National Institute for Health and Care Excellence

Final

Type 2 diabetes in adults: management (medicines update)

[F2.3] Evidence reviews for subsequent pharmacological management of type 2 diabetes – Appendix D2

NICE guideline

Evidence reviews underpinning recommendations 1.9.1 to 1.9.5, 1.10.1 to 1.18.4, 1.19.1 to 1.19.3, 1.22.1 to 1.31.2 and recommendations for research in the NICE guideline

February 2026

Final

This evidence review was developed by NICE

FINAL

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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.

1. Cefalu, 2015

Bibliographic Reference	Cefalu, W. T.; Leiter, L. A.; de Bruin, T. W.; Gause-Nilsson, I.; Sugg, J.; Parikh, S. J.; Dapagliflozin's effects on glycemia and cardiovascular risk factors in high-risk patients with type 2 diabetes: A 24-week, multicenter, randomized, double-blind, placebo-controlled study with a 28-week extension; Diabetes Care; 2015; vol. 38 (no. 7); 1218-1227

1.1. 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	NCT01031680
Study type	Randomised controlled trial (RCT)
Study location	Multicentre trial.
Study setting	Outpatient follow-up.
Study dates	No additional information.
Sources of funding	Supported by Bristol-Myers Squibb and AstraZeneca. An author was supported in part by a grant from the National Institute of General Medical Sciences of the National Institutes of Health (1-U54-GM-104940).
Inclusion criteria	Men aged at least 45 years or women aged at least 50 years (not of childbearing potential) with type 2 diabetes, cardiovascular disease (states cerebrovascular disease, but presumed a typo due to later explanation about cardiovascular disease. Cardiovascular disease defined as prior documented coronary heart disease including history of myocardial infarction, history of revascularisation or coronary artery stenosis >50% confirmed with angiography of stress test imaging or prior documented stroke or TIA or prior documented peripheral artery disease treated with revascularisation - amputation was not accepted) and hypertension (physician diagnosis, treatment with two or more antihypertensives with

	one of the agents started for lowering blood pressure, or treatment with one antihypertensive and a previous blood pressure reading exceeding 130/80 mmHg); receiving monotherapy or dual combination therapy with oral antidiabetic drugs, insulin therapy in combination with oral antidiabetic drugs or insulin monotherapy on a daily basis for 8 weeks; were stable for at least 4 weeks before enrolment; showed inadequate glycaemic control (7.2-10.5% HbA1c); people receiving antihypertensive treatment should have used this uninterruptedly on a daily basis in the 4 weeks before enrolment.
Exclusion criteria	Diagnosis of type 1 diabetes; using more than three oral antidiabetic medications; fasting plasma glucose >15mmol/L at randomisation; diabetic ketoacidosis; recent cardiovascular event (acute coronary syndrome, hospitalisation for unstable angina or acute myocardial infarction, acute stroke or TIA, coronary artery revascularisation) within 2 months prior to enrolment; systolic BP at least 165mmH, diastolic BP at least 100mmHg; congestive heart failure defined as NYHA class IV; unstable or acute CHF; creatinine clearance <60mL/min; severe hepatic insufficiency and/or significant abnormal liver function (AST >3x upper limit of normal (ULN) or ALT >3x ULN) or creatine kinase >3x ULN.
Recruitment / selection of participants	No additional information.
Intervention(s)	Dapagliflozin N=455 Dapagliflozin 10mg once daily.
Cointervention	Concomitant therapy: Pre-existing stable background treatment, excluding rosiglitazone.
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear Excluded "congestive heart failure (CHF) defined as New York Heart Association class IV, unstable or acute CHF", otherwise unclear. No information in baseline characteristics
Strata 2: People with atherosclerotic cardiovascular disease	People with atherosclerotic cardiovascular diseases Inclusion criteria "documented pre-existing cardiovascular disease (CVD), and a history of hypertension. Cardiovascular (CV) disease was defined as 1) prior documented coronary heart disease, including history of myocardial infarction or history of revascularization, or coronary artery stenosis >50%, confirmed with angiography or abnormal imaging at stress test, compatible with ischemia or prior myocardial infarction, or 2) prior documented stroke or transient ischemic attack, or 3) prior documented peripheral artery disease treated with revascularization (amputation was not accepted)."
Strata 3: People with type 2 diabetes mellitus and	Not stated/unclear Not an inclusion/exclusion criteria. No information in baseline characteristics

chronic kidney disease	
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	Not stated/unclear
Subgroup 1: People with moderate or severe frailty	Not stated/unclear
Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear
Subgroup 3: People with non-alcoholic fatty liver disease	Not stated/unclear
Subgroup 4: People with obesity	Not stated/unclear
Subgroup 5: eGFR category at baseline	Not stated/unclear
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Population subgroups	No additional information.
Comparator	Placebo N=459 Matching placebo.
Number of participants	922
Duration of follow-up	24 weeks double blind trial, 28 week extension period.

Indirectness	No additional information.
Method of analysis	ACA Full analysis set, last observation carried forward - all people who received at least one dose of the study medication with a non-missing baseline value and at least one postbaseline value for at least one efficacy variable at week 24. Per protocol Also observed
Additional comments	No additional information.

1.2. Study arms

1.2.1. Dapagliflozin (N = 455)

Dapagliflozin 10mg once daily. Concomitant therapy: Pre-existing stable background treatment, excluding rosiglitazone.

1.2.2. Placebo (N = 459)

Matching placebo. Concomitant therapy: Pre-existing stable background treatment, excluding rosiglitazone.

1.3. Characteristics

1.3.1. Arm-level characteristics

Characteristic	Dapagliflozin (N = 455)	Placebo (N = 459)
% Male Sample size	n = 309 ; % = 68	n = 315 ; % = 69
Mean age (SD) (years) Mean (SD)	62.8 (7)	63 (7.7)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA
White	n = 391 ; % = 85.2	n = 376 ; % = 82.6

Characteristic	Dapagliflozin (N = 455)	Placebo (N = 459)
Sample size		
Black/African American Sample size	n = 27 ; % = 5.9	n = 26 ; % = 5.7
Asian Sample size	n = 38 ; % = 8.3	n = 49 ; % = 10.8
Other Sample size	n = 3 ; % = 0.7	n = 4 ; % = 0.9
Comorbidities Sample size	n = NA ; % = NA	n = NA ; % = NA
Coronary heart disease Sample size	n = 349 ; % = 76	n = 338 ; % = 74.3
Stroke or TIA Sample size	n = 89 ; % = 19.4	n = 100 ; % = 22
Peripheral artery disease Sample size	n = 18 ; % = 3.9	n = 15 ; % = 3.3
Presence of frailty Sample size	n = NR ; % = NR	n = NR ; % = NR
Time since type 2 diabetes diagnosed (years) Mean (SD)	12.3 (8.2)	12.6 (8.7)
Smoking status Sample size	n = NR ; % = NR	n = NR ; % = NR
Alcohol consumption Sample size	n = NR ; % = NR	n = NR ; % = NR
Presence of severe mental illness Sample size	n = NR ; % = NR	n = NR ; % = NR
People with significant cognitive impairment Sample size	n = NR ; % = NR	n = NR ; % = NR
People with a learning disability	n = NR ; % = NR	n = NR ; % = NR

Characteristic	Dapagliflozin (N = 455)	Placebo (N = 459)
Sample size		
Number of people with obesity Sample size	n = NR ; % = NR	n = NR ; % = NR
Other antidiabetic medication used Sample size	n = NA ; % = NA	n = NA ; % = NA
Oral antidiabetic drug Sample size	n = 221 ; % = 48.6	n = 217 ; % = 47.3
Oral antidiabetic drug and insulin Sample size	n = 158 ; % = 34.7	n = 165 ; % = 35.9
Insulin only Sample size	n = 76 ; % = 16.7	n = 77 ; % = 16.8
1 oral antidiabetic drug Sample size	n = 192 ; % = 42.2	n = 185 ; % = 40.3
2 oral antidiabetic drugs Sample size	n = 183 ; % = 40.2	n = 195 ; % = 42.5
>2 oral antidiabetic drugs Sample size	n = 4 ; % = 0.9	n = 2 ; % = 0.4
Blood pressure-lowering medication used Sample size	n = 455 ; % = 98.9	n = 454 ; % = 98.3
ACEIs/ARBs Sample size	n = 408 ; % = 88.7	n = 409 ; % = 88.5
Diuretics Sample size	n = 212 ; % = 46.1	n = 241 ; % = 52.24
Loop diuretics Sample size	n = 81 ; % = 17.6	n = 100 ; % = 21.6
Statins/lipid-lowering medication used Sample size	n = 387 ; % = 84.1	n = 409 ; % = 88.5
Other treatment being received Sample size	n = NA ; % = NA	n = NA ; % = NA

Characteristic	Dapagliflozin (N = 455)	Placebo (N = 459)
Acetylsalicylic acid Sample size	n = 329 ; % = 71.5	n = 409 ; % = 88.5

2. Cefalu, 2013

Bibliographic Reference	Cefalu, W. T.; Leiter, L. A.; Yoon, K. H.; Arias, P.; Niskanen, L.; Xie, J.; Balis, D. A.; Canovatchel, W.; Meininger, G.; Efficacy and safety of canagliflozin versus glimepiride in patients with type 2 diabetes inadequately controlled with metformin (CANTATA-SU): 52 week results from a randomised, double-blind, phase 3 non-inferiority trial; Lancet; 2013; vol. 382 (no. 9896); 941-50

2.1. Study details

Secondary publication of another included study- see primary study for details	No
Other publications associated with this study included in review	2-year results reported in: • Leiter, L. A., Yoon, K. H., Arias, P., Langslet, G., Xie, J., Balis, D. A., ... & Meininger, G. (2015). Canagliflozin provides durable glycemic improvements and body weight reduction over 104 weeks versus glimepiride in patients with type 2 diabetes on metformin: a randomized, double-blind, phase 3 study. *Diabetes care*, *38*(3), 355-364.
Trial name / registration number	(CANagliflozin Treatment And Trial Analysis versus SUlphonylurea) CANTATA-SU/NCT00968812
Study type	Randomised controlled trial (RCT) Double-blind parallel-group RCT
Study location	International (157 centres in 19 countries: Argentina, Bulgaria, Canada, Costa Rica, Denmark, Finland, Germany, India, Israel, Republic of Korea, Mexico, Norway, Philippines, Poland, Puerto Rico, Romania, Russian Federation, Slovakia, Ukraine, USA)
Study setting	Outpatient (Diabetes centres)
Study dates	08/2008 to 12/2011
Sources of funding	Funded by Janssen Research and Development, LLC
Inclusion criteria	• Aged 18–80 years • Diagnosis of type 2 diabetes • HbA1c level 7·0–9·5% inclusive

	• Receiving stable metformin therapy (≥2000 mg per day or ≥1500 mg per day if unable to tolerate a higher dose) for at least 10 weeks • If receiving metformin in combination with one other oral non-thiazolidinedione antihyperglycaemic drug at screening then discontinued the second antihyperglycaemic drug and, if needed, had metformin dose increased; If receiving metformin at doses lower than specified in protocol had metformin dose increased before entering metformin dose-stable run-in period (up to 2 weeks) before the 2 week placebo run-in period
Exclusion criteria	• History of ≥1 severe hypoglycaemic episode (within 6 months) • Repeated measurements of fasting plasma glucose or fasting self-monitored blood glucose, or both, of 15·0 mmol/L or more during the pretreatment phase • eGFR<55 mL/min/1.73 m2 (or <60 mL/min/1.73 m2 if based on restriction of metformin use in local label) or serum creatinine concentrations of 124 µmol/L or more for men and 115 µmol/L or more for women • Given thiazolidinedione within 16 weeks before screening
Recruitment / selection of participants	Participants recruited from 157 centres in 19 countries. Eligible participants entered 2-week single-blind placebo run-in period (single-blind matching daily placebo capsules), followed by 52 weeks double-blind treatment period (reported in article), followed by 52-week double-blind extension period (data not reported in article). Block randomisation (using permuted blocks of 3) in 1:1:1 ratio to 1 of 3 arms using computer-generated randomisation schedule and assigned by interactive voice or web response system, with stratification by metformin status (stable; adjusted), whether had metformin combination therapy (yes and discontinued; no), and country. HbA1c and FPG masked to study centre staff unless glycaemic rescue criteria met. Participants, investigators and sponsor masked to treatment assignment until final database lock. Study drugs supplied in 5 levels to allow masked increases/decreases of glimepiride during treatment period.
Intervention(s)	• Canagliflozin 100 mg daily • Canagliflozin 300 mg daily Oral canagliflozin 100 or 300 mg daily for 52 weeks, in addition to concurrent metformin therapy. Participants in these groups were mock up-titrated to match procedure for those in glimepiride group.
Cointervention	• Metformin Metformin ≥2000 mg daily or ≥1500 mg daily if unable to tolerate higher dose. Participants receiving an additional oral non-thiazolidinedione anti-hyperglycaemic drug at screening discontinued this and, if needed, had metformin dose increased. Participants receiving lower metformin dose (<2000 mg daily or <1500 mg if not able to tolerate) at screening had dose increased before entering 12-week metformin dose-stable run-in period before the 2-week single-blind placebo run-in period.

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 "an estimated glomerular filtration rate (GFR) of less than 55 mL/min/1·73 m² (or <60 mL/min/1·73 m² if based on restriction of metformin use in local label)", 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	eGFR ≥30mL/min/1.73m2 Exclusion criteria: eGFR<55 mL/min/1.73 m2 (or <60 mL/min/1.73 m2 if based on restriction of metformin use in local label)
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Comparator	• Glimepiride 6 or 8 mg daily Oral glimepiride up-titrated to 6 or 8 mg daily for 52 weeks, in addition to concurrent stable metformin dose. Starting dose of 1 mg daily to maximum of 6 mg or 8 mg (on basis of maximum approved dose in country of investigation site) after 2 or more weeks at current dose if participants met glycaemic criteria (i.e. ≥50% of fasting self-monitored blood glucose readings >6.0 mmol/L, with no hypoglycaemic events during the 2 weeks preceding clinic visit or telephone contact).
Number of participants	N=1452
Duration of follow-up	52 weeks
Indirectness	None
Method of analysis	Modified ITT mITT LOCF analysis (all randomised participants receiving at lease one dose study drug) for efficacy; safety analysis conducted on all randomised participants according to predominant treatment received (same as mITT population since no participants received treatment other than that to which they were randomly assigned).

2.2. Study arms

2.2.1. Glimepiride 6/8 mg daily (N = 484)

Oral glimepiride up-titrated to 6 or 8 mg daily for 24 months (12 months followed by 12 month extension period) in addition to stable metformin dose.

2.2.2. Canagliflozin 100 mg daily (N = 483)

Oral canagliflozin 100 mg daily for 24 months (12 months followed by 12 month extension period) in addition to stable metformin dose.

2.2.3. Canagliflozin 300 mg daily (N = 485)

Oral canagliflozin 300 mg daily for 24 months (12 months followed by 12 month extension period) in addition to stable metformin dose.

