent (i.e. stable dose(s) of metformin ≥ 1500 mg/day ± SU agent
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear Patients were excluded from the study if they had a history of significant cardiovascular disease. No further details given. No information in baseline characteristics.
Strata 2: People with atherosclerotic cardiovascular disease	Not stated/unclear Patients were excluded from the study if they had a history of significant cardiovascular disease. No further details given. No information in baseline characteristics.
Strata 3: People with type 2 diabetes mellitus and	Not stated/unclear CKD not an inclusion/exclusion criteria. Study population described as "people with type 2 diabetes and mild renal insufficiency

chronic kidney disease	(eGFR≥60and<90mL/min/1.73m2,calculatedby the Chronic Kidney Disease Epidemiology Collaboration[CKD-epi] serum creatinine equation." 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	eGFR ≥30mL/min/1.73m2
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Population subgroups	NA
Comparator	NA
Number of participants	614 participants were randomised: 307 to sitagliptin and 307 to dapagliflozin. 595 (96.9%) of participants completed the study and 494 (80.5%) completed study medication.

Duration of follow-up	24 weeks
Indirectness	Directly applicable
Method of analysis	Other Full analysis set - all randomised participants who received at least one dose of study treatment and a baseline or a postbaseline measurement. A longitudinal data analysis (LDA) model was used to evaluate the continuous endpoints with fixed effect for treatment, time, background AHA, the interaction of time by background AHA, and the interaction of time by treatment, with a constraint that the true mean at baseline is common to all treatment groups. Missing data were handled implicitly by the LDA model.
Additional comments	Discontinuation criteria included eGFR persistently <50 mL/min/1.73m2 from visit 3/day 1 prior to visit 5/week 10 or persistently <60 mL/min/1.73m2 from visit 5/week 10 through visit 7/week 24. Other discontinuation criteria were related to hyperglycaemia, hypoglycaemia, and liver function.

429.2. Study arms

429.2.1. Sitagliptin (N = 307)

429.2.2. Dapagliflozin (N = 307)

429.3. Characteristics

429.3.1. Arm-level characteristics

Characteristic	Sitagliptin (N = 307)	Dapagliflozin (N = 307)
Mean age (SD) Mean (SD)	67.7 (8.5)	66.6 (8.6)
Ethnicity Sample size	n = NR ; % = NR	n = NR ; % = NR
White Sample size	n = 240 ; % = 78.2	n = 234 ; % = 76.5

Characteristic	Sitagliptin (N = 307)	Dapagliflozin (N = 307)
Multiple Sample size	n = 30 ; % = 9.8	n = 39 ; % = 12.7
American Indian/ Alaska Native Sample size	n = 18 ; % = 5.9	n = 14 ; % = 4.6
Asian Sample size	n = 11 ; % = 3.6	n = 7 ; % = 2.3
Black or African American Sample size	n = 8 ; % = 2.6	n = 11 ; % = 3.6
Native Hawaiian or other Pacific Islander Sample size	n = 0 ; % = 0	n = 1 ; % = 0.3
Neither Hispanic nor Latino Sample size	n = 195 ; % = 63.5	n = 194 ; % = 63.4
Hispanic or Latino Sample size	n = 109 ; % = 35.5	n = 109 ; % = 35.6
Not reported Sample size	n = 3 ; % = 1	n = 2 ; % = 0.7
Unknown Sample size	n = 0 ; % = 0	n = 1 ; % = 0.3
Comorbidities Nominal	NR	NR
Presence of frailty Nominal	NR	NR
Time since type 2 diabetes diagnosed Mean (SD)	10.5 (7)	10.7 (7.4)
Cardiovascular risk factors Nominal	NR	NR
Smoking status Nominal	NR	NR
Alcohol consumption	NR	NR

Characteristic	Sitagliptin (N = 307)	Dapagliflozin (N = 307)
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
Weight (kg) Mean (SD)	87.4 (20.2)	88.7 (18)
BMI (kg/m2) Mean (SD)	31.8 (5.7)	31.5 (5.3)
Number of people with obesity Nominal	NR	NR
Other antidiabetic medication used Sample size	n = NA ; % = NA	n = NA ; % = NA
Metformin alone Sample size	n = 212 ; % = 69.1	n = 225 ; % = 73.5
metformin + SU Sample size	n = 95 ; % = 30.9	n = 81 ; % = 26.5
Blood pressure-lowering medication used Nominal	NR	NR
Statins/lipid-lowering medication used Nominal	NR	NR
Other treatment being received Nominal	NR	NR
% Female Sample size	n = 138 ; % = 45	n = 120 ; % = 39.2

1

2

430. Seck, 2010

Bibliographic Reference	Seck, T.; Nauck, M.; Sheng, D.; Sunga, S.; Davies, M. J.; Stein, P. P.; Kaufman, K. D.; Amatruda, J. M.; Safety and efficacy of treatment with sitagliptin or glipizide in patients with type 2 diabetes inadequately controlled on metformin: a 2-year study; Int J Clin Pract; 2010; vol. 64 (no. 5); 562-76

430.1. Study details

Secondary publication of another included study- see primary study for details	Nauck, M. A.; Meininger, G.; Sheng, D.; Terranella, L.; Stein, P. P.; Efficacy and safety of the dipeptidyl peptidase-4 inhibitor, sitagliptin, compared with the sulfonylurea, glipizide, in patients with type 2 diabetes inadequately controlled on metformin alone: a randomized, double-blind, non-inferiority trial; Diabetes Obes Metab; 2007; vol. 9 (no. 2); 194-205
Trial name / registration number	Sitagliptin Protocol 024 [NCT00094770]
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear As per Nauck 2007B
Strata 2: People with atherosclerotic cardiovascular disease	Not stated/unclear As per Nauck 2007B
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear As per Nauck 2007B
Strata 4: People with type 2 diabetes mellitus and high	Not stated/unclear

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

1

2

431. Secnik Boye, 2006

Bibliographic Reference	Secnik Boye, Kristina; Matza, Louis S; Oglesby, Alan; Malley, Karen; Kim, Sunny; Hayes, Risa P; Brodows, Robert; Patient-reported outcomes in a trial of exenatide and insulin glargine for the treatment of type 2 diabetes.; Health and quality of life outcomes; 2006; vol. 4; 80

431.1. Study details

Secondary publication of another included study- see primary study for details	Heine 2005
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear Based on Heine 2005
Strata 2: People with atherosclerotic cardiovascular disease	Not stated/unclear Based on Heine 2005
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear Based on Heine 2005

432. Seino, 2021

Bibliographic Reference	Seino, Y.; Kaku, K.; Kadowaki, T.; Okamoto, T.; Sato, A.; Shirakawa, M.; O'Neill, E. A.; Engel, S. S.; Kaufman, K. D.; A randomized, placebo-controlled trial to assess the efficacy and safety of sitagliptin in Japanese patients with type 2 diabetes and inadequate glycaemic control on ipragliflozin; Diabetes, Obesity & Metabolism; 2021; vol. 23 (no. 6); 1342-1350

432.1. 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	NCT02577016
Study type	Randomised controlled trial (RCT)
Study location	Japan
Study setting	27 trial centres
Study dates	November 2015 and November 2016,
Sources of funding	MSD K.K., a subsidiary of Merck & Co
Inclusion criteria	• Aged ≥20 years with T2D • On a stable dose of an SGLT2 inhibitor for ≥4 weeks and during the 8 weeks prior to screening, either not on another OHA with HbA1c ≥7.0% and ≤10.0%, or on any additional single or low-dose dual combination oral OHA therapy with HbA1c ≥6.5% and ≤9.0% (Group A) OR on a stable dose (≥10 weeks) of ipragliflozin 50 mg once daily and not on any additional OHAs during the 8 weeks prior to screening with HbA1c ≥7.0% and ≤10.0% (Group B)