2.3. Characteristics

2.3.1. Arm-level characteristics

Characteristic	Glimepiride 6/8 mg daily (N = 484)	Canagliflozin 100 mg daily (N = 483)	Canagliflozin 300 mg daily (N = 485)
% Male Sample size	n = 263 ; % = 55	n = 252 ; % = 52	n = 241 ; % = 50
Mean age (SD) (years) Mean (SD)	56.3 (9)	56.4 (9.5)	55.8 (9.2)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
Asian Sample size	n = 93 ; % = 19	n = 99 ; % = 21	n = 92 ; % = 19
Black/African-American Sample size	n = 22 ; % = 5	n = 20 ; % = 4	n = 19 ; % = 4
Other Sample size	n = 45 ; % = 9	n = 41 ; % = 9	n = 41 ; % = 9
White Sample size	n = 322 ; % = 67	n = 323 ; % = 67	n = 333 ; % = 69
Comorbidities Nominal	NR	NR	NR
Presence of frailty Nominal	NR	NR	NR
Time since type 2 diabetes diagnosed (years) Mean (SD)	6.6 (5)	6.5 (5.5)	6.7 (5.5)

Characteristic	Glimepiride 6/8 mg daily (N = 484)	Canagliflozin 100 mg daily (N = 483)	Canagliflozin 300 mg daily (N = 485)
Cardiovascular risk factors Nominal	NR	NR	NR
Smoking status Nominal	NR	NR	NR
Alcohol consumption Nominal	NR	NR	NR
Presence of severe mental illness Nominal	NR	NR	NR
People with significant cognitive impairment Nominal	NR	NR	NR
People with a learning disability Nominal	NR	NR	NR
Number of people with obesity Nominal	NR	NR	NR
Other antidiabetic medication used Entered antihyperglycaemic drug adjustment period Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
Yes Sample size	n = 171 ; % = 36	n = 173 ; % = 36	n = 178 ; % = 37
No Sample size	n = 311 ; % = 65	n = 310 ; % = 64	n = 307 ; % = 63
Blood pressure-lowering medication used Nominal	NR	NR	NR

Characteristic	Glimepiride 6/8 mg daily (N = 484)	Canagliflozin 100 mg daily (N = 483)	Canagliflozin 300 mg daily (N = 485)
Statins/lipid-lowering medication used Nominal	NR	NR	NR
Other treatment being received Nominal	NR	NR	NR

Baseline characteristics for glimepiride group are for n=482

3. Charbonnel, 2006

Bibliographic Reference	Charbonnel, B.; Karasik, A.; Liu, J.; Wu, M.; Meininger, G.; Efficacy and safety of the dipeptidyl peptidase-4 inhibitor sitagliptin added to ongoing metformin therapy in patients with type 2 diabetes inadequately controlled with metformin alone; Diabetes Care; 2006; vol. 29 (no. 12); 2638-43

3.1. 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	NCT00086515
Study type	Randomised controlled trial (RCT) Double-blind parallel group RCT
Study location	International (100 centres in 25 countries: Australia, Austria, Belgium, Brazil, Chile, Denmark, France, Germany, Hong Kong, Israel, Italy, Malaysia, Mexico, Netherlands, New Zealand, Norway, Peru, Philippines, Portugal, Singapore, Spain, Sweden, Switzerland, Taiwan, Thailand, USA)
Study setting	Outpatient (Diabetes centres)
Study dates	07/2004 to 02/2007
Sources of funding	Funded by Merck Research Laboratories
Inclusion criteria	• Men and women aged 18-78 years inclusive • Type 2 diabetes • Inadequate glycaemic control (HbA1c≥7% and ≤10%) • Stable dose metformin monotherapy≥1500 mg/day on entry or after dose-stable-run-in period (people who were drug naive, or on any

	oral antihyperglycaemic agent with or without metformin were eligible if inadequate glycaemic control)
Exclusion criteria	• History of type 1 diabetes • Insulin use within 8-wks of screening • Renal function impairment inconsistent with metformin use • At or just before randomisation, FPG>14.4 mmol/l • Use of other oral antihyperglycaemic agent during trial Concurrent lipid-lowering and antihypertensive medications, thyroid medications, hormone replacement therapy, birth control medications permitted but expected to remain at stable doses.
Recruitment / selection of participants	Participants recruited from 100 centres in 25 countries. Participants who satisfied entry criteria at screening entered 2-wk placebo run-in period and were randomised to sitagliptin or placebo groups. Participants not taking oral antihyperglycaemic agent, those on other oral monotherapy with or without metformin, at screening, entered metformin monotherapy titration period (up to 19 weeks). After dose-stable run-in period, participants with HbA1c 7-10% entered 2-wk placebo run-in period and were randomised. Randomisation was in 2:1 ratio sitagliptin: placebo. Participants who exceeded glycaemic limits (FPG>15 mmol/L from baseline to week6, >13.3 mmol/L wk 6-12, and >11.1 mmol/L wk 12+) during trial given rescue therapy (pioglitazone) until end of treatment.
Intervention(s)	• Sitagliptin 100 mg once daily Oral sitagliptin 100 mg once daily for 24 weeks.
Cointervention	Metformin≥1500 mg daily
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	Not stated/unclear

type 2 diabetes mellitus and high cardiovascular risk	
Subgroup 1: People with moderate or severe frailty	Not stated/unclear
Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear
Subgroup 3: People with non-alcoholic fatty liver disease	Not stated/unclear
Subgroup 4: People with obesity	Not stated/unclear
Subgroup 5: eGFR category at baseline	Not stated/unclear
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Comparator	• Placebo Matched oral placebo for 24 weeks.
Number of participants	N=701
Duration of follow-up	24 weeks
Indirectness	None
Method of analysis	Modified ITT mITT analysis (all randomised participants who received at least one study drug dose, and had baseline and at least one post-baseline measurement) for HbA1c level) but unclear what missing data strategy is; safety analysis

	included all randomised participants who received at least one double blind study drug.

3.2. Study arms

3.2.1. Sitagliptin 100 mg daily (N = 464)

Oral sitagliptin 100 mg daily for 24 weeks, in addition to metformin >=1500 mg daily.

3.2.2. Placebo (N = 237)

Matching placebo for 24 weeks, in addition to metformin>=1500 mg daily.

3.3. Characteristics

3.3.1. Arm-level characteristics

Characteristic	Sitagliptin 100 mg daily (N = 464)	Placebo (N = 237)
% Male Sample size	n = 259 ; % = 55.8	n = 141 ; % = 59.5
Mean age (SD) (years) Mean (SD)	54.4 (10.4)	54.7 (9.7)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA
Asian Sample size	n = 49 ; % = 10.6	n = 26 ; % = 11
Black Sample size	n = 31 ; % = 6.7	n = 14 ; % = 5.9
Hispanic Sample size	n = 72 ; % = 15.5	n = 28 ; % = 11.8
Other Sample size	n = 19 ; % = 4.1	n = 10 ; % = 4.2
White Sample size	n = 293 ; % = 63.1	n = 159 ; % = 67.1

Characteristic	Sitagliptin 100 mg daily (N = 464)	Placebo (N = 237)
Comorbidities Nominal	NR	NR
Presence of frailty Nominal	NR	NR
Time since type 2 diabetes diagnosed (years) Mean (SD)	6 (5)	6.6 (5.5)
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 At screening Sample size	n = NA ; % = NA	n = NA ; % = NA
Antihyperglycaemic monotherapy Sample size	n = 277 ; % = 59.7	n = 154 ; % = 65
Antihyperglycaemic combination therapy Sample size	n = 160 ; % = 34.5	n = 69 ; % = 29.1

Characteristic	Sitagliptin 100 mg daily (N = 464)	Placebo (N = 237)
Antihyperglycaemic drug naive Sample size	n = 27 ; % = 5.8	n = 14 ; % = 5.9
Blood pressure-lowering medication used Nominal	NR	NR
Statins/lipid-lowering medication used Nominal	NR	NR
Other treatment being received Nominal	NR	NR

4. Charbonnel, 2013

Bibliographic Reference	Charbonnel, B.; Steinberg, H.; Eymard, E.; Xu, L.; Thakkar, P.; Prabhu, V.; Davies, M. J.; Engel, S. S.; Efficacy and safety over 26 weeks of an oral treatment strategy including sitagliptin compared with an injectable treatment strategy with liraglutide in patients with type 2 diabetes mellitus inadequately controlled on metformin: a randomised clinical trial; Diabetologia; 2013; vol. 56 (no. 7); 1503-11

4.1. 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	NCT01296412
Study type	Randomised controlled trial (RCT) Open-label parallel-group RCT
Study location	International (111 sites in 21 countries)
Study setting	Outpatient (Diabetes centres)
Study dates	03/2011 to 02/2012
Sources of funding	Sponsored by Merck Sharp & Dohme Corp, subsidiary of Merck & Co., Inc.
Inclusion criteria	• Aged 18–79 years • Stable dose of metformin monotherapy ≥1,500 mg/day for ≥12 weeks • HbA1c ≥7.0% (53 mmol/mol) and ≤11.0% (97 mmol/mol) • Fasting fingerstick glucose (FFG) <15 mmol/L • Deemed capable by investigator of using a Victoza pen injection device (containing 6 mg/ml liraglutide; Novo Nordisk, Bagsværd, Denmark)

	• Women agreed to remain abstinent or use acceptable method of birth control during study
Exclusion criteria	• Type 1 diabetes mellitus • History of ketoacidosis • Uncontrolled hypertension • New or worsening signs/symptoms (within past 3 months) of cardiovascular disease • Presence of severe active peripheral vascular disease • History of hypersensitivity or any contraindication to antihyperglycaemic agents used in study or treated with any antihyperglycaemic therapy other than metformin monotherapy within 12 weeks before screening • History of malignancy or clinically important haematological disorder that required disease-specific treatment • Personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia syndrome type 2 • Elevated serum creatinine value (≥124 µmol/l [1.4mg/dl] for men and ≥115 µmol/l [1.3mg/dl] for women) • Estimated glomerular filtration rate (eGFR)<60 ml min−1 (1.73 m)−2 or an alanine or aspartate amino-transferase level >2 times the upper limit of the normal range.
Recruitment / selection of participants	Participants had measurements taken and were randomised 1:1 to oral or injectable strategy. Randomisation performed via computer-generated allocation scheme and via interactive voice response system. Participants discontinued due to hypoglycaemia if (1) they had repeated fasting plasma glucose (FPG) or fingerstick glucose values <2.8 mmol/l with or without symptoms; (2) FPG or fingerstick glucose ≤3.9 mmol/l with symptoms and without a reasonable explanation (for glimepiride-treated participants, if these episodes occurred after interrupting glimepiride). Patients were discontinued due to hyperglycaemia if: (1) FPG (with value repeated and confirmed within 7 days) >15mmol/l from randomisation through to week 6; (2)FPG >13.33 mmol/l after week 6 through to week 18; FPG >11.11 mmol/l after week 18 through to week 26.
Intervention(s)	• Oral strategy - Sitagliptin 100 mg daily for 26 weeks plus glimepiride at week 12 if HbA1c≥7% and FFG>6.1 mmol/L Oral sitagliptin 100 mg daily for 26 weeks plus glimepiride at week 12 if HbA1c≥7% and FFG>6.1 mmol/L for 14 weeks. At week 12, 135 of 269 (per protocol analysis set) of participants received additional glimepiride (study end dose 3.1 mg daily).
Cointervention	Metformin≥1500 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 Excluded "new or worsening signs/symptoms (within past 3 months) of cardiovascular disease, presence of severe active peripheral vascular disease", otherwise unclear. No information in baseline characteristics
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear Excluded ", an estimated glomerular filtration rate (eGFR) <60 ml min−1 (1.73 m)−2", 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	
Comparator	• Injectable strategy - Liraglutide 1.2 mg daily, increased to 1.8 mg daily if HbA1c≥7% at week 12 Subcutaneous liraglutide injection 1.2 mg daily for 26 weeks, increased to 1.8 mg daily if HbA1c≥7% at week 12. Liraglutide initially started at 0.6 mg daily for first week, up-titrated to 1.2 mg daily. At week 12, 72 of 253 participants had liraglutide up-titrated to 1.8 mg daily.
Number of participants	N=653
Duration of follow-up	26 weeks
Method of analysis	Per protocol Per-protocol analysis conducted for efficacy (HbA1c change) analysis in all randomised participants with HbA1c measurements at baseline and week 26. Modified ITT Safety analysis conducted on all randomised participants who took at least one dose of study medication. Additional efficacy analysis (Full analysis set) conducted in all randomised participants who had baseline measurement and at least one post-baseline measurement.

4.2. Study arms

4.2.1. Sitagliptin 100 mg daily (N = 326)

Oral strategy with sitagliptin 100 mg daily for 26 weeks. At week 12, glimepiride added if HbA1c>=7% and FPG>=6.1 mmol/L.

4.2.2. Liraglutide 1.2 mg daily (N = 327)

Injectable strategy with liraglutide 1.2 mg daily for 26 weeks. At week 12, if BhA1c>=7%, liraglutide up-titrated to 1.8 mg daily.

4.3. Characteristics

4.3.1. Arm-level characteristics

Characteristic	Sitagliptin 100 mg daily (N = 326)	Liraglutide 1.2 mg daily (N = 327)
% Male Sample size	n = 178 ; % = 55	n = 180 ; % = 55
Mean age (SD) (years) Mean (SD)	56.9 (10)	57.6 (10.8)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA
Black Sample size	n = 9 ; % = 3	n = 20 ; % = 6
Multiracial Sample size	n = 21 ; % = 6	n = 20 ; % = 6
Other Sample size	n = 15 ; % = 5	n = 14 ; % = 4
White Sample size	n = 281 ; % = 86	n = 273 ; % = 84
Comorbidities Nominal	NR	NR
Presence of frailty Nominal	NR	NR
Time since type 2 diabetes diagnosed (years) Mean (SD)	7.6 (4.8)	8.2 (6.2)
Cardiovascular risk factors Nominal	NR	NR
Smoking status Nominal	NR	NR
Alcohol consumption Nominal	NR	NR

Characteristic	Sitagliptin 100 mg daily (N = 326)	Liraglutide 1.2 mg daily (N = 327)
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
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
Other treatment being received Nominal	NR	NR

5. Charbonnel, 2005

Bibliographic Reference	Charbonnel, B; Schernthaner, G; Brunetti, P; Matthews, D R; Urquhart, R; Tan, M H; Hanefeld, M; Long-term efficacy and tolerability of add-on pioglitazone therapy to failing monotherapy compared with addition of gliclazide or metformin in patients with type 2 diabetes.; Diabetologia; 2005; vol. 48 (no. 6); 1093-104

5.1. Study details

Secondary publication of another included study- see primary study for details	For Pioglitazone v Metformin trial, see: • Hanefeld, M., Brunetti, P., Schernthaner, G. H., Matthews, D. R., Charbonnel, B. H., & QUARTET Study Group. (2004). One-year glycemic control with a sulfonylurea plus pioglitazone versus a sulfonylurea plus metformin in patients with type 2 diabetes. *Diabetes care*, *27*(1), 141-147. For Pioglitazone v Gliclazide trial, see: • Matthews, D. R., Charbonnel, B. H., Hanefeld, M., Brunetti, P., & Schernthaner, G. (2005). Long-term therapy with addition of pioglitazone to metformin compared with the addition of gliclazide to metformin in patients with type 2 diabetes: a randomized, comparative study. *Diabetes/metabolism research and reviews*, *21*(2), 167-174.
Other publications associated with this study included in review	2-year lipid/cholesterol results reported in: • Betteridge, D. J., & Verges, B. (2005). Long-term effects on lipids and lipoproteins of pioglitazone versus gliclazide addition to metformin and pioglitazone versus metformin addition to sulphonylurea in the treatment of type 2 diabetes. *Diabetologia*, *48*, 2477-2481.
Trial name / registration number	Not reported
Study type	Randomised controlled trial (RCT) Both trials were double-blind parallel-group RCTs
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 Exclusion criteria: History of myocardial infarction, transient ischemic attacks, or stroke in previous 6-mo. Could include participants with history of other atherosclerotic heart disease.
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	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

5.2. Study arms

5.2.1. Pioglitazone 15-45 mg daily (N = 319)

Oral pioglitazone 15-45 mg daily for 104 weeks, in addition to concurrent metformin therapy (Pioglitazone v Gliclazide trial)

5.2.2. Gliclazide 80-320 mg daily (N = 313)

Oral gliclazide 80-320 mg daily for 104 weeks, in addition to concurrent metformin therapy (Pioglitazone v Gliclazide trial)

5.2.3. Pioglitazone 15-45 mg daily (N = 319)

Oral pioglitazone 15-45 mg daily for 104 weeks, in addition to concurrent sulphonylurea therapy (Pioglitazone v Metformin trial)

5.2.4. Metformin 850-2550 mg daily (N = 320)

Oral metformin 580-2550 mg daily for 104 weeks, in addition to concurrent sulphonylurea therapy (Pioglitazone v Metformin trial)

5.3. Characteristics

5.3.1. Study-level characteristics

Characteristic	Study (N = 639)
Other antidiabetic medication used Type of concurrent sulphonylurea therapy (Pioglitazone v Metformin trial) Sample size	n = NA ; % = NA
Glibenclamide Pioglitazone v metformin trial Sample size	n = 268 ; % = 42
Gliclazide Pioglitazone v metformin trial Sample size	n = 198 ; % = 31
Glimepiride Pioglitazone v metformin trial Sample size	n = 121 ; % = 19

5.3.2. Arm-level characteristics

Characteristic	Pioglitazone 15-45 mg daily (N = 319)	Gliclazide 80-320 mg daily (N = 313)	Pioglitazone 15-45 mg daily (N = 319)	Metformin 850-2550 mg daily (N = 320)
% Male Sample size	n = 161 ; % = 50.8	n = 154 ; % = 49.2	n = 171 ; % = 53.6	n = 175 ; % = 54.7
Mean age (SD) (years) Mean (SD)	56 (9.2)	57 (9)	60 (8.8)	60 (8)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
Black Sample size	n = 0 ; % = 0	n = 0 ; % = 0	n = 2 ; % = 0.6	n = 3 ; % = 0.9
Caucasian Sample size	n = 315 ; % = 99.4	n = 313 ; % = 100	n = 317 ; % = 99.4	n = 315 ; % = 98.4
Other Sample size	n = 2 ; % = 0.6	n = 0 ; % = 0	n = 0 ; % = 0	n = 2 ; % = 0.6
Comorbidities Nominal	NR	NR	NR	NR
Presence of frailty Nominal	NR	NR	NR	NR
Time since type 2 diabetes diagnosed (years) Mean (SD)	5.8 (5.1)	5.5 (5.1)	7 (5.6)	7.1 (5.6)
Cardiovascular risk factors Nominal	NR	NR	NR	NR
Smoking status Nominal	NR	NR	NR	NR
Alcohol consumption Nominal	NR	NR	NR	NR

Characteristic	Pioglitazone 15-45 mg daily (N = 319)	Gliclazide 80-320 mg daily (N = 313)	Pioglitazone 15-45 mg daily (N = 319)	Metformin 850-2550 mg daily (N = 320)
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
Number of people with obesity Nominal	NR	NR	NR	NR
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

Data for Pioglitazone v Gliclazide trial is n=317 for Pioglitazone arm.

6. Charpentier, 2009

Bibliographic Reference	Charpentier, G.; Halimi, S.; Earlier triple therapy with pioglitazone in patients with type 2 diabetes; Diabetes Obes Metab; 2009; vol. 11 (no. 9); 844-54

6.1. 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 but authors report on behalf of the F-PIO-100 Study Investigators
Study type	Randomised controlled trial (RCT) Double-blind parallel group RCT
Study location	France (52 hospitals, diabetology or internal medical services and 16 diabetes specialists)
Study setting	Outpatient
Study dates	Not reported
Sources of funding	Sponsored by Takeda France
Inclusion criteria	• Male or female aged≥ 30 years • Diagnosis of type 2 diabetes≥2 years before trial inclusion • At least 3 months metformin combination therapy (≥1700 mg/day) with a sulphonylurea or a glinide at maximal tolerated dose • HbA1c level 7-9.5% inclusive within 3 months of trial • BMI 24-35 kg/m2 inclusive
Exclusion criteria	• Diagnosis of type 1 diabetes • History of ketoacidosis

	• Treatment with oral glucose–lowering monotherapy, more than two oral glucose–lowering agents or insulin • History of insulin therapy lasting more than 1 week • Myocardial infarction within 6 months of inclusion • Class I–IV heart failure • Hypersensitivity to pioglitazone • Current renal dialysis • Severe or malignant disease • Pregnant or breastfeeding status • Participation in another clinical trial <1 month previously
Recruitment / selection of participants	Participants recruited from 52 French hospitals, diabetology or internal medicine services and 16 diabetes specialists. After initial 3-wk run-in period, participants randomised to pioglitazone 30 mg or placebo for 3 months. If HbA1c level≤6.5%, participants in pioglitazone group continued on 30 mg for additional 4 months, otherwise titrated up to 45 mg. If symptomatic hypoglycaemia, sulphonylurea or meglitinide dose could be reduced or stopped.
Intervention(s)	• Pioglitazone 30 or 45 mg daily Pioglitazone 30 mg daily for 3 months then continued for 4 months if HbA1c level≤6.5%, otherwise up titrated to 45 mg daily.
Cointervention	• Metformin ≥1700 mg daily + a sulphonylurea or a meglitinide All participants were on metformin combination therapy for duration of trial. Reduction of sulphonylurea or glinide, or stopping completely, permitted in case of symptomatic hypoglycaemia.
Strata 1: People with type 2 diabetes mellitus and heart failure	People without heart failure Excluded "class I–IV heart failure".
Strata 2: People with atherosclerotic cardiovascular disease	Not stated/unclear Excluded "myocardial infarction within 6 months of inclusion", prior to this unclear. "Three quarters of patients in the pioglitazone group and two thirds in the placebo group had a history of macrovascular disease", no other information given and unclear if this includes all CVD definitions in protocol.
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	Not stated/unclear

type 2 diabetes mellitus and high cardiovascular risk	
Subgroup 1: People with moderate or severe frailty	Not stated/unclear
Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear
Subgroup 3: People with non-alcoholic fatty liver disease	Not stated/unclear
Subgroup 4: People with obesity	Not stated/unclear
Subgroup 5: eGFR category at baseline	Not stated/unclear
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Comparator	• Placebo Matching placebo for 7 months, in addition to concurrent metformin therapy with or without a sulphonylurea or meglitinide.
Number of participants	N=299
Duration of follow-up	7 months
Indirectness	None

Method of analysis	Modified ITT mITT analysis (full analysis set, all randomised participants who received at least one treatment dose and had at least one HbA1c measurement at inclusion and at least one HbA1c measurement during treatment) for all efficacy outcomes using observed data only. Safety population was all randomised participants who received at least one treatment dose.

6.2. Study arms

6.2.1. Pioglitazone 30 mg daily (N = 145)

Oral pioglitazone 30 mg daily for 7 months (with option of increasing to 45 mg daily from week 12), in addition to concurrent metformin (at least 1700 mg/day) therapy with either a sulphonylurea or a glinide at maximal tolerated dose.

6.2.2. Placebo (N = 154)

Oral placebo for 7 months, in addition to concurrent metformin (at least 1700 mg/day) therapy with either a sulphonylurea or a glinide at maximal tolerated dose.

6.3. Characteristics

6.3.1. Study-level characteristics

Characteristic	Study (N = 289)
Other antidiabetic medication used Sample size	n = NA ; % = NA
Metformin only Sample size	n = 2 ; % = 0.7
Metformin + Glibenclamide Sample size	n = 105 ; % = 37
Metformin + Glimepiride Sample size	n = 97 ; % = 33.8
Metformin + Glicazide Sample size	n = 91 ; % = 31.7
Metformin + Glipizide Sample size	n = 2 ; % = 0.7

Characteristic	Study (N = 289)
Metformin + Carbutamide Sample size	n = 1 ; % = 0.35
Metformin + repaglinide Sample size	n = 2 ; % = 0.7
Metformin + a sulphonylurea + acarbose Sample size	n = 1 ; % = 0.35
Blood pressure-lowering medication used Sample size	n = NA ; % = NA
Angiotensin-converting enzyme inhibitors Sample size	n = 95 ; % = 33.2
Beta-blockers Sample size	n = 65 ; % = 22.8
Statins/lipid-lowering medication used Sample size	n = NA ; % = NA
Lipid-altering agents Sample size	n = 176 ; % = 61.3

6.3.2. Arm-level characteristics

Characteristic	Pioglitazone 30 mg daily (N = 145)	Placebo (N = 154)
% Male Sample size	n = 94 ; % = 66.2	n = 95 ; % = 64.6
Mean age (SD) (years) Mean (SD)	59.2 (9.6)	60.2 (9.3)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA
Caucasian Sample size	n = 124 ; % = 87.3	n = 124 ; % = 84.4
Comorbidities	n = NA ; % = NA	n = NA ; % = NA

Characteristic	Pioglitazone 30 mg daily (N = 145)	Placebo (N = 154)
Sample size		
Experienced at least one diabetic complication Sample size	n = 56 ; % = 39.1	n = 57 ; % = 39.1
Presence of frailty Nominal	NR	NR
Time since type 2 diabetes diagnosed (years) Mean (SD)	12.1 (7.9)	12.5 (9)
Cardiovascular risk factors Sample size	n = NA ; % = NA	n = NA ; % = NA
History of macrovascular disease Sample size	n = 107 ; % = 75	n = 98 ; % = 66.67
Hypertension Sample size	n = 99 ; % = 69.7	n = 85 ; % = 57.8
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

Baseline characteristics are for N=142 in pioglitazone 30/45 mg arm, and N=147 in placebo arm.

7. Chen, 2017

Bibliographic Reference	Chen, Weena J Y; Diamant, Michaela; de Boer, Karin; Harms, Hendrik J; Robbers, Lourens F H J; van Rossum, Albert C; Kramer, Mark H H; Lammertsma, Adriaan A; Knaapen, Paul; Effects of exenatide on cardiac function, perfusion, and energetics in type 2 diabetic patients with cardiomyopathy: a randomized controlled trial against insulin glargine.; Cardiovascular diabetology; 2017; vol. 16 (no. 1); 67

7.1. Study details

Secondary publication of another included study- see primary study for details	No additional information.
Other publications associated with this study included in review	No additional information.
Trial name / registration number	NCT00766857.
Study type	Randomised controlled trial (RCT)
Study location	The Netherlands.
Study setting	Outpatient follow-up.
Study dates	No additional information.
Sources of funding	Supported by Eli Lilly which had a partnership with Amylin, the manufacturer of exenatide at the time the trial was designed and data was collected.
Inclusion criteria	People with type 2 diabetes and LV dysfunction; LV ejection fraction <50% (as documented in the medical records, measured using echocardiograms, radionuclide angiogram or cardiovascular MRI); above 18 years; BMI of 25-40kg/m2; HbA1c of 6.5-10%.
Exclusion criteria	Renal or liver impairment; malignancy; cardiovascular events <3 months; insulin; thiazolidinediones; incretin-based therapies <4 months; chronic glucocorticoid us; people with contraindication for positron emission tomography or CMR (e.g. claustrophobia, implanted metal devices, rhythm other than sinus).

Recruitment / selection of participants	No additional information.
Intervention(s)	Exenatide N=14 5 micrograms exenatide twice daily subcutaneously 15 minutes before breakfast and dinner for 4 weeks followed by an increased to 10 micrograms twice daily for the remainder of the study. 26 weeks in total.
Cointervention	Concomitant therapy: People received oral glucose lowering therapy (metformin or metformin and sulfonylurea). These were started during a run in period of 10 weeks.
Strata 1: People with type 2 diabetes mellitus and heart failure	People with heart failure People with LV ejection fracture <50%. Unclear if all had symptoms but all had at least structural heart damage consistent with heart failure. Clinical trial record indicates people had congestive heart failure.
Strata 2: People with atherosclerotic cardiovascular disease	People with atherosclerotic cardiovascular diseases 24 out of 26 included people had coronary artery disease.
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear Excluded "renal or liver impairment", 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	Insulin N=12 Insulin glargine 10 IU once daily injected subcutaneously. People were instructed to increase the dose based on fasting blood glucose levels (<5.6 mmol/L) according to a prespecified treat-to-target algorithm.
Number of participants	26
Duration of follow-up	26 weeks
Indirectness	No additional information.
Method of analysis	Per protocol Appears to be completers only
Additional comments	No additional information.

7.2. Study arms

7.2.1. Exenatide (N = 14)

5 micrograms exenatide twice daily subcutaneously 15 minutes before breakfast and dinner for 4 weeks followed by an increased to 10 micrograms twice daily for the remainder of the study. 26 weeks in total. Concomitant therapy: People received oral

glucose lowering therapy (metformin or metformin and sulfonylurea). These were started during a run in period of 10 weeks.

7.2.2. Insulin (N = 12)

Insulin glargine 10 IU once daily injected subcutaneously. People were instructed to increase the dose based on fasting blood glucose levels (<5.6 mmol/L) according to a prespecified treat-to-target algorithm. Concomitant therapy: People received oral glucose lowering therapy (metformin or metformin and sulfonylurea). These were started during a run in period of 10 weeks.

7.3. Characteristics

7.3.1. Arm-level characteristics

Characteristic	Exenatide (N = 14)	Insulin (N = 12)
% Male Sample size	n = 14 ; % = NR	n = 12 ; % = 100
Mean age (SD) Mean (SD)	NR (NR)	NR (NR)
Ethnicity Sample size	n = NR ; % = NR	n = NR ; % = NR
Comorbidities Sample size	n = NR ; % = NR	n = NR ; % = NR
Presence of frailty Sample size	n = NR ; % = NR	n = NR ; % = NR
Time since type 2 diabetes diagnosed Mean (SD)	NR (NR)	NR (NR)

8. Chen, 2016

Bibliographic Reference	Chen, Xiaoyan; Wang, Jing; Huang, Xiaochun; Tan, Yuyu; Deng, Shunyou; Fu, Yingyu; Effects of vildagliptin versus saxagliptin on daily acute glucose fluctuations in Chinese patients with T2DM inadequately controlled with a combination of metformin and sulfonylurea.; Current medical research and opinion; 2016; vol. 32 (no. 6); 1131-6

8.1. 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	ChiCTR-TRC-13003858
Study type	Randomised controlled trial (RCT) Open-label active-controlled parallel-group randomised trial.
Study location	Guangzhou, China
Study setting	Outpatient
Study dates	05/2013 to 08/2014
Sources of funding	Reports study not funded.
Inclusion criteria	• Aged 18 years or more • Type 2 diabetes diagnosis (WHO 1999 criteria) • Inadequate glycaemic control on stable dose of metformin + gliclazide >3 months
Exclusion criteria	• Lactating or planning pregnancy • Type 1 or secondary diabetes

	• History of acute renal failure, pancreatitis, or liver disease (cirrhosis, hepatitis B or hepatitis C, or any abnormalities [alanine aminotransferase or aspartate aminotransferase >3 times the upper limit of normal (ULN), or total bilirubin >3 times ULN]) • Requiring treatment within the past 6 months for myocardial infarction, coronary artery bypass surgery, unstable angina, arrhythmias, or congestive heart failure indications • Chronic lung disease • Cancers within the past 5 years • Acute infection with fever or leukocytosis
Recruitment / selection of participants	Participants recruited from First Affiliated Hospital, Guangzhou Medical University and randomised 1:1 to arms. No further information provided.
Intervention(s)	• Vildagliptin 100 mg daily Oral vildagliptin 50 mg twice daily for 24 weeks, in addition to metformin and gliclazide.
Cointervention	• Metformin • Gliclazide All participants received stable dose of metformin and gliclazide with doses unchanged for duration of trial.
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear "Patients requiring treatment within the past 6 months for myocardial infarction, coronary artery bypass surgery, unstable angina, arrhythmias, or congestive heart failure indications" stated in the exclusion criteria. No information about heart failure preceding the past 6 months. No information in baseline characteristics.
Strata 2: People with atherosclerotic cardiovascular disease	Not stated/unclear "Patients requiring treatment within the past 6 months for myocardial infarction, coronary artery bypass surgery, unstable angina, arrhythmias, or congestive heart failure indications" stated in the exclusion criteria. No information about atherosclerotic cardiovascular disease preceding the past 6 months. No information in baseline characteristics.
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear "Patients with a history of acute renal failure" in the exclusion criteria. No further information about kidney problems. No information in baseline characteristics.
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	People without non-alcoholic fatty liver disease Exclusion criteria: history of any liver disease or any liver abnormalities
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	• Saxagliptin 5 mg daily Oral saxagliptin 5 mg daily for 24 weeks, in addition to metformin and gliclazide.
Number of participants	N=85
Duration of follow-up	24 weeks
Indirectness	None
Method of analysis	Modified ITT Analysis type not reported, appears to be mITT completer analysis (randomised participants who completed/did not discontinue trial) for efficacy and safety outcomes.
Additional comments	

8.2. Study arms

8.2.1. Vildagliptin 100 mg daily (N = 37)

Oral vildagliptin 50 mg twice daily for 24 weeks, in addition to stable metformin and gliclazide.

8.2.2. Saxagliptin 5 mg daily (N = 36)

Oral saxagliptin 5 mg daily for 24 weeks, in addition to stable metformin and gliclazide.

8.3. Characteristics

8.3.1. Arm-level characteristics

Characteristic	Vildagliptin 100 mg daily (N = 37)	Saxagliptin 5 mg daily (N = 36)
% Male Sample size	n = 21 ; % = 56.8	n = 19 ; % = 52.8
Mean age (SD) (years) Mean (SD)	63.68 (6.33)	62.11 (6.75)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA
Chinese Sample size	n = 37 ; % = 100	n = 36 ; % = 100
Comorbidities Sample size	n = NA ; % = NA	n = NA ; % = NA
Hypertension Sample size	n = 14 ; % = 37.8	n = 18 ; % = 50
Presence of frailty Nominal	NR	NR
Time since type 2 diabetes diagnosed (years) Mean (SD)	6.62 (2.38)	7.33 (2.26)

Characteristic	Vildagliptin 100 mg daily (N = 37)	Saxagliptin 5 mg daily (N = 36)
Cardiovascular risk factors Nominal	NR	NR
Smoking status Participants who smoke Sample size	n = 9 ; % = 24.3	n = 6 ; % = 16.7
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
Blood pressure-lowering medication used Sample size	n = NA ; % = NA	n = NA ; % = NA
ACE inhibitor or ARB Sample size	n = 11 ; % = 29.7	n = 14 ; % = 38.9
Beta-blocker Sample size	n = 0 ; % = 0	n = 0 ; % = 0
Calcium channel blocker Sample size	n = 6 ; % = 16.2	n = 9 ; % = 25
Diuretic Sample size	n = 3 ; % = 8.1	n = 2 ; % = 5.6
Statins/lipid-lowering medication used Sample size	n = NA ; % = NA	n = NA ; % = NA

Characteristic	Vildagliptin 100 mg daily (N = 37)	Saxagliptin 5 mg daily (N = 36)
Statins Sample size	n = 22 ; % = 59.5	n = 27 ; % = 75
Fenofibrate Sample size	n = 3 ; % = 8.1	n = 2 ; % = 5.6
Other treatment being received Nominal	NR	NR

9. Chen, 2018

Bibliographic Reference	Chen, Y.; Liu, X.; Li, Q.; Ma, J.; Lv, X.; Guo, L.; Wang, C.; Shi, Y.; Li, Y.; Johnsson, E.; et, al.; Saxagliptin add-on therapy in Chinese patients with type 2 diabetes inadequately controlled by insulin with or without metformin: results from the SUPER study, a randomized, double-blind, placebo-controlled trial; Diabetes Obes Metab; 2018; vol. 20 (no. 4); 1044-1049

9.1. Study details

Secondary publication of another included study- see primary study for details	No further information.
Other publications associated with this study included in review	No further information.
Trial name / registration number	SUPER study: NCT02104804
Study type	Randomised controlled trial (RCT)
Study location	China
Study setting	Hospital setting
Study dates	2017
Sources of funding	Industry funding - AstraZeneca
Inclusion criteria	Adults (age ≥ 18 years) with type 2 diabetes who had inadequate glycaemic control (glycated haemoglobin [HbA1c] 7.5% to 10.5%; FPG <15 mmol/L [270 mg/dL]) and who had been receiving a stable regimen of insulin or insulin plus metformin (total daily insulin dose 20- 150 U) for at least 8 weeks were eligible for inclusion in the study, provided that their insulin type was intermediate-acting, long-acting or pre-mixed (short- or rapid-acting insulin could be one component of the mix). Patients had to have a BMI ≤45 kg/m^2.