	• 2 weeks prior to randomization: on diet and exercise therapy ≥6 weeks; OHAs except ipragliflozin discontinued for ≥8 weeks; on a stable dose of ipragliflozin 50 mg once daily ≥10 weeks; HbA1c ≥7.0% and ≤10.0%; and FPG ≤230 mg/dL
Exclusion criteria	• Type 1 diabetes or a history of ketoacidosis, unstable diabetic retinopathy, poorly controlled hypertension, significant cardiovascular disease, active liver disease, renal disease or urological disorders, a history of malignancy or haematological disorders • If they had been treated with insulin or thiazolidinediones within 12 weeks prior to screening or with sitagliptin within 8 weeks prior to screening. • Serum alanine aminotransferase or aspartate aminotransferase levels >2 times the upper limit of normal, C-peptide, <0.6 ng/mL, estimated glomerular filtration rate <60 mL/min/1.73 haemoglobin <11 g/dL (male) or <10 g/dL (female), or thyroid stimulating hormone outside the central laboratory normal range.
Recruitment / selection of participants	There was a screening of up to 2 weeks, a medication stabilization period of 8 weeks for patients requiring initiation/stabilization of ipragliflozin 50 mg once daily and/or discontinuation of other OHAs (Group A); a 2-week placebo run-in period for all patients (Group A and B); and a 24-week treatment period.
Intervention(s)	Sitagliptin 50 mg once daily
Cointervention	Ipragliflozin 50 mg once daily
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear Heart failure not an inclusion/exclusion criteria. Exclusion criteria state "Patients were excluded from the study if they had significant cardiovascular disease", no further description. No information in baseline characteristics.
Strata 2: People with atherosclerotic cardiovascular disease	Not stated/unclear CVD not an inclusion/exclusion criteria. Exclusion criteria state "Patients were excluded from the study if they had significant cardiovascular disease", no further description. No information in baseline characteristics.
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear CKD not an inclusion/exclusion criteria. Patients were excluded from the study if they had renal disease. No further definition 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	Not stated/unclear
Subgroup 5: eGFR category at baseline	eGFR ≥30mL/min/1.73m2 People with eGFR < 60 mL/min/1.73 m2 were excluded
Population subgroups	NA
Comparator	Placebo
Number of participants	173 people were screened and 141 were randomised. Of 70 participants allocated to sitagliptin, 2 discontinued and 68 completed study medication. Of 71 participants allocated to placebo, 2 discontinued and 69 completed study medication.
Duration of follow-up	24 weeks
Indirectness	Directly applicable
Method of analysis	ITT Safety analyses - not explicitly stated, but defined as all randomised participants who received ≥1 dose of study medication

	Modified ITT Efficacy analyses - not explicitly defined, but described as all randomized participants who received at least on dose of study medication and who had ≥1 measurement (baseline or post-baseline) of the specific endpoint and had a baseline measurement if required.
Additional comments	NA

432.2. Study arms

432.2.1. Sitagliptin (N = 70)

432.2.2. Placebo (N = 71)

432.3. Characteristics

432.3.1. Arm-level characteristics

Characteristic	Sitagliptin (N = 70)	Placebo (N = 71)
% Male Sample size	n = 54 ; % = 77.1	n = 45 ; % = 63.4
Mean age (SD) Mean (SD)	57 (11.6)	54 (9.5)
Ethnicity Nominal	NR	NR
Comorbidities Nominal	NR	NR
Presence of frailty Nominal	NR	NR
Time since type 2 diabetes diagnosed (years) Mean (SD)	10 (5.4)	8.3 (4.5)
Cardiovascular risk factors Nominal	NR	NR

Characteristic	Sitagliptin (N = 70)	Placebo (N = 71)
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
BMI (kg/m2) Mean (SD)	26.8 (4.4)	27.1 (4.6)
Number of people with obesity Nominal	NR	NR
Other antidiabetic medication used Prior use of other OHAs Sample size	n = 24 ; % = 34.3	n = 25 ; % = 35.2
Blood pressure-lowering medication used Nominal	NR	NR
Statins/lipid-lowering medication used Nominal	NR	NR
Other treatment being received Nominal	NR	NR

1

2

433. Seino, 2016

Bibliographic Reference	Seino, Y.; Kaneko, S.; Fukuda, S.; Osonoi, T.; Shiraiwa, T.; Nishijima, K.; Bosch-Traberg, H.; Kaku, K.; Combination therapy with liraglutide and insulin in Japanese patients with type 2 diabetes: A 36-week, randomized, double-blind, parallel-group trial; J Diabetes Invest; 2016; vol. 7 (no. 4); 565-73

433.1. 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	NCT01572740
Study type	Randomised controlled trial (RCT)
Study location	23 sites in Japan
Study setting	NR
Study dates	April 2012 to March 2013
Sources of funding	Novo Nordisk
Inclusion criteria	• Aged ≥20 years • Type 2 diabetes for ≥6 months • HbA1c 7.5–11.0% and BMI <45.0 kg/m2 • Received stable insulin therapy in addition to diet and exercise ≥12 weeks before screening (Insulin therapy was defined as basal insulin, premixed insulin or basal-bolus regimen. The insulin dose was required to be stable (daily fluctuation ±20%) for ≥12 weeks before screening and current dose ≥10(I) U/day

Exclusion criteria	• An anticipated change in concomitant medication known to interfere significantly with glucose metabolism • Known proliferative retinopathy or maculopathy requiring treatment, or use of a GLP-1 receptor agonist or any oral antidiabetic drugs (OADs) within 12 weeks prior to screening • Recurrent severe hypoglycaemia (>1 severe hypoglycaemic episode during last 12 months), hypoglycaemic unawareness as judged by the investigator, or hospitalization for diabetic ketoacidosis during the previous 6 months
Recruitment / selection of participants	NR
Intervention(s)	Liraglutide self-injected once daily at approximately the same time each day. The starting dose was 0.3 mg/day, then 0.6 mg/day after 1 week and 0.9 mg/day after a further week.
Cointervention	Participants continued pretrial insulin therapy. Until 16 weeks insulin dosage could not be changed, except due to unacceptable hypoglycaemia or adverse events. During the subsequent 20 weeks, insulin titration was allowed based on self-measured plasma glucose.
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
Population subgroups	NA
Comparator	Placebo
Number of participants	296 people were screened and 257 were randomised. Of 127 participants allocated to liraglutide, 6 withdrew, 121 completed, and 127 were included in the analysis sets. Of 130 participants allocated to placebo, 5 participants withdrew, 125 completed, and 130 were analysed in the analysis sets.
Duration of follow-up	36 weeks
Indirectness	Directly applicable
Method of analysis	ITT The full analysis set included randomised patients receiving at least one dose of the trial product. A last observation carried forward approach was used for participants with at least one valid post-baseline measurement. Data were analysed by ANCOVA. Other The report describes that the safety analysis included participants receiving at least one dose and participants contributed 'as treated'. This is unclear, as the same number of participants were in the 'as randomised' and 'as treated' sets, and there is no mention of protocol deviation in the report.

Additional comments	NA

433.2. Study arms

433.2.1. Liraglutide (N = 127)

433.2.2. Placebo (N = 130)

433.3. Characteristics

433.3.1. Arm-level characteristics

Characteristic	Liraglutide (N = 127)	Placebo (N = 130)
% Male Sample size	n = 69 ; % = 54.3	n = 75 ; % = 57.7
Mean age (SD) Mean (SD)	61.3 (11)	59.8 (11.3)
Ethnicity Nominal	NR	NR
Comorbidities Nominal	NR	NR
Presence of frailty Nominal	NR	NR
Time since type 2 diabetes diagnosed (years) Mean (SD)	14.32 (8.89)	14.69 (8.6)
Cardiovascular risk factors Nominal	NR	NR
Smoking status Nominal	NR	NR
Alcohol consumption	NR	NR