Exclusion criteria	A history of cardiovascular events in the 3 months preceding screening; unstable or rapidly progressing renal disease; and significantly abnormal liver function. In addition, women must not have been nursing or pregnant and all participants must not have received any antidiabetic therapy other than metformin or insulin for more than three consecutive days or seven non-consecutive days in the 8 weeks before screening.
Recruitment / selection of participants	Patients with type 2 diabetes who had inadequate glycaemic control and had been receiving a stable regimen of insulin or insulin and metformin for at least 8 weeks prior to the commencement of the study. The proportion of patients in the study receiving metformin was capped at 80%. The study consisted of a lead-in period, patients were then randomised 1:1 to receive saxagliptin 5 mg once daily or placebo, stratified by metformin use. Patients receiving metformin continued taking their medication at the pre-screening dose (500-2500 mg/d).
Intervention(s)	Saxagliptin 5mg once daily
Cointervention	All participants were receiving insulin (intermediate and/long acting), some participants also required rescue medication through the provision of short/rapid acting insulin. Some participants received metformin (66.8%).
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 "a history of cardiovascular events in the 3 months preceding screening", prior to this unclear. No information in baseline characteristics.
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear Excluded "unstable or rapidly progressing renal disease", otherwise unclear. No information in baseline characteristics.
Strata 4: People with type 2 diabetes	Not stated/unclear

mellitus and high cardiovascular risk	
Subgroup 1: People with moderate or severe frailty	Not stated/unclear
Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear
Subgroup 3: People with non-alcoholic fatty liver disease	Mixed population
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 further information.
Comparator	Placebo once daily, orally
Number of participants	N=466
Duration of follow-up	24 weeks
Indirectness	
Method of analysis	Modified ITT
Additional comments	The study consisted of a lead-in period where patients maintained their pre-study insulin (and metformin, if applicable) regimen and received instruction on diet, exercise and self-monitoring blood glucose levels.

	After week 4, individuals who experienced inadequate glycaemic control (fasting plasma glucose level > 13.3 mmol/L [240 mg/dL]) required "rescue" through adjustment of their insulin regimen (adding short- or rapid-acting insulin, if necessary). After rescue, patients remained in the study. In response to clinically established hypoglycaemia (including, but not limited to, a documented fingerstick glucose value ≤3.1 mmol/L [54 mg/dL]), down titration of insulin was permitted at the discretion of the investigators.

9.2. Study arms

9.2.1. Saxagliptin + insulin (N = 232)

Saxagliptin 5 mg administered orally once daily + all types of insulin

9.2.2. Placebo + insulin (N = 230)

Placebo administered daily + all types of insulin

9.3. Characteristics

9.3.1. Arm-level characteristics

Characteristic	Saxagliptin + insulin (N = 232)	Placebo + insulin (N = 230)
% Male No of events	n = 109 ; % = 47	n = 100 ; % = 43.5
Mean age (SD) (years) Mean (SD)	59.3 (7.9)	58.9 (8.2)
Ethnicity Nominal	NR	NR
Comorbidities Nominal	NR	NR
Presence of frailty Nominal	NR	NR
Time since type 2 diabetes diagnosed (Years (mean, SD))	13.4 (7.3)	13.3 (6.4)

Characteristic	Saxagliptin + insulin (N = 232)	Placebo + insulin (N = 230)
Mean (SD)		
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
Blood pressure-lowering medication used Nominal	NR	NR
Statins/lipid-lowering medication used Nominal	NR	NR
Intermediate acting insulin No of events	n = 14 ; % = 6	n = 6 ; % = 2.6
Long-acting insulin No of events	n = 32 ; % = 13.8	n = 36 ; % = 15.7
Intermediate/long acting + fast acting No of events	n = 185 ; % = 79.7	n = 184 ; % = 80
Long acting, intermediate/long-acting + fast acting No of events	n = 1 ; % = 0	n = 3 ; % = 1.3
Metformin No of events	n = 155 ; % = 66.8	n = 154 ; % = 67

10. Cherney, 2022

Bibliographic Reference	Cherney, David Z I; Cosentino, Francesco; Pratley, Richard E; Dagogo-Jack, Samuel; Frederich, Robert; Maldonado, Mario; Liu, Jie; Pong, Annpey; Liu, Chih-Chin; Cannon, Christopher P; The differential effects of ertugliflozin on glucosuria and natriuresis biomarkers: Prespecified analyses from VERTIS CV.; Diabetes, obesity & metabolism; 2022; vol. 24 (no. 6); 1114-1122

10.1. Study details

Secondary publication of another included study- see primary study for details	VERTIS CV trial. Cannon Christopher, P, Pratley, Richard, Dagogo-Jack, Samuel et al. (2020) Cardiovascular Outcomes with Ertugliflozin in Type 2 Diabetes. The New England journal of medicine 383(15): 1425-1435
Other publications associated with this study included in review	Cannon Christopher, P, McGuire Darren, K, Pratley, Richard et al. (2018) Design and baseline characteristics of the eValuation of ERTugliflozin efflcacy and Safety CardioVascular outcomes trial (VERTIS-CV). American heart journal 206: 11-23 Cosentino, F, Cannon C, P, Cherney D, Z.I et al. (2020) Efficacy of Ertugliflozin on Heart Failure-Related Events in Patients with Type 2 Diabetes Mellitus and Established Atherosclerotic Cardiovascular Disease: Results of the VERTIS CV Trial. Circulation
Trial name / registration number	VERTIS CV/NCT01986881

11. Cherrington, 2024

Bibliographic Reference	Cherrington, Andrea L; Tripputi, Mark T; Younes, Naji; Herman, William H; Katona, Aimee; Groessl, Erik J; Craig, Jacqueline; Gonzalez, Jeffrey S; Garg, Rajesh; Casula, Sabina; Kuo, Shihchen; Florez, Hermes J; Impact of Glucose-Lowering Medications on Health-Related Quality of Life in Glycemia Reduction Approaches in Diabetes: A Comparative Effectiveness Study (GRADE).; Diabetes care; 2024

11.1. 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]

12. Chirila, 2016

Bibliographic Reference	Chirila, Costel; Zheng, Qingyao; Davenport, Eric; Kaschinski, Dagmar; Pfarr, Egon; Hach, Thomas; Palencia, Roberto; Treatment satisfaction in type 2 diabetes patients taking empagliflozin compared with patients taking glimepiride.; Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation; 2016; vol. 25 (no. 5); 1199-207

12.1. Study details

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

13. Cho, 2019

Bibliographic Reference	Cho, Kyu Yong; Nakamura, Akinobu; Omori, Kazuno; Takase, Takahiro; Miya, Aika; Manda, Naoki; Kurihara, Yoshio; Aoki, Shin; Atsumi, Tatsuya; Miyoshi, Hideaki; Effect of switching from pioglitazone to the sodium glucose co-transporter-2 inhibitor dapagliflozin on body weight and metabolism-related factors in patients with type 2 diabetes mellitus: An open-label, prospective, randomized, parallel-group comparison trial; Diabetes, obesity & metabolism; 2019; vol. 21 (no. 3); 710-714

13.1. Study details

Secondary publication of another included study- see primary study for details	No additional information.
Other publications associated with this study included in review	No additional information.
Trial name / registration number	The trial was registered with the University Hospital Medical Information Network (UMIN) Center (UMIN000022804) before enrolment.
Study type	Randomised controlled trial (RCT)
Study location	Japan
Study setting	Hospital
Study dates	07/2016 - 02/2017
Sources of funding	There was no financial support for this trial.
Inclusion criteria	Japanese patients with T2DM; age, 20–80 years; HbA1c, 6.5%-8.5%; BMI ≥23 kg/m2 ; estimated glomerular filtration rate (eGFR) ≥45 mL min−1 1.73 m−2 ; and treatment with pioglitazone for ≥12 weeks before enrolment.
Exclusion criteria	Current treatment with an SGLT2 inhibitor; hypersensitivity to dapagliflozin; severe or unstable retinopathy; severe liver damage (approximately Child-Pugh class C) or renal failure; severe diabetic ketosis, pre-coma, or coma; severe infection or trauma, or perioperative condition; pregnant or

	lactating; patients considered unsuitable for inclusion according to the physician's judgment.
Recruitment / selection of participants	All participants were taking pioglitazone (15-30 mg) at baseline. Participants were assigned randomly to continue taking the Japanese standard dose of pioglitazone (15-30 mg) or to switch to the Japanese standard dose of dapagliflozin (5 mg/d).
Intervention(s)	Dapagliflozin 5 mg
Cointervention	Other antidiabetic drugs were maintained at a stable dose from enrolment until the end of the treatment period. However, the dose of sulfonylureas and insulin could be reduced if there was a risk of hypoglycaemia with dapagliflozin (5 mg/d).
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
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear Included "eGFR: >45 ml/min/1.73m2 ", 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	Mixed population

Subgroup 3: People with non-alcoholic fatty liver disease	Not stated/unclear
Subgroup 4: People with obesity	Not stated/unclear
Subgroup 5: eGFR category at baseline	eGFR ≥30mL/min/1.73m2
Subgroup 6: Albuminuria category at baseline	Mixed population
Population subgroups	No additional information.
Comparator	Pioglitazone 15/30 mg
Number of participants	N=71
Duration of follow-up	24 weeks
Indirectness	
Method of analysis	Not stated/unclear
Additional comments	

13.2. Study arms

13.2.1. Dapagliflozin 5mg (N = 36)

Administered orally, once daily

13.2.2. Pioglitazone 15 - 30mg (N = 35)

Administered orally, once daily

13.3. Characteristics

13.3.1. Arm-level characteristics

Characteristic	Dapagliflozin 5mg (N = 36)	Pioglitazone 15 - 30mg (N = 35)
% Male No of events	n = 23 ; % = 63.9	n = 19 ; % = 54.3
Mean age (SD) (Years (mean, SD)) Mean (SD)	63.1 (10)	63.6 (10.2)
Ethnicity Nominal	NR	NR
Hypertension No of events	n = 23 ; % = 63.9	n = 28 ; % = 80
Dyslipidaemia No of events	n = 33 ; % = 91.7	n = 30 ; % = 85.7
fatty liver No of events	n = 7 ; % = 19.7	n = 8 ; % = 22.9
Atherosclerotic vascular disease - coronary No of events	n = 5 ; % = 13.9	n = 6 ; % = 17.1
Atherosclerotic vascular disease - cerebrovascular No of events	n = 2 ; % = 5.6	n = 4 ; % = 11.4
Atherosclerotic vascular disease - peripheral No of events	n = 1 ; % = 2.8	n = 3 ; % = 8.6
Presence of frailty Nominal	NR	NR
< 5 No of events	n = 5 ; % = 13.9	n = 4 ; % = 11.4
>5-10 No of events	n = 8 ; % = 22.2	n = 6 ; % = 17.1
>10-15	n = 11 ; % = 30.6	n = 9 ; % = 25.7

Characteristic	Dapagliflozin 5mg (N = 36)	Pioglitazone 15 - 30mg (N = 35)
No of events		
>15 No of events	n = 10 ; % = 27.8	n = 16 ; % = 45.7
Current smoker No of events	n = 8 ; % = 22.2	n = 7 ; % = 20
Former smoker No of events	n = 9 ; % = 25	n = 9 ; % = 25.7
Alcohol consumption No of events	n = 5 ; % = 13.9	n = 2 ; % = 5.7
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
Albumin creatinine ratio (mg/g) median (25-75% CI)	22.1 (8.3-32.9)	26.5 (10.6 - 46.3)
Pioglitazone 15mg No of events	n = 30 ; % = 83.3	n = 24 ; % = 68.6
Pioglitazone 30mg No of events	n = 6 ; % = 16.7	n = 11 ; % = 31.4
Biguanide No of events	n = 20 ; % = 55.6	n = 26 ; % = 74.3
Sulfonylurea No of events	n = 10 ; % = 27.8	n = 9 ; % = 25.7
Glinidie No of events	n = 2 ; % = 5.6	n = 2 ; % = 5.7

Characteristic	Dapagliflozin 5mg (N = 36)	Pioglitazone 15 - 30mg (N = 35)
DPP-4 inhibitor No of events	n = 15 ; % = 41.7	n = 22 ; % = 62.9
Insulin No of events	n = 6 ; % = 16.7	n = 4 ; % = 11.4
GLP-1 analog No of events	n = 3 ; % = 8.3	n = 2 ; % = 5.7
Alpha-glucosidase inhibitor No of events	n = 6 ; % = 16.7	n = 5 ; % = 14.3
ACE inhibitor/ARB No of events	n = 21 ; % = 58.3	n = 23 ; % = 65.7
Calcium channel blocker No of events	n = 15 ; % = 41.7	n = 20 ; % = 57.1
Beta-blocker No of events	n = 1 ; % = 2.8	n = 4 ; % = 11.4
Diuretic No of events	n = 2 ; % = 5.6	n = 2 ; % = 5.7
Statin No of events	n = 23 ; % = 63.9	n = 27 ; % = 77.1
Fibrate No of events	n = 7 ; % = 19.4	n = 6 ; % = 17.1
Ezetimibe No of events	n = 4 ; % = 11.1	n = 5 ; % = 14.3

14. Civera, 2008

Bibliographic Reference	Civera, M.; Merchante, A.; Salvador, M.; Sanz, J.; Martínez, I.; Safety and efficacy of repaglinide in combination with metformin and bedtime NPH insulin as an insulin treatment regimen in type 2 diabetes; Diabetes Res Clin Pract; 2008; vol. 79 (no. 1); 42-7

14.1. 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	Spain
Study setting	Hospital
Study dates	No additional information.
Sources of funding	No additional information
Inclusion criteria	Patients between 40 and 70 years of age with type 2 diabetes (basal C peptide > 0.7 ng/ml and negative anti glutamic acid decarboxylase antibodies) with over 3 years of evaluation and HbA1c > 8% (determined on two occasions with a 3-month interval).
Exclusion criteria	Pregnancy, BMI > 40 kg/ m2 , renal or hepatic failure, pulmonary or cardiac disease which would contraindicate the use of metformin or intolerance and any severe systemic disease.
Recruitment / selection of participants	Study included patients with type 2 diabetes selected by consecutive sampling in the external consultations at the hospital. In total 42 participants were selected and 37 of them were randomised.

Intervention(s)	Metformin 850 mg after breakfast and dinner The study also included a third arm, however this was deemed to be out of scope: Repaglinide 2mg + metformin 850 mg + NPH insulin (n=12)
Cointervention	Both groups received NPH insulin before dinner. Patients were instructed to administer subcutaneous insulin injection in the thigh by means of a pre-loaded disposable pen (Flexpen; Novo Nordisk), half an hour before eating and how to recognise hypoglycaemia (defined by blood sugar <60 mg/dl and presence of typical syndromes)
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 "renal or hepatic failure", 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
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	NPH insulin before breakfast
Number of participants	N = 37
Duration of follow-up	6 months
Indirectness	No additional information.
Method of analysis	ITT
Additional comments	All patients had poor control despite double or triple therapy with oral antidiabetic medication (one being metformin) for more than 3 months.

14.2. Study arms

14.2.1. Metformin (N = 12)

Administered after breakfast and dinner

14.2.2. NPH insulin (N = 13)

Administered before breakfast

14.3. Characteristics

14.3.1. Arm-level characteristics

Characteristic	Metformin (N = 12)	NPH insulin (N = 13)
% Male No of events	n = 7 ; % = 58	n = 7 ; % = 54
Mean age (SD) (years) Mean (SD)	61.6 (9.2)	61.8 (10.2)
Ethnicity Nominal	NR	NR
Comorbidities Nominal	NR	NR
Presence of frailty Nominal	NR	NR
Time since type 2 diabetes diagnosed (years) Mean (SD)	7 (3.3)	11.1 (6.7)
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

Characteristic	Metformin (N = 12)	NPH insulin (N = 13)
metformin + sulfonylureas No of events	n = 8 ; % = 67	n = 7 ; % = 54
Metformin + repaglinide No of events	n = 3 ; % = 25	n = 5 ; % = 38
Glitazones + metformin + sulfonylureas No of events	n = 1 ; % = 8	n = 1 ; % = 8
Blood pressure-lowering medication used Nominal	NR	NR
Statins/lipid-lowering medication used Nominal	NR	NR

15. Cooper, 2019

Bibliographic Reference	Cooper, Mark E; Perkovic, Vlado; Groop, Per-Henrik; Hocher, Berthold; Hehnke, Uwe; Meinicke, Thomas; Koitka-Weber, Audrey; van der Walt, Sandra; von Eynatten, Maximilian; Hemodynamic effects of the dipeptidyl peptidase-4 inhibitor linagliptin with renin-angiotensin system inhibitors in type 2 diabetic patients with albuminuria.; Journal of hypertension; 2019; vol. 37 (no. 6); 1294-1300

15.1. Study details

Secondary publication of another included study- see primary study for details	Yes - see Groop, P. H., Cooper, M. E., Perkovic, V., Hocher, B., Kanasaki, K., Haneda, M., ... & Von Eynatten, M. (2017). Linagliptin and its effects on hyperglycaemia and albuminuria in patients with type 2 diabetes and renal dysfunction: the randomized MARLINA-T2D trial. *Diabetes, obesity and metabolism*, *19*(11), 1610-1619.
Other publications associated with this study included in review	Primary publication: • Groop, P. H., Cooper, M. E., Perkovic, V., Hocher, B., Kanasaki, K., Haneda, M., ... & Von Eynatten, M. (2017). Linagliptin and its effects on hyperglycaemia and albuminuria in patients with type 2 diabetes and renal dysfunction: the randomized MARLINA-T2D trial. *Diabetes, obesity and metabolism*, *19*(11), 1610-1619.
Trial name / registration number	MARLINA-T2D/NCT01792518
Study type	Randomised controlled trial (RCT) Double-blind parallel group RCT
Study location	
Study setting	International (80 clinical centres in 12 countries: Canada, Denmark, Finland, France, Germany, Japan, the Philippines, South Korea, Spain, Taiwan, USA and Vietnam)
Study dates	
Sources of funding	Boehringer Ingelheim and Eli Lilly and Company Diabetes Alliance.
Inclusion criteria	See primary study, Groop 2017

Exclusion criteria	See primary study, Groop 2017
Recruitment / selection of participants	See primary study, Groop 2017
Intervention(s)	• Linagliptin 5 mg once daily Oral linagliptin 5 mg once daily for 24 weeks.
Cointervention	See primary study, Groop 2017
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	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	People without non-alcoholic fatty liver disease
Subgroup 4: People with obesity	Not stated/unclear
Subgroup 5: eGFR category at baseline	eGFR ≥30mL/min/1.73m2 Inclusion criteria: eGFR≥30 mL/min/1.73 m2 based on MDRD equation
Subgroup 6: Albuminuria category at baseline	Mixed population Inclusion criteria UACR 30-3000 mg/g
Population subgroups	
Comparator	• Placebo Matching placebo for 24 weeks.
Number of participants	N=360
Duration of follow-up	24 weeks
Indirectness	None
Method of analysis	ACA Available case analysis for blood pressure and heart rate outcomes. Modified ITT mITT analysis (all randomised participants who received at least 1 dose of study drug) for additional safety analysis/adverse events.

15.2. Study arms

15.2.1. Linagliptin 5 mg once daily (N = 182)

Oral linagliptin 5 mg once daily for 24 weeks.

15.2.2. Placebo (N = 178)

Placebo once daily for 24 weeks.

16. Cosentino, 2020

Bibliographic Reference	Cosentino, F; Cannon C, P; Cherney D, Z.I; Masiukiewicz, U; Pratley, R; Dagogo, Jack; S; Frederich, R; Charbonnel, B; Mancuso, J; Shih W, J; Terra S, G; Cater N, B; Gantz, I; McGuire D, K; Efficacy of Ertugliflozin on Heart Failure-Related Events in Patients with Type 2 Diabetes Mellitus and Established Atherosclerotic Cardiovascular Disease: Results of the VERTIS CV Trial; Circulation; 2020

16.1. Study details

Secondary publication of another included study- see primary study for details	VERTIS CV trial. Cannon Christopher, P, Pratley, Richard, Dagogo-Jack, Samuel et al. (2020) Cardiovascular Outcomes with Ertugliflozin in Type 2 Diabetes. The New England journal of medicine 383(15): 1425-1435
Other publications associated with this study included in review	Cannon Christopher, P, McGuire Darren, K, Pratley, Richard et al. (2018) Design and baseline characteristics of the eValuation of ERTugliflozin efflcacy and Safety CardioVascular outcomes trial (VERTIS-CV). American heart journal 206: 11-23 Cherney, David Z I, Cosentino, Francesco, Pratley, Richard E et al. (2022) The differential effects of ertugliflozin on glucosuria and natriuresis biomarkers: Prespecified analyses from VERTIS CV. Diabetes, obesity & metabolism 24(6): 1114-1122
Trial name / registration number	VERTIS CV/NCT01986881

17. Cusi, 2019

Bibliographic Reference	Cusi, K.; Bril, F.; Barb, D.; Polidori, D.; Sha, S.; Ghosh, A.; Farrell, K.; Sunny, N. E.; Kalavalapalli, S.; Pettus, J.; Ciaraldi, T. P.; Mudaliar, S.; Henry, R. R.; Effect of canagliflozin treatment on hepatic triglyceride content and glucose metabolism in patients with type 2 diabetes; Diabetes Obes Metab; 2019; vol. 21 (no. 4); 812-821

17.1. Study details

Secondary publication of another included study- see primary study for details	No additional information.
Other publications associated with this study included in review	No additional information.
Trial name / registration number	NCT02009488
Study type	Randomised controlled trial (RCT)
Study location	USA
Study setting	Veterans Administration Medical Center University of California University of Florida
Study dates	09/2014 - 06/2016
Sources of funding	Funding by Janssen Research & Development
Inclusion criteria	1. Adults aged 25-75 years of age (inclusive) with a diagnosis of type 2 diabetes for at least 3 months who meets one of the two following criteria:

	• On metformin monotherapy at a stable dose of ≥1,000 mg per day for at least 12 weeks prior to Screening with an HbA1c of ≥7.0% and ≤9.5% (≥53 and ≤80 mmol/mol) at Screening, ***or*** • On combination therapy of metformin ≥1,000 mg per day and a DPP-4 inhibitor at stable daily doses for at least 12 weeks prior to screening with an HbA1c of ≥7.0% and ≤9.5% (≥53 and ≤80 mmol/mol) at Screening. 2. FPG ≥100 mg/dL and £240 mg/dL before randomisation. 3. If a woman, before entry she must be: • Postmenopausal, defined as • >45 years of age with amenorrhea for at least 18 months, ***or*** • >45 years of age with amenorrhea for at least 6 months but less than 18 months prior to Screening and a serum follicle stimulating hormone (FSH) level >40 mIU/mL at Screening ***or*** • Surgically sterile due to a hysterectomy, or bilateral oophorectomy, or bilateral tubal ligation, ***or*** • Heterosexually active and practicing a highly effective method of birth control, including hormonal prescription oral contraceptives, contraceptive injections, contraceptive patch, intrauterine device, double-barrier method (e.g., condoms, diaphragm, or cervical cap with spermicidal foam, cream, or gel), or male partner sterilisation, consistent with local regulations regarding use of birth control methods for subjects participating in clinical studies, for the duration of their participation in the study, ***or*** • Not sexually active 4. If a woman, has a negative urine pregnancy test (b–human chorionic gonadotropin [b-hCG]) at Screening and on Day -14, and she must agree not to donate eggs (ova, oocytes) for the purposes of assisted reproduction 5. Subject must be medically stable on the basis of clinical laboratory, physical examination, medical history, vital signs, and 12-lead ECG performed at Screening. 6. Willing and able to adhere to the prohibitions and restrictions the protocol. 7. Each subject (or their legally acceptable representative) must sign an informed consent form (ICF) indicating that he or she understands the purpose of and procedures required for the study and are willing to participate in the study. 8. Adequately comply with the Run-In Period study procedures, including performance of the self-monitoring blood glucose (SMBG) measurements (completed at least 3 SMBG measurements per week), as documented in the subject diary, comply with the standard diet, and ≥80% compliance (confirmed by pill count) with single-blind placebo capsules during the 14-day Single-Blind Placebo Run-In Period prior to starting the single-blind placebo baseline period.
Exclusion criteria	Patients with liver conditions other than NAFLD or taking medications that could promote steatosis were excluded. Patients with eGFR <65mL/min/1.73 m2 were also excluded.
Recruitment / selection of participants	Participants were recruited from the general population of California and Florida in response to newspaper and radio advertisements or from diabetes outpatient clinics at both sites.

Intervention(s)	Canagliflozin treatment was initiated at 100 mg/d, with up-titration to 300 mg/d if well-tolerated and eGFR was ≥60 mL/min/1.73m2
Cointervention	Metformin +/- DPP-4 inhibitor
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear Excluded "history of New York Heart Association (NYHA) Class III-IV cardiac disease", otherwise unclear. No information in baseline characteristics.
Strata 2: People with atherosclerotic cardiovascular disease	Not stated/unclear Excluded "Myocardial infarction, unstable angina, pulmonary hypertension, revascularization procedure (e.g., stent or bypass graft surgery), or cerebrovascular accident within 6 months before Screening", prior unclear. No information in baseline characteristics.
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear Excluded "eGFR <65 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	Mixed population

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	
Comparator	Placebo
Number of participants	N=56
Duration of follow-up	24 week
Indirectness	No additional information.
Method of analysis	Per protocol

17.2. Study arms

17.2.1. Canagliflozin 300 mg daily (N = 26)

Administered orally

17.2.2. Placebo daily (N = 30)

Administered orally

17.3. Characteristics

17.3.1. Arm-level characteristics

Characteristic	Canagliflozin 300 mg daily (N = 26)	Placebo daily (N = 30)
% Male No of events	n = 16 ; % = 62	n = 21 ; % = 70
Mean age (SD) Mean (SD)	58 (9)	58 (10)
White No of events	n = 18 ; % = 69	n = 20 ; % = 67
African-American No of events	n = 6 ; % = 23	n = 8 ; % = 27
Asian No of events	n = 1 ; % = 4	n = 1 ; % = 3
Other No of events	n = 1 ; % = 4	n = 1 ; % = 3
Metformin No of events	n = 26 ; % = 100	n = 30 ; % = 100
Metformin + DPP-4 inhibitor No of events	n = 3 ; % = 12	n = 4 ; % = 13

18. da Silva, 2016

Bibliographic Reference	da Silva, G. M.; Nogueira, K. C.; Fukui, R. T.; Correia, M. R. S.; dos Santos, R. F.; da Silva, M. E.; Short and long term effects of a DPP-4 inhibitor versus bedtime NPH insulin as ADD-ON therapy in patients with type 2 diabetes; Curr Pharm Design; 2016; vol. 22 (no. 44); 6716-6721

18.1. Study details

Secondary publication of another included study- see primary study for details	No additional information
Other publications associated with this study included in review	No additional information
Trial name / registration number	NCT02607410
Study type	Randomised controlled trial (RCT)
Study location	Brazil
Study setting	Hospital
Study dates	01/2010 to 01/2012
Sources of funding	São Paulo Research Foundation
Inclusion criteria	• Outpatients with inadequately controlled type 2 diabetes with metformin + glyburide • HbA1c levels between 6.6 and 10% • body mass index < 35 kg/m2
Exclusion criteria	• Heart or respiratory failure • Uncontrolled hypertension • Hepatic, renal, endocrine and gastrointestinal disorders • Malignancy • Alcohol abuse

	• Previous use of insulin or incretin therapy.
Recruitment / selection of participants	Patients with inadequately controlled type 2 diabetes with metformin + sulfonylurea (glyburide)
Intervention(s)	Sitagliptin 100 mg once daily
Cointervention	Metformin + glyburide
Strata 1: People with type 2 diabetes mellitus and heart failure	People without heart failure Excluded heart failure
Strata 2: People with atherosclerotic cardiovascular disease	Not stated/unclear Not an inclusion/exclusion criteria. No information in baseline characteristics.
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear Excluded "renal disorders" but 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	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	
Comparator	Bedtime NPH insulin
Number of participants	N=35
Duration of follow-up	12 months
Indirectness	
Method of analysis	Per protocol
Additional comments	

18.2. Study arms

18.2.1. Sitagliptin (N = 18)

18.2.2. NPH Insulin (N = 17)

18.3. Characteristics

18.3.1. Arm-level characteristics

Characteristic	Sitagliptin (N = 18)	NPH Insulin (N = 17)
% Male No of events	n = 9 ; % = 50	n = 6 ; % = 35
Mean age (SD) Mean (SD)	55.1 (6.7)	58.4 (6.9)
Ethnicity Nominal	NR	NR
Comorbidities Nominal	NR	NR
Presence of frailty Nominal	NR	NR
Time since type 2 diabetes diagnosed Mean (SD)	10.9 (5.8)	10.9 (7.5)
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 No of events	n = 18 ; % = 100	n = 17 ; % = 100
Sulfonylurea (glyburide)	n = 18 ; % = 100	n = 17 ; % = 100

Characteristic	Sitagliptin (N = 18)	NPH Insulin (N = 17)
No of events		
Blood pressure-lowering medication used Nominal	NR	NR
Statins/lipid-lowering medication used No of events	n = 14 ; % = 77.8	n = 11 ; % = 64.7
Other treatment being received Nominal	NR	NR

19. Dagogo-Jack, 2018

Bibliographic Reference	Dagogo-Jack, S.; Liu, J.; Eldor, R.; Amorin, G.; Johnson, J.; Hille, D.; Liao, Y.; Huyck, S.; Golm, G.; Terra, S. G.; et, al.; Efficacy and safety of the addition of ertugliflozin in patients with type 2 diabetes mellitus inadequately controlled with metformin and sitagliptin: the VERTIS SITA2 placebo-controlled randomized study; Diabetes Obes Metab; 2018; vol. 20 (no. 3); 530-540

19.1. Study details

Secondary publication of another included study- see primary study for details	No additional information.
Other publications associated with this study included in review	No additional information.
Trial name / registration number	NCT02036515 VERTIS SITA2
Study type	Randomised controlled trial (RCT)
Study location	12 countries: USA Argentina Colombia Czech Republic Hungary Israel Romania Slovakia Republic of Korea Malaysia Bulgaria Finland
Study setting	Medical centres
Study dates	04/2014 - 06/2016

Sources of funding	Funding was provided by Merck & Co.
Inclusion criteria	Adult patients with T2DM according to American Diabetes Association guidelines.
Exclusion criteria	• History of type 1 diabetes mellitus or assessment as possibly having type 1 diabetes mellitus, confirmed with a C-peptide <0.23 nmol/L (0.7 ng/mL) • History of ketoacidosis; history of myocardial infarction, unstable angina, arterial revascularisation, stroke, transient ischaemic attack or functional class III–IV heart failure according to the New York Heart Association within 3 months of screening • Mean value for triplicate sitting systolic BP (SBP) >160 mm Hg and/or diastolic BP (DBP) >90 mm Hg (patients receiving BP medication must have a stable regimen for ≥4 weeks prior to randomisation) • Treatment in the previous 12 weeks with insulin of any type or antihyperglycaemic agents (AHA) other than metformin, DPP-4 inhibitors or sulphonylureas • Active, obstructive uropathy or indwelling urinary catheter • Estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m2 • Serum creatinine ≥115 µmol/L (1.3 mg/dL) in men or ≥106 µmol/L (1.2 mg/dL) in women • FPG >14.4 mmol/L (260 mg/dL) prior to the placebo run-in period and confirmed within 7 days.
Recruitment / selection of participants	Adult patients with T2DM according to American Diabetes Association guidelines,11 who were receiving stable treatment with metformin (≥1500 mg/d, any formulation) and sitagliptin (100 mg/d) for ≥8 weeks, and had an HbA1c level of 7.0% to 10.5% (53-91 mmol/mol) at the screening visit, entered a 2-week single-blind, placebo run-in period prior to randomisation. Patients undergoing this regimen for <8 weeks, receiving metformin ≥1500 mg/d along with a sulphonylurea, or receiving lower doses of metformin and/or another DPP-4 inhibitor at screening, were eligible if they met the above criteria after the appropriate dose/ medication adjustment, stabilisation or washout period. Patients with adequate compliance during the placebo run-in period (≥80% based on pill count) were randomised 1:1:1 to receive ertugliflozin 5 mg once daily, ertugliflozin 15 mg once daily, or placebo once daily using a computer generated randomisation schedule.
Intervention(s)	Ertugliflozin 5 mg or 15 mg taken orally once daily in the morning.
Cointervention	All patients were on metformin (100%) + DPP-4 i (66.9%) or sulphonylureas (34.2%)

	A small number of patients, 1.3% (6/462) were on three antihyperglycaemic agents.
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear Excluded "history of functional class III–IV heart failure according to the New York Heart Association within 3 months of screening", otherwise unclear. No information in baseline characteristics.
Strata 2: People with atherosclerotic cardiovascular disease	Not stated/unclear Excluded "history of myocardial infarction, unstable angina, arterial revascularization, stroke, transient ischaemic attack or functional class III–IV heart failure according to the New York Heart Association within 3 months of screening", prior to this unclear. No information in baseline characteristics.
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear Excluded "eGFR <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	Not stated/unclear
Subgroup 3: People with non-alcoholic fatty liver disease	Not stated/unclear
Subgroup 4: People with obesity	Not stated/unclear

Subgroup 5: eGFR category at baseline	eGFR ≥30mL/min/1.73m2
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Population subgroups	No additional information.
Comparator	Placebo taken orally in the morning.
Number of participants	N=462
Duration of follow-up	52-week follow-up The primary time point was at week 26 (phase A) and treatment was continued into a 26-week extension period (phase B). The 52-week time point includes phases A + B.
Indirectness	No additional information.
Method of analysis	ITT Modified ITT
Additional comments	Glycaemic rescue therapy with open-label glimepiride (or insulin glargine if glimepiride was not considered appropriate) was prescribed for patients meeting glycaemic rescue criteria. Seem to have used mITT analysis for efficacy endpoints and ITT analysis for safety assessments.