Characteristic	Liraglutide (N = 127)	Placebo (N = 130)
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
BMI (kg/m2) Mean (SD)	26.2 (4.9)	25.2 (4)
Number of people with obesity Nominal	NR	NR
Other antidiabetic medication used Sample size	n = NR ; % = NR	n = NR ; % = NR
Basal insulin Sample size	n = 50 ; % = 39.4	n = 50 ; % = 38.5
Basal-bolus insulin Sample size	n = 27 ; % = 21.3	n = 28 ; % = 21.5
Premix insulin Sample size	n = 50 ; % = 39.4	n = 52 ; % = 40
Blood pressure-lowering medication used Nominal	NR	NR
Statins/lipid-lowering medication used Nominal	NR	NR
Other treatment being received Nominal	NR	NR

1

2

434. Seino, 2012

Bibliographic Reference	Seino, Y.; Min, K. W.; Niemoeller, E.; Takami, A.; Randomized, double-blind, placebo-controlled trial of the once-daily GLP-1 receptor agonist lixisenatide in Asian patients with type 2 diabetes insufficiently controlled on basal insulin with or without a sulfonylurea (GetGoal-L-Asia); Diabetes Obes Metab; 2012; vol. 14 (no. 10); 910-7

434.1. 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-L Asia
Study type	Randomised controlled trial (RCT)
Study location	57 centres in four countries in Asia (Japan, Republic of Korea, Taiwan and the Philippines)
Study setting	NR
Study dates	NR
Sources of funding	Sanofi
Inclusion criteria	• Male and female patients aged 25–81 years with type 2 diabetes (≥1 year duration) • Currently on stable basal insulin therapy with or without a sulfonylurea • HbA1c between 7 and 10%, inclusive • Received treatment with a stable basal insulin regimen for at (least 3 months, including a stable ±20%) dose of at least 10 U/day for at least 2 months prior to the screening visit, with or without

	sulfonylurea at a stable dose for at least 3months prior to the screening visit
Exclusion criteria	• Use of oral or injectable glucose-lowering agents other than sulfonylurea or basal insulin within 3months prior to the time of screening • Fasting plasma glucose (FPG) at screening >250 mg/dl (13.9 mmol/l) • In a placebo-controlled study • Patients in a severely uncontrolled glycaemic situation • 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 • History within the previous 6 months of myocardial infarction, stroke or heart failure requiring hospitalization or drug or alcohol abuse • Uncontrolled/inadequately controlled hypertension at the time of screening • Resting systolic blood pressure greater than 180mmHg or diastolic blood pressure greater than 95 mmHg • Amylase and/or lipase greater than three times or aspartate aminotransferase (AST), alanine aminotransferase (ALT) or alkaline phosphatase (ALP) greater than two times the upper limit of the normal laboratory range • End-stage renal disease and/or dialysis and clinically relevant history of gastrointestinal disease, with prolonged nausea and vomiting during the previous 6 months
Recruitment / selection of participants	There was a 2-week screening phase and a 1-week placebo run-in period
Intervention(s)	Lixisenatide (10 ug for 1 week, 15 ug for 1, then 20 ug) administered subcutaneously once daily within 1 hour before breakfast
Cointervention	All patients continued treatment throughout the study with their established doses of basal insulin with or without sulfonylureas. Doses of insulin/sulfonylurea were adjusted depending on HbA1c at screening.
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear Exclusion criteria state: "history within the previous 6 months of myocardial infarction, stroke or heart failure requiring hospitalization." No information in baseline characteristics.
Strata 2: People with atherosclerotic cardiovascular disease	Not stated/unclear Exclusion criteria state: "history within the previous 6 months of myocardial infarction, stroke or heart failure requiring hospitalization." No information in baseline characteristics.

Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear CKD 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	Placebo administered subcutaneously once daily within 1 hour before breakfast

Number of participants	311 participants were randomised (154 to lixisenatide and 157 to placebo). 34 participants (10.9% discontinued prematurely from study treatment [21 (13.6%) lixisenatide, 13 (8.3%) placebo, mainly because of adverse events.
Duration of follow-up	24 weeks
Indirectness	Directly applicable
Method of analysis	Modified ITT Defined as all participants who received at least one dose of double-blind study drug, and had both a baseline assessment and at least one post-baseline assessment of any primary or secondary efficacy variable. Analyses used LOCF and were performed using ANCOVA. Other The safety population included all randomised participants exposed to at lease one dose of study drug. The on-treatment period was defined as the time from the first dose of double-blind study drug up to 3 days after the last dose.
Additional comments	NA

434.2. Study arms

434.2.1. Lixisenatide (N = 154)

434.2.2. Placebo (N = 157)

434.3. Characteristics

434.3.1. Study-level characteristics

Characteristic	**Study (N = 311)**
Insulin use Sample size	n = NA ; % = NA
Glargine Sample size	n = 187 ; % = 60

Characteristic	Study (N = 311)
Detemir Sample size	n = 83 ; % = 27
NPH Sample size	n = 39 ; % = 13
Premix Sample size	n = 2 ; % = 0.6

434.3.2. Arm-level characteristics

Characteristic	Lixisenatide (N = 154)	Placebo (N = 157)
% Male Sample size	n = 69 ; % = 44.8	n = 80 ; % = 51
Mean age (SD) (years) Mean (SD)	58.7 (10.2)	58 (10.1)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA
Asian/Oriental Sample size	n = 154 ; % = 100	n = 157 ; % = 100
Japan Sample size	n = 72 ; % = 46.8	n = 87 ; % = 55.4
Republic of Korea Sample size	n = 67 ; % = 43.5	n = 56 ; % = 35.7
Philippines Sample size	n = 13 ; % = 8.4	n = 5 ; % = 3.2
Taiwan Sample size	n = 2 ; % = 1.3	n = 9 ; % = 5.7
Comorbidities Nominal	NR	NR
Presence of frailty Nominal	NR	NR

Characteristic	Lixisenatide (N = 154)	Placebo (N = 157)
Time since type 2 diabetes diagnosed Mean (SD)	13.7 (7.7)	14.1 (7.7)
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
BMI (kg/m2) Mean (SD)	25.4 (3.7)	25.2 (3.9)
Number of people with obesity Nominal	NR	NR
Other antidiabetic medication used Sample size	n = 108 ; % = 70.1	n = 111 ; % = 70.7
Blood pressure-lowering medication used Nominal	NR	NR
Statins/lipid-lowering medication used Nominal	NR	NR
Other treatment being received Nominal	NR	NR

1

2

435. Seino, 2011

Bibliographic Reference	Seino, Y.; Rasmussen, M. F.; Nishida, T.; Kaku, K.; Glucagon-like peptide-1 analog liraglutide in combination with sulfonylurea safely improves blood glucose measures vs sulfonylurea monotherapy in japanese patients with type 2 diabetes: Results of a 52-week, randomized, multicenter trial; J Diabetes Invest; 2011; vol. 2 (no. 4); 280-286

435.1. Study details

Secondary publication of another included study- see primary study for details	Secondary publication reporting 52-week data for Kaku 2010
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear People with serious heart disease were excluded. No definition given. No information in baseline characteristics.
Strata 2: People with atherosclerotic cardiovascular disease	Not stated/unclear People with serious heart disease were excluded. No definition given. No information in baseline characteristics.
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear CKD not an inclusion/exclusion criteria. People with impaired renal function were excluded. No further information. No information in baseline characteristics.

436. Sesti, 2020

Bibliographic Reference	Sesti, G.; Bardtrum, L.; Dagdelen, S.; Halladin, N.; Haluzik, M.; Orsy, P.; Rodriguez, M.; Aroda, V.R.; 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; 2020

436.1. Study details

Secondary publication of another included study- see primary study for details	Aroda, V. R., Gonzalez-Galvez, G., Gron, R. et al. (2019) 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 7(8): 596-605
Other publications associated with this study included in review	No additional information.
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear Transferred from parent study (Aroda 2019A)
Strata 2: People with atherosclerotic cardiovascular disease	Not stated/unclear Transferred from parent study (Aroda 2019A)
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear Transferred from parent study (Aroda 2019A)