19.2. Study arms

19.2.1. Ertugliflozin 15mg once daily (N = 153)

Administered orally in the morning

19.2.2. Ertugliflozin 5mg once daily (N = 156)

Administered orally in the morning

19.2.3. Placebo once daily (N = 153)

Administered orally in the morning

19.3. Characteristics

19.3.1. Arm-level characteristics

Characteristic	Ertugliflozin 15mg once daily (N = 153)	Ertugliflozin 5mg once daily (N = 156)	Placebo once daily (N = 153)
% Male No of events	n = 82 ; % = 53.6	n = 81 ; % = 51.9	n = 100 ; % = 65.4
Mean age (SD) Mean (SD)	59.7 (8.6)	59.2 (9.3)	58.3 (9.2)
White No of events	n = 115 ; % = 75.2	n = 114 ; % = 73.1	n = 108 ; % = 70.6
Asian No of events	n = 28 ; % = 18.3	n = 33 ; % = 21.2	n = 33 ; % = 21.6
Black/African-American No of events	n = 4 ; % = 2.6	n = 2 ; % = 1.3	n = 3 ; % = 2
American indian / Alaska native No of events	n = 5 ; % = 3.3	n = 1 ; % = 0.6	n = 5 ; % = 3.3
Multiple No of events	n = 1 ; % = 0.7	n = 6 ; % = 3.8	n = 4 ; % = 2.6
Hispanic/Latino No of events	n = 25 ; % = 16.3	n = 23 ; % = 14.7	n = 24 ; % = 15.7
Presence of frailty Nominal	NR	NR	NR
Time since type 2 diabetes diagnosed (years) Mean (SD)	9.2 (5.3)	9.9 (6.1)	9.4 (5.6)
Smoking status	NR	NR	NR

Characteristic	Ertugliflozin 15mg once daily (N = 153)	Ertugliflozin 5mg once daily (N = 156)	Placebo once daily (N = 153)
Nominal			
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
Biguanides No of events	n = 153 ; % = 100	n = 156 ; % = 100	n = 153 ; % = 100
DPP4-inhibitors No of events	n = 100 ; % = 65.4	n = 107 ; % = 68.6	n = 102 ; % = 66.7
Sulphonylureas No of events	n = 54 ; % = 35.3	n = 52 ; % = 33.3	n = 52 ; % = 34
Renin-angiotensin system agents No of events	n = 95 ; % = 62.1	n = 94 ; % = 60.3	n = 99 ; % = 64.7
Beta-blocker No of events	n = 39 ; % = 25.5	n = 44 ; % = 28.2	n = 41 ; % = 26.8
Calcium-channel blocker No of events	n = 36 ; % = 23.5	n = 30 ; % = 19.2	n = 31 ; % = 20.3
Diuretic No of events	n = 31 ; % = 20.3	n = 29 ; % = 18.6	n = 36 ; % = 23.5
Other antihypertensives	n = 8 ; % = 5.2	n = 8 ; % = 5.1	n = 9 ; % = 5.9

Characteristic	Ertugliflozin 15mg once daily (N = 153)	Ertugliflozin 5mg once daily (N = 156)	Placebo once daily (N = 153)
No of events			

20. Dahl, 2022

Bibliographic Reference	Dahl, D.; Onishi, Y.; Norwood, P.; Huh, R.; Bray, R.; Patel, H.; Rodriguez, A.; Effect of Subcutaneous Tirzepatide vs Placebo Added to Titrated Insulin Glargine on Glycemic Control in Patients With Type 2 Diabetes: The SURPASS-5 Randomized Clinical Trial; JAMA; 2022; vol. 327 (no. 6); 534-545

20.1. 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	NCT04039503 SURPASS-5
Study type	Randomised controlled trial (RCT)
Study location	The study was conducted at 45 medical research centres and hospitals in the following countries: • US • Japan • Czech Republic • Germany • Poland • Puerto Rico • Slovakia • Spain
Study setting	Medical research centres and hospitals
Study dates	03/2020 - 01/2021
Sources of funding	Eli Lilly and Company

Inclusion criteria	• Adults with type 2 diabetes • Baseline HbA1c of 7.0% to 10.5% (53-91 mmol/mol) • BMI of at least 23 receiving stable doses of once daily insulin glargine (>20 IU/d or 0.25 IU/kg/d) with or without metformin (≥1500 mg/d)
Exclusion criteria	• Presence of type 1 diabetes • History of pancreatitis • Non-proliferative diabetic retinopathy requiring acute treatment • Proliferative diabetic retinopathy • Diabetic maculopathy, hepatitis • Hypoglycemia unawareness • Gastroparesis • Estimated glomerular filtration rate (eGFR) less than 30 mL/min/1.73 m2 (or <45 mL/min/1.73 m2 for patients receiving metformin) • Use of any other antihyperglycemia medication in the 3 months before screening
Recruitment / selection of participants	Phase 3 trial, double-blind RCT; Patients were randomised 1:1:1:1 ratio to receive 5 mg, 10 mg or 15 mg of tirzepatide or volume-matched placebo once-weekly subcutaneous injections.
Intervention(s)	Tirzepatide 15 mg Tirzepatide 10 mg Tirzepatide 5 mg Administered once weekly subcutaneously
Cointervention	Insulin glargine + metformin
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear Excluded "New York Heart Association Functional Classification III and IV CHF", otherwise unclear. No information in baseline characteristics.
Strata 2: People with atherosclerotic cardiovascular disease	Not stated/unclear Excluded "acute myocardial infarction, or cerebrovascular accident (stroke) or hospitalization due to congestive heart failure, within 2 months", prior to this unclear. No information in baseline characteristics.
Strata 3: People with type 2 diabetes mellitus and	Not stated/unclear Excluded "eGFR less than 30 mL/min/1.73 m2", otherwise unclear. No information in baseline characteristics.

chronic kidney disease	
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	Not stated/unclear
Subgroup 1: People with moderate or severe frailty	Not stated/unclear
Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear
Subgroup 3: People with non-alcoholic fatty liver disease	Mixed population
Subgroup 4: People with obesity	Not stated/unclear
Subgroup 5: eGFR category at baseline	eGFR ≥30mL/min/1.73m2
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Population subgroups	No additional information.
Comparator	Placebo at equal volume to tirzepatide administered subcutaneously once weekly.
Number of participants	N=475
Duration of follow-up	40 weeks Adverse events reported through to 4 weeks after treatment discontinuation.

Indirectness	No additional information.
Method of analysis	Modified ITT
Additional comments	The authors note that the study was not designed to represent the racial diversity of each of the participating countries.

20.2. Study arms

20.2.1. Tirzepatide 15 mg once weekly (N = 120)

Administered subcutaneously

20.2.2. Tirzepatide 10 mg once weekly (N = 119)

Administered subcutaneously

20.2.3. Tirzepatide 5 mg once weekly (N = 116)

Administered subcutaneously

20.2.4. Placebo once weekly (N = 120)

Administered subcutaneously

20.3. Characteristics

20.3.1. Arm-level characteristics

Characteristic	Tirzepatide 15 mg once weekly (N = 120)	Tirzepatide 10 mg once weekly (N = 119)	Tirzepatide 5 mg once weekly (N = 116)	Placebo once weekly (N = 120)
% Male No of events	n = 65 ; % = 54	n = 72 ; % = 61	n = 61 ; % = 53	n = 66 ; % = 55
Mean age (SD) Mean (SD)	61 (10)	60 (10)	62 (10)	60 (10)

Characteristic	Tirzepatide 15 mg once weekly (N = 120)	Tirzepatide 10 mg once weekly (N = 119)	Tirzepatide 5 mg once weekly (N = 116)	Placebo once weekly (N = 120)
American-Indian/Alaska Native No of events	n = 1 ; % = 0.8	n = 1 ; % = 0.8	n = 0 ; % = 0	n = 0 ; % = 0
Asian No of events	n = 22 ; % = 18.3	n = 21 ; % = 17.8	n = 20 ; % = 17.2	n = 22 ; % = 18.5
Black or African American No of events	n = 3 ; % = 2.5	n = 2 ; % = 1.7	n = 1 ; % = 0.9	n = 0 ; % = 0
White No of events	n = 94 ; % = 78.3	n = 94 ; % = 79.7	n = 95 ; % = 81.9	n = 97 ; % = 81.5
Comorbidities Nominal	NR	NR	NR	NR
Presence of frailty Nominal	NR	NR	NR	NR
Time since type 2 diabetes diagnosed Mean (SD)	13.7 (7.5)	12.6 (6.2)	14.1 (8.1)	12.9 (7.4)
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

Characteristic	Tirzepatide 15 mg once weekly (N = 120)	Tirzepatide 10 mg once weekly (N = 119)	Tirzepatide 5 mg once weekly (N = 116)	Placebo once weekly (N = 120)
People with a learning disability Nominal	NR	NR	NR	NR
Number of people with obesity Nominal	NR	NR	NR	NR
Insulin glargine No of events	n = 120 ; % = 100	n = 119 ; % = 100	n = 116 ; % = 100	n = 120 ; % = 100
Metformin No of events	n = 97 ; % = 80.8	n = 99 ; % = 83.2	n = 99 ; % = 85.3	n = 99 ; % = 82.5
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

21. D'Alessio, 2015

Bibliographic Reference	D'Alessio, D.; Haring, H. U.; Charbonnel, B.; de Pablos-Velasco, P.; Candelas, C.; Dain, M. P.; Vincent, M.; Pilorget, V.; Yki-Jarvinen, H.; Comparison of insulin glargine and liraglutide added to oral agents in patients with poorly controlled type 2 diabetes; Diabetes Obes Metab; 2015; vol. 17 (no. 2); 170-178

21.1. 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	EAGLE trial
Study type	Randomised controlled trial (RCT)
Study location	Recruitment from the following countries: • Austria • Brazil • Canada • Czech Republic • Finland • France • Greece • Ireland • Israel • Mexico • Netherlands • Russian Federation • Slovakia • Spain • Sweden • Turkey • United States

Study setting	Hospital setting
Study dates	08/2010 - 10/2012
Sources of funding	Sanofi
Inclusion criteria	• Participants who were aged 35–75 years with a diagnosis of T2DM for ≥1 year were eligible if they had an HbA1c level >7.5 and ≤12% (>58 and ≤108 mmol/mol) • Body mass index between 25 and 40 kg/m2 and were willing to comply with study requirements. • Subjects were also required to be on metformin at a minimum dose of 1 g/day, alone or in combination with sulphonylurea, glinides or a dipeptidyl peptidase-4 inhibitor for >3 month • Subjects receiving liraglutide who had fasting plasma glucose levels ≥13.9 mmol/L at weeks 12 or 18 (early switch), or HbA1c levels ≥7.0% at week 24 of the comparative study were eligible to be switched to insulin glargine for a 24-week study extension
Exclusion criteria	• Those treated with GLP-1 receptor agonists or insulin in the previous year, or with thiazolidinediones or α-glucosidase inhibitors in the previous 3 months • Impaired renal (estimated glomerular filtration rate<60 ml/min) or hepatic (alanine aminotransferase/ aspartate aminotransferase >2.5 × upper limit of normal) function, or any condition that investigators felt would compromise the patient's safety or participation in the study
Recruitment / selection of participants	Participants were recruited from 17 countries and entered into an open-label trial. A total of 1456 participants were screened and of these, 978 were randomised to insulin glargine (n=489) and liraglutide (n=489). The study consisted of a 2-week screening period and a 24-week treatment period with insulin glargine or liraglutide. Eligible subjects were allocated to liraglutide or insulin glargine randomly through a central coordinating centre in the order in which they qualified for the study, and stratified by site to ensure a balance in each treatment group (1:1 ratio).
Intervention(s)	Liraglutide 0.6 mg once daily injected subcutaneously in the morning or evening using a prefilled pen. The dose was then increased to 1.2 and 1.8 mg daily at weekly intervals if it was well tolerated; doses could be reduced to 1.2 mg in subjects having difficulty with the higher dose
Cointervention	• All subjects continued metformin except for one in the insulin glargine group • Sulphonylureas were initially taken by 60% of those on insulin glargine and 63% receiving liraglutide; at week 24, 49% and 48% respectively were still taking them

Strata 1: People with type 2 diabetes mellitus and heart failure	People without heart failure <2% had heart failure
Strata 2: People with atherosclerotic cardiovascular disease	Not stated/unclear Not an inclusion/exclusion criteria. Breakdown by individual CVD in baseline characteristics but overlap unclear.
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear Excluded "impaired renal (estimated glomerular filtration rate <60 ml/min)", 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	Mixed population
Subgroup 3: People with non-alcoholic fatty liver disease	Not stated/unclear
Subgroup 4: People with obesity	Mixed population

Subgroup 5: eGFR category at baseline	eGFR ≥30mL/min/1.73m2
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Population subgroups	No additional information.
Comparator	Insulin glargine on a titration schedule, adjusted every 3 days, to attain fasting plasma glucose levels of ≥4.0 and ≤5.5 mmol/l
Number of participants	N=978
Duration of follow-up	24 weeks
Indirectness	No additional information
Method of analysis	Modified ITT
Additional comments	

21.2. Study arms

21.2.1. Liraglutide 0.6 mg - 1.8 mg once daily (N = 470)

subcutaneously administered in the morning or evening

21.2.2. Insulin glargine (N = 474)

21.3. Characteristics

21.3.1. Arm-level characteristics

Characteristic	Liraglutide 0.6 mg - 1.8 mg once daily (N = 470)	Insulin glargine (N = 474)
% Male	n = 263 ; % = 56	n = 250 ; % = 53

Characteristic	Liraglutide 0.6 mg - 1.8 mg once daily (N = 470)	Insulin glargine (N = 474)
No of events		
Mean age (SD) Mean (SD)	57.4 (8.9)	57.1 (8.8)
Ethnicity Nominal	NR	NR
Myocardial infarction No of events	n = 19 ; % = 4	n = 19 ; % = 4
Angina Pectoris No of events	n = 26 ; % = 5.5	n = 24 ; % = 5.1
Coronary artery disease No of events	n = 55 ; % = 11.7	n = 47 ; % = 9.9
Heart failure No of events	n = 8 ; % = 1.7	n = 4 ; % = 0.8
Stroke No of events	n = 10 ; % = 2.1	n = 9 ; % = 1.9
TIA No of events	n = 11 ; % = 2.3	n = 4 ; % = 0.8
Peripheral vascular disease No of events	n = 42 ; % = 8.9	n = 34 ; % = 7.2
Diabetic neuropathy No of events	n = 143 ; % = 30.4	n = 130 ; % = 27.4
Diabetic nephropathy No of events	n = 46 ; % = 9.8	n = 42 ; % = 8.9
Diabetic retinopathy No of events	n = 40 ; % = 8.5	n = 42 ; % = 8.9
Time since type 2 diabetes diagnosed Nominal	NR	NR
Smoking status Nominal	NR	NR

Characteristic	Liraglutide 0.6 mg - 1.8 mg once daily (N = 470)	Insulin glargine (N = 474)
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 No of events	n = 469 ; % = 99.8	n = 472 ; % = 99.6
Sulphonylurea No of events	n = 321 ; % = 68.3	n = 320 ; % = 67.5
DPP4-inhibitors No of events	n = 100 ; % = 21.3	n = 100 ; % = 21.1
Glinides No of events	n = 16 ; % = 3.4	n = 14 ; % = 3
Alpha-glucosidase inhibitors No of events	n = 1 ; % = 0.2	n = 1 ; % = 0.2
Thiazolidinediones No of events	n = 1 ; % = 0.2	n = 1 ; % = 0.2
Beta-blocker No of events	n = 115 ; % = 23.9	n = 113 ; % = 23.3
Calcium-channel blockers No of events	n = 76 ; % = 15.8	n = 88 ; % = 18.2
Renin-angiotensin system agents No of events	n = 315 ; % = 65.5	n = 317 ; % = 65.5

Characteristic	Liraglutide 0.6 mg - 1.8 mg once daily (N = 470)	Insulin glargine (N = 474)
Lipid-modifying agents No of events	n = 294 ; % = 61.1	n = 306 ; % = 63.2
Anti-thrombotic agents No of events	n = 189 ; % = 39.3	n = 191 ; % = 39.5

22. Davies, 2016

Bibliographic Reference	Davies, M. J.; Bain, S. C.; Atkin, S. L.; Rossing, P.; Scott, D.; Shamkhalova, M. S.; Bosch-Traberg, H.; Syren, A.; Umpierrez, G. E.; Efficacy and safety of liraglutide versus placebo as add-on to glucose-lowering therapy in patients with type 2 diabetes and moderate renal impairment (LIRA-RENAL): A randomized clinical trial; Diabetes Care; 2016; vol. 39 (no. 2); 222-230

22.1. 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	LIRA-RENAL/NCT01620489
Study type	Randomised controlled trial (RCT) Double-blind RCT
Study location	International (78 sites in 6 countries: France [4], Poland [8], Russian Federation [15], Ukraine [6], UK [9], USA [36])
Study setting	Outpatient
Study dates	06/2012 to 08/2013
Sources of funding	Sponsored by Novo Nordisk A/S.
Inclusion criteria	• Aged 18-80 years (inclusive) • Previous type 2 diabetes diagnosis • HbA1c 7-10% (inclusive) • On stable diabetes treatment >90 days before screening (monotherapy or dual-therapy combinations of metformin and/or SU and/or pioglitazone, monotherapy with basal or premix insulin, or any combination of basal or premix insulin with metformin and/or pioglitazone)

	• Moderate renal impairment (eGFR 30-59 mL/min/1.73 m2) >90 days before, and confirmed at, screening • BMI 25-45 kg/m2 (inclusive)
Exclusion criteria	At screening, main exclusion criteria were: • Hypoglycemic unawareness and/or recurrent severe hypoglycemia as judged by the investigator • Impaired liver function (alanine transaminase ≥2.5 x upper limit of normal [ULN]) • History of chronic pancreatitis or idiopathic acute pancreatitis; New York Heart Association Functional Classification IV heart failure • Episode of unstable angina, acute coronary event, cerebral stroke/transient ischemic attack, or other significant cardiovascular event within past 180 days • Systolic blood pressure (SBP) ≥180 mmHg or diastolic blood pressure (DBP) ≥100 mmHg • Screening calcitonin value ≥50 ng/L • Personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia syndrome type 2.
Recruitment / selection of participants	Trial recruited participants from 78 sites in 6 countries and randomised 1:1 using sponsor-provided telephone or web-based randomisation system to subcutaneous liraglutide or placebo. Trial site personnel, participants, and sponsor were blinded until trial completion. Stratification based on renal function (eGFR <45, ≥45 mL/min/1.73 m2 [MDRD formula]) using standardized creatinine measurements and insulin (basal, premix, no insulin) treatment. For participants using insulin with HbA1c ≤8% (64 mmol/mol) at screening, pretrial insulin dose reduced by 20% at day 0 and kept fixed until liraglutide dose escalation complete. Titration to pretrial insulin dose allowed at discretion of investigator. Participants maintained background diabetes medication throughout trial. Participants using insulin or a sulfonylurea (SU) allowed to reduce dose of these agents if hypoglycemic episodes occurred. Two participants in placebo group did not receive allocated intervention (randomised in error, n=1; meet withdrawal criteria, n=1).
Intervention(s)	• Liraglutide 1.8 mg once daily Initiated with starting dose of 0.6 mg daily, increased weekly to 1.2 mg daily until 1.8 mg daily reached for 26 weeks, plus additional 1 week follow up period. Dose escalation could be extended at discretion of investigator by up to 4 weeks if there were gastrointestinal adverse effects.
Cointervention	• Background diabetes medication
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear Excluded "New York Heart Association Functional Classification IV heart failure", otherwise unclear. No information in baseline characteristics.

Strata 2: People with atherosclerotic cardiovascular disease	Not stated/unclear Excluded "episode of unstable angina, acute coronary event, cerebral stroke/transient ischemic attack, or other significant cardiovascular event within the past 180 days", prior to this unclear. No information in baseline characteristics.
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	People with chronic kidney disease Inclusion criteria was "moderate renal impairment >90 days before screening (confirmed at screening). Stage 3 CKD (moderate renal impairment), defined as eGFR 30–59 mL/min/1.73 m2.
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 Subcutaneous placebo injection for 26 weeks. Initiated with starting dose of 0.6 mg daily, increased weekly to 1.2 mg daily until 1.8 mg daily reached for 26 weeks, plus additional 1 week follow up period. Dose escalation could be extended at discretion of investigator by up to 4 weeks if there were gastrointestinal adverse effects.
Number of participants	N=279
Duration of follow-up	26 weeks + 1 week FU
Indirectness	None
Method of analysis	Modified ITT mITT analysis (all participants who received at least one dose of trial medication) for all outcomes.

22.2. Study arms

22.2.1. Liraglutide 1.8 mg once daily (N = 140)

Subcutaneous injection of liraglutide 1.8 mg once daily for 26 weeks.

22.2.2. Placebo (N = 139)

Subcutaneous placebo injection for 26 weeks.

22.3. Characteristics

22.3.1. Arm-level characteristics

Characteristic	Liraglutide 1.8 mg once daily (N = 140)	Placebo (N = 139)
% Male Sample size	n = 75 ; % = 53.6	n = 65 ; % = 47.4
Mean age (SD) Mean (SD)	68 (8.3)	66.3 (8)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA

Characteristic	Liraglutide 1.8 mg once daily (N = 140)	Placebo (N = 139)
Asian Indian Sample size	n = 1 ; % = 0.7	n = 0 ; % = 0
Asian non-Indian Sample size	n = 2 ; % = 1.4	n = 1 ; % = 0.7
Black of African American Sample size	n = 14 ; % = 10	n = 4 ; % = 2.9
Native Hawaiian or other Pacific Islander Sample size	n = 0 ; % = 0	n = 1 ; % = 0.7
Other Sample size	n = 0 ; % = 0	n = 2 ; % = 1.5
White Sample size	n = 123 ; % = 87.9	n = 129 ; % = 94.2
Comorbidities Sample size	n = NA ; % = NA	n = NA ; % = NA
Hypertension Sample size	n = 126 ; % = 90	n = 121 ; % = 88.3
Presence of frailty Nominal	NR	NR
Time since type 2 diabetes diagnosed Mean (SD)	15.9 (8.9)	14.2 (7.5)
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	Liraglutide 1.8 mg once daily (N = 140)	Placebo (N = 139)
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 = 14 ; % = 10	n = 12 ; % = 8.8
Sulfonylurea Sample size	n = 15 ; % = 10.7	n = 19 ; % = 13.9
Pioglitazone Sample size	n = 1 ; % = 0.7	n = 1 ; % = 0.7
Metformin + Sulfonylurea Sample size	n = 26 ; % = 18.6	n = 25 ; % = 18.2
Repaglinide This combination was not permitted according to protocol Sample size	n = 1 ; % = 0.7	n = 0 ; % = 0
Metformin + Pioglitazone Sample size	n = 1 ; % = 0.7	n = 1 ; % = 0.7
Sulfonylurea + Pioglitazone Sample size	n = 1 ; % = 0.7	n = 1 ; % = 0.7
Metformin + Sulfonylurea fixed combination This combination was not permitted according to protocol Sample size	n = 1 ; % = 0.7	n = 1 ; % = 0.7
Metformin + Sulfonylurea + Pioglitazone Sample size	n = 1 ; % = 0.7	n = 0 ; % = 0
Metformin + Sulfonylurea + Acarbose This combination was not permitted according to protocol	n = 1 ; % = 0.7	n = 0 ; % = 0

Characteristic	Liraglutide 1.8 mg once daily (N = 140)	Placebo (N = 139)
Sample size		
Blood pressure-lowering medication used Nominal	NR	NR
Statins/lipid-lowering medication used Nominal	NR	NR
Other treatment being received Sample size	n = NA ; % = NA	n = NA ; % = NA
Basal insulin Sample size	n = 29 ; % = 20.7	n = 24 ; % = 17.5
Premix insulin Sample size	n = 48 ; % = 34.3	n = 52 ; % = 38
No insulin treatment Sample size	n = 63 ; % = 45	n = 61 ; % = 44.5

23. Davies, 2015

Bibliographic Reference	Davies, M. J.; Bergenstal, R.; Bode, B.; Kushner, R. F.; Lewin, A.; Skjoth, T. V.; Andreasen, A. H.; Jensen, C. B.; DeFronzo, R. A.; Group, N. N. Study; Efficacy of liraglutide for weight loss among patients with type 2 diabetes: The SCALE diabetes randomized clinical trial; JAMA; 2015; vol. 314 (no. 7); 687-99

23.1. 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	NCT01272232
Study type	Randomised controlled trial (RCT)
Study location	Study was conducted at 126 sites in 9 countries: • France • Germany • Israel • South Africa • Spain • Sweden • Turkey • UK (England and Scotland only) • US
Study setting	Hospital
Study dates	06/2011 - 01/2013

Sources of funding	Novo Nordisk
Inclusion criteria	• Type 2 diabetes diagnosis • BMI of 27.0 or greater • age ≥ 18 years • Taking 0 to 3 oral hypoglycemic agents (metformin, thiazolidinedione, sulfonylurea) • Stable body weight • Glycated hemoglobin level 7.0% to 10.0%
Exclusion criteria	• Treatment with GLP-1 receptor agonists (including liraglutide or exenatide), dipeptidyl peptidase-4 (DPP-4) inhibitors or insulin within the last 3 months • Treatment with any hypoglycemic agent(s) other than metformin, sulfonylurea and glitazone in the 3 months prior to screening • Recurrent major hypoglycemia or hypoglycemic unawareness as judged by the investigator • Use of any drug (except for metformin, sulfonylurea or glitazone), which in the investigator's opinion could interfere with glucose level • Receipt of any other anti-diabetic investigational drug within 3 months prior to screening for this trial, or receipt of any investigational drugs not affecting diabetes within 1 month prior to screening for this trial • Known proliferative retinopathy or maculopathy requiring acute treatment, as judged by the investigator • Untreated or uncontrolled hypothyroidism/hyperthyroidism defined as thyroid-stimulating hormone (TSH) >6 mIU/L or <0.4 mIU/L • History of chronic pancreatitis or idiopathic acute pancreatitis • Obesity induced by other endocrinologic disorders • Current or history of treatment with medications that may cause significant weight gain, within 3 months prior to screening for this trial • Diet attempts using herbal supplements or over-the-counter medications within 3 months prior to screening into this trial • Current participation in an organized weight reduction program (or within the last 3 months) and/or are currently using or have used within 3 months prior to screening for this trial: pramlintide, sibutramine, orlistat, zonisamide, topiramate or phenteremine • Previous surgical treatment for obesity • Screening calcitonin value ≥50 ng/L • Familial or personal history of multiple endocrine neoplasia type 2 or familial medullary thyroid carcinoma • Personal history of non-familial medullary thyroid carcinoma • Simultaneous participation in any other clinical trial of an investigational drug • History of Major Depressive Disorder within the last 2 years • A patient health questionnaire -9 (PHQ-9) score of ≥15 • History of other severe psychiatric disorders, e.g., schizophrenia, bipolar disorder • Suicidal attempt, behaviour and ideation (within previous month) • Surgery scheduled during trial period • Uncontrolled treated/untreated hypertension • Cancer

	• Known or suspected abuse of alcohol or narcotics • Language barrier, mental incapacity, unwillingness or inability to understand and be able to complete the mental health questionnaires in the provided language • Participants from the same household • Female of childbearing potential • The receipt of any investigational product within 4 weeks prior to screening for this trial • The following exclusion criteria were applicable to France in addition to the criteria listed above: (1) Treatment with diet and exercise only (2) Treatment with sulfonylurea as single agent therapy or glitazone as single agent therapy, unless the patient has metformin contraindication or metformin intolerance (3) Treatment with triple oral antidiabetic therapy (4) Abnormality of the thyroid identified during the physical examination at screening
Recruitment / selection of participants	Participants with type 2 diabetes treated with diet and exercise alone or in combination with 1 to 3 oral antidiabetic agents. Participants were centrally randomised 2:1:1 to: liraglutide 3.0 mg; liraglutide 1.8 mg; or placebo.
Intervention(s)	• Liraglutide 1.8 mg administered once daily by subcutaneous injection using a modified insulin pen device (FlexPen; Novo Nordisk) • Liraglutide 3 mg administered once daily by subcutaneous injection using a modified insulin pen device (FlexPen; Novo Nordisk)
Cointervention	Metformin, metformin + glitazone, metformin + sulfonylurea, metformin + sulfonylurea + glitazone, sulfonylurea, sulfonylurea + glitazone. The proportion of participants treated with sulfonylurea mono- or combination therapy was restricted to a maximum of 30% of total randomized participants. When the target was reached, participants treated with sulfonylurea as background treatment were not to be randomised in the trial. Some participants used diet and exercise only as the background intervention: Liraglutide 3.0 mg (11.2%), Liraglutide 1.8 mg (14.2%), placebo (9.5%)
Strata 1: People with type 2 diabetes mellitus and heart failure	People without heart failure Not an exclusion criteria. CVD (including cardiac failure) at screening was <20%.
Strata 2: People with	People without atherosclerotic cardiovascular diseases Not an exclusion criteria. CVD at screening was <20%.

atherosclerotic cardiovascular disease	
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	People with obesity
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 administered once daily by subcutaneous injection.
Number of participants	N=846
Duration of follow-up	68-week study (including a 12-week off-drug follow-up period) but results reported for 56-week end-point.
Indirectness	
Method of analysis	Modified ITT
Additional comments	Novo Nordisk was involved in the study design and protocol development, provided logistical support, and obtained the data, which were evaluated jointly by the authors and the sponsor.

23.2. Study arms

23.2.1. Liraglutide 3.0mg daily (N = 423)

Administered subcutaneously

23.2.2. Liraglutide 1.8 mg daily (N = 211)

Administered subcutaneously

23.2.3. Placebo daily (N = 212)

Administered subcutaneously

23.3. Characteristics

23.3.1. Arm-level characteristics

Characteristic	Liraglutide 3.0mg daily (N = 423)	Liraglutide 1.8 mg daily (N = 211)	Placebo daily (N = 212)
% Male No of events	n = 220 ; % = 52	n = 108 ; % = 51	n = 97 ; % = 46
Mean age (SD) (year) Mean (SD)	55 (10.8)	54.9 (10.7)	54.7 (9.8)

Characteristic	Liraglutide 3.0mg daily (N = 423)	Liraglutide 1.8 mg daily (N = 211)	Placebo daily (N = 212)
Asian No of events	n = 11 ; % = 2.6	n = 4 ; % = 1.9	n = 4 ; % = 1.9
Black or African American No of events	n = 44 ; % = 10.4	n = 27 ; % = 12.8	n = 27 ; % = 12.7
White No of events	n = 353 ; % = 83.5	n = 177 ; % = 83.9	n = 175 ; % = 82.5
Other No of events	n = 13 ; % = 3.1	n = 3 ; % = 1.4	n = 5 ; % = 2.4
Time since type 2 diabetes diagnosed (year) Mean (SD)	7.5 (5.65)	7.4 (5.26)	6.7 (5.07)
Smoking status Nominal	NR	NR	NR
Alcohol consumption Nominal	NR	NR	NR
People with significant cognitive impairment Nominal	NR	NR	NR
People with a learning disability Nominal	NR	NR	NR
30.0 - 34.9 BMI (obese class I) No of events	n = 139 ; % = 32.9	n = 62 ; % = 29.4	n = 59 ; % = 27.8
35.0 - 39.9 BMI (obese class II) No of events	n = 108 ; % = 25.5	n = 50 ; % = 23.7	n = 60 ; % = 28.3
>40 BMI (obese class III) No of events	n = 124 ; % = 29.3	n = 65 ; % = 30.8	n = 63 ; % = 29.7
Total obese No of events	n = 371 ; % = 88	n = 177 ; % = 84	n = 182 ; % = 86

Characteristic	Liraglutide 3.0mg daily (N = 423)	Liraglutide 1.8 mg daily (N = 211)	Placebo daily (N = 212)
Metformin No of events	n = 237 ; % = 57.5	n = 111 ; % = 54.4	n = 126 ; % = 59.7
Metformin + glitazone No of events	n = 22 ; % = 5.3	n = 13 ; % = 6.4	n = 10 ; % = 4.7
Metformin + Sulfonylurea No of events	n = 86 ; % = 20.9	n = 44 ; % = 21.6	n = 48 ; % = 22.7
Metformin + sulfonylurea + glitazone No of events	n = 10 ; % = 2.4	n = 4 ; % = 2	n = 4 ; % = 1.9
Sulfonylurea No of events	n = 7 ; % = 1.7	n = 2 ; % = 1	n = 2 ; % = 0.9
Sulfonylurea + glitazone No of events	n = 4 ; % = 1	n = 1 ; % = 0.5	n = 1 ; % = 0.5

24. Davies, 2009

Bibliographic Reference	Davies, M. J.; Donnelly, R.; Barnett, A. H.; Jones, S.; Nicolay, C.; Kilcoyne, A.; Exenatide compared with long-acting insulin to achieve glycaemic control with minimal weight gain in patients with type 2 diabetes: results of the Helping Evaluate Exenatide in patients with diabetes compared with Long-Acting insulin (HEELA) study; Diabetes Obes Metab; 2009; vol. 11 (no. 12); 1153-62

24.1. 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	HEELA study
Study type	Randomised controlled trial (RCT)
Study location	Multicentre at 36 centres in the UK
Study setting	NR
Study dates	June 2006 to April 2008
Sources of funding	NR. A. K. and C. N. are employees of Eli Lilly and Company
Inclusion criteria	type 2 diabetes; body mass index (BMI) >27 kg/m2]; inadequate glycaemic control (HbA1c 7.5–10.0%), despite treatment with stable doses of two or three OADs (metformin, sulphonylurea and thiazolidinedione) for at least 3 months; at least one cardiovascular risk factor defined as either a previous cardiovascular event, peripheral vascular disease, or an abnormal risk factor [low-density lipoprotein (LDL) >3.0 mmol/l, high-density lipoprotein (HDL) <1.0 mmol/l (men) or <1.3 mmol/l (women), triglyceride >1.7 mmol/l, systolic blood pressure (BP) >130 mmHg,

	diastolic BP >80 mmHg or increased waist circumference (European: >94 cm, men, >80 cm, women; Asian: >90 cm, men, >80 cm, women)].
Exclusion criteria	history of malignancy, Class III or IV heart disease, uncontrolled hypertension (systolic BP ≥180 mmHg, diastolic BP ≥105 mmHg), renal transplantation or dialysis, chronic renal impairment (serum creatinine ≥135 μmol/l for males and ≥110 μmol/l for females) or liver disease (serum alanine aminotransferase >3 × upper limit of normal)
Recruitment / selection of participants	NR
Intervention(s)	Exenatide
Cointervention	2-3 OADs (metformin, sulphonylurea and thiazolidinedione). Previous OADs were continued at the same stable dosages unless one or more confirmed or suspected hypoglycaemic event occurred, when the sulphonylurea dose could be reduced.
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear Excluded "Class III or IV heart disease", otherwise unclear.
Strata 2: People with atherosclerotic cardiovascular disease	People without atherosclerotic cardiovascular diseases 15.8% had macroangiopathy (included angina pectoris, cerebral infarction, cerebrovascular accident, coronary artery disease, intermittent claudication, myocardial ischaemia, peripheral vascular disorder and transient ischaemic attack)
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear Excluded "chronic renal impairment (serum creatinine ≥135 μmol/l for males and ≥110 μmol/l for females)", otherwise unclear.
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	People at higher risk of developing cardiovascular disease at least one cardiovascular risk factor defined as either a previous cardiovascular event, peripheral vascular disease, or an abnormal risk factor [low-density lipoprotein (LDL) >3.0 mmol/l, high-density lipoprotein (HDL) <1.0 mmol/l (men) or <1.3 mmol/l (women), triglyceride >1.7 mmol/l, systolic blood pressure (BP) >130 mmHg, diastolic BP >80 mmHg or increased waist circumference (European: >94 cm, men, >80 cm, women; Asian: >90 cm, men, >80 cm, women)]
Population subgroups	NR
Comparator	Insulin glargine

Number of participants	235
Duration of follow-up	26 weeks
Indirectness	None
Method of analysis	Modified ITT
Additional comments	randomized patients who received at least one dose of study drug. 118 patients randomized to exenatide and 117 patients randomized to insulin glargine (116 treated - this number included in baseline characteristics table below, not the 117 randomised).

24.2. Study arms

24.2.1. Exenatide (N = 118)

5-10 mcg b.i.d. All treatments were self-administered using reusable injection pens with prefilled cartridges by subcutaneous injection in the abdomen, within 15 min before morning and evening meals. Exenatide was administered at 5 µg b.i.d. for the first 4 weeks, then 10 µg b.i.d. for the remainder of the study.

24.2.2. Insulin glargine (N = 117)

Self-administered using reusable injection pen with prefilled cartridges by subcutaneous injection in the abdomen, once daily at bedtime. Insulin glargine was initiated at 10 IU/day and titrated weekly according to a target fasting plasma glucose level ≤5.6 mmol/l (≤100 mg/dl). For mean self monitored fasting plasma glucose levels ≥10 mmol/l, the increase in insulin glargine dosage was 8 IU/day; for fasting plasma glucose levels of 7.8–9.9 mmol/l, the increase in insulin glargine dosage was 6 IU/day and for fasting plasma glucose levels of 6.7–7.7 or 5.6–6.6 mmol/l, the increase in insulin glargine dosage was 4 or 2 IU/day respectively.

24.3. Characteristics

24.3.1. Arm-level characteristics

Characteristic	Exenatide (N = 118)	Insulin glargine (N = 117)
% Male Sample size	n = 83 ; % = 70.3	n = 77 ; % = 66.4

Characteristic	Exenatide (N = 118)	Insulin glargine (N = 117)
Mean age (SD) Mean (SD)	56.8 (10.2)	56.2 (7.9)
Ethnicity Nominal	NR	NR
Comorbidities Sample size	n = NA ; % = NA	n = NA ; % = NA
Hypertension Sample size	n = 85 ; % = 72	n = 79 ; % = 68.1
Dyslipidaemia Sample size	n = 35 ; % = 29.7	n = 39 ; % = 33.6
Hypercholesterolaemia Sample size	n = 21 ; % = 17.8	n = 19 ; % = 16.4
Macroangiopathy Sample size	n = 16 ; % = 13.6	n = 21 ; % = 18.1
Presence of frailty Nominal	NR	NR
Time since type 2 diabetes diagnosed Mean (SD)	9 (4.6)	8.4 (4.4)
Cardiovascular risk factors Nominal	NR	NR
Smoking status Nominal	NR	NR
Alcohol consumption Mean (SD)	NR (NR)	NR (NR)
Presence of severe mental illness Nominal	NR	NR
People with significant cognitive impairment Nominal	NR	NR

Characteristic	Exenatide (N = 118)	Insulin glargine (N = 117)
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 and SU Sample size	n = 50 ; % = 42.4	n = 49 ; % = 42.2
Metformin and TZD Sample size	n = 17 ; % = 14.4	n = 15 ; % = 12.9
SU and TZD Sample size	n = 2 ; % = 1.7	n = 4 ; % = 3.4
Metformin + SU + TZD Sample size	n = 48 ; % = 40.7	n = 47 ; % = 40.5
Blood pressure-lowering medication used Nominal	NR	NR
Statins/lipid-lowering medication used Nominal	NR	NR
Other treatment being received Nominal	NR	NR

25. Davies, 2021

Bibliographic Reference	Davies, M.; Færch, L.; Jeppesen, O. K.; Pakseresht, A.; Pedersen, S. D.; Perreault, L.; Rosenstock, J.; Shimomura, I.; Viljoen, A.; Wadden, T. A.; et, al.; Semaglutide 2·4 mg once a week in adults with overweight or obesity, and type 2 diabetes (STEP 2): a randomised, double-blind, double-dummy, placebo-controlled, phase 3 trial; Lancet (london, england); 2021; vol. 397 (no. 10278); 971-984

25.1. Study details

Secondary publication of another included study- see primary study for details	Parent paper for STEP 2
Other publications associated with this study included in review	NA
Trial name / registration number	STEP 2 NCT03552757
Study type	Randomised controlled trial (RCT)
Study location	149 outpatient clinics in 12 countries across Europe, North America, South America, the Middle East, South Africa, and Asia
Study setting	outpatient clinics
Study dates	June 4 to Nov 14, 2018
Sources of funding	Novo Nordisk
Inclusion criteria	18 years or older, reported at least one unsuccessful dietary effort to lose weight, had a body-mass index of at least 27 kg/m², HbA1c of 7–10% (53–86 mmol/mol), and had been diagnosed with type 2 diabetes at least 180 days before screening. Participants were managed with diet and exercise alone or treated with a stable dose of up to three oral glucose-lowering agents (metformin, sulfonylureas, SGLT2 inhibitors, or thiazolidinediones) for at least 90 days before screening.

Exclusion criteria	self-reported changes in bodyweight of more than 5 kg within 90 days before screening, and previous or planned (ie, set to occur during the trial period) obesity treatment with surgery or a weight-loss device. 1. Treatment with any medication for the indication of diabetes or obesity other than stated in the inclusion criteria within the past 90 days before screening. 2. Receipt of any other glucose-lowering investigational drug within 90 days prior to screening for this trial, or receipt of any investigational drugs not affecting diabetes within 30 days before screening for this trial. 3. Treatment with a glucagon-like peptide-1 receptor agonist within 180 days prior to screening. 4. Renal impairment measured as estimated glomerular filtration rate value of <30 mL/min/1·73 m2 (<60 mL/min/1·73 m2 in patients treated with SGLT2i) according to Chronic Kidney Disease Epidemiology Collaboration creatinine equation as defined by Kidney Disease: Improving Global Outcomes 2012 by the central laboratory at screening. 5. Uncontrolled and potentially unstable diabetic retinopathy or maculopathy, verified by a pharmacologically pupil-dilated fundus examination performed by an ophthalmologist or an equally qualified healthcare provider (e.g. optometrist) within the past 90 days before screening or in the period between screening and randomisation. 6. A self-reported change in body weight of >5 kg (11 lbs) within 90 days before screening, irrespective of medical records. 7. Previous or planned (during the trial period) obesity treatment with surgery or a weight-loss device. However, the following are allowed: (1) liposuction and/or abdominoplasty, if performed >1 year before screening; (2) lap banding, if the band has been removed >1 year before screening; (3) intragastric balloon, if the balloon has been removed >1 year before screening; or (4) duodenal–jejunal bypass sleeve, if the sleeve has been removed >1 year before screening. 8. Uncontrolled thyroid disease, defined as thyroid-stimulating hormone >6·0 mIU/L or <0·4 mIU/L as measured by central laboratory at screening. 9. History of major depressive disorder within 2 years before screening. 10. Diagnosis of other severe psychiatric disorder (e.g. schizophrenia, bipolar disorder). 11. A score of ≥15 on the Patient Health Questionnaire-9 at screening. 12. A lifetime history of a suicidal attempt.

	13. Suicidal behaviour within 30 days before screening. 14. Suicidal ideation corresponding to type 4 or 5 on the Columbia-Suicide Severity Rating Scale within the past 30 days before screening. 15. Use of non-herbal Chinese medicine or other non-herbal local medicine with unknown/unspecified content within 90 days before screening. 16. Presence of acute pancreatitis within the past 180 days prior to the day of screening. 17. History or presence of chronic pancreatitis. 18. Calcitonin ≥100 ng/L as measured by the central laboratory at screening. 19. Personal or first-degree relative(s) history of multiple endocrine neoplasia type 2 or medullary thyroid carcinoma. 20. History of malignant neoplasms within the past 5 years prior to screening. Basal and squamous cell skin cancer and any carcinoma in situ are allowed. 21. Any of the following: myocardial infarction, stroke, hospitalisation for unstable angina, or transient ischemic attack within the past 60 days prior to screening. 22. Patient presently classified as being in New York Heart Association Class IV. 23. Surgery scheduled for the duration of the trial, except for minor surgical procedures, in the opinion of the investigator. 24. Known or suspected abuse of alcohol or recreational drugs. 25. Known or suspected hypersensitivity to trial product(s) or related products. 26. Previous participation in this trial. Participation is defined as signed informed consent. 27. Participation in another clinical trial within 90 days before screening. 28. Other patient(s) from the same household participating in any semaglutide trial. 29. Woman who is pregnant, breast-feeding, or intends to become pregnant, or is of child-bearing potential and not using a highly effective contraceptive method.

	30. Any disorder, unwillingness, or inability, not covered by any of the other exclusion criteria, which in the investigator's opinion, might jeopardise the patient's safety or compliance with the protocol.
Recruitment / selection of participants	Overweight or obese and meeting inclusion criteria
Intervention(s)	Semaglutide s.c. injection once weekly
Cointervention	Diet and exercise alone (4.6%) or background OADs (95.4%)
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear Excludes class IV, otherwise not an inclusion/exclusion criteria. No information in baseline characteristics
Strata 2: People with atherosclerotic cardiovascular disease	Not stated/unclear Excludes myocardial infarction, stroke, hospitalisation for unstable angina, or transient ischemic attack within the past 60 days prior to screening, otherwise unknown. Only CAD given in baseline characteristics
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear Excludes eGFR <30, otherwise unknown. Only eGFR categories given 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	Mixed population 21.6% had NAFLD
Subgroup 4: People with obesity	People with obesity 82.6% had a BMI over 30kg/m2. Therefore, even taking ethnicity into account, >80% of cut-off had obesity.
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
Number of participants	1210
Duration of follow-up	68 weeks
Indirectness	None
Method of analysis	ITT
Additional comments	Efficacy outcomes were assessed using intention-to-treat analysis (ie, the full set of all randomly assigned patients). Safety outcomes were assessed using the safety analysis set of all randomly allocated patients exposed to at least one dose of randomised intervention. The treatment policy estimand, which quantified average treatment effect among all randomly assigned patients, regardless of adherence to treatment or initiation of rescue intervention (patients in trial; intention to treat). Missing data were imputed 1000 times from retrieved patients of the same randomised treatment and the results were combined using Rubin's rules.

25.2. Study arms

25.2.1. Semaglutide 2.4mg (N = 404)

Semaglutide 2.4mg once weekly s.c. injection. Two injections once a week: active product plus placebo. Semaglutide was started at 0·25 mg per week and escalated in a fixed-dose regimen every 4 weeks until the target dose was reached. Plus lifestyle intervention. To mitigate risk of hypoglycaemia, patients on sulfonylureas were to reduce the dose by approximately 50% at treatment start, at the investigator's discretion. Patients could intensify glucose-lowering therapy as judged by the investigator according to local guidelines. Insulin was permitted only in cases of persistent hyperglycaemia

25.2.2. Semaglutide 1.0mg (N = 403)

Semaglutide 1.0mg once weekly s.c. injection. Two injections once a week: active product plus placebo or placebo plus placebo. Semaglutide was started at 0·25 mg per week and escalated in a fixed-dose regimen every 4 weeks until the target dose was reached. Plus lifestyle intervention. To mitigate risk of hypoglycaemia, patients on sulfonylureas were to reduce the dose by approximately 50% at treatment start, at the investigator's discretion. Patients could intensify glucose-lowering therapy as judged by the investigator according to local guidelines. Insulin was permitted only in cases of persistent hyperglycaemia

25.2.3. Placebo (N = 403)

Visually matched placebo. Two injections once a week: active product plus placebo or placebo plus placebo plus lifestyle intervention. To mitigate risk of hypoglycaemia, patients on sulfonylureas were to reduce the dose by approximately 50% at treatment start, at the investigator's discretion. Patients could intensify glucose-lowering therapy as judged by the investigator according to local guidelines. Insulin was permitted only in cases of persistent hyperglycaemia

25.3. Characteristics

25.3.1. Arm-level characteristics

Characteristic	Semaglutide 2.4mg (N = 404)	Semaglutide 1.0mg (N = 403)	Placebo (N = 403)
% Male Sample size	n = 181 ; % = 44.8	n = 200 ; % = 49.6	n = 213 ; % = 52.9
Mean age (SD) Mean (SD)	55 (11)	56 (10)	55 (11)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA

Characteristic	Semaglutide 2.4mg (N = 404)	Semaglutide 1.0mg (N = 403)	Placebo (N = 403)
Asian Sample size	n = 112 ; % = 27.7	n = 97 ; % = 24.1	n = 108 ; % = 26.8
Black or African American Sample size	n = 35 ; % = 8.7	n = 28 ; % = 6.9	n = 37 ; % = 9.2
White Sample size	n = 237 ; % = 58.7	n = 272 ; % = 67.5	n = 242 ; % = 60
Hispanic or Latino Sample size	n = 47 ; % = 11.6	n = 59 ; % = 14.6	n = 49 ; % = 12.2
Other Sample size	n = 20 ; % = 5	n = 6 ; % = 1.5	n = 16 ; % = 4
Comorbidities Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
Coronary artery disease Sample size	n = 26 ; % = 6.4	n = 40 ; % = 9.9	n = 33 ; % = 8.2
Dislipidaemia Sample size	n = 265 ; % = 65.6	n = 277 ; % = 68.7	n = 284 ; % = 70.5
Hypertension Sample size	n = 276 ; % = 68.3	n = 285 ; % = 70.7	n = 287 ; % = 71.2
NAFLD Sample size	n = 85 ; % = 21	n = 82 ; % = 20.3	n = 94 ; % = 23.2
Presence of frailty Nominal	NR	NR	NR
Time since type 2 diabetes diagnosed Mean (SD)	8.2 (6.2)	7.7 (5.9)	8.2 (6.2)
Cardiovascular risk factors Nominal	NR	NR	NR
Smoking status Nominal	NR	NR	NR

Characteristic	Semaglutide 2.4mg (N = 404)	Semaglutide 1.0mg (N = 403)	Placebo (N = 403)
Alcohol consumption Mean (SD)	NR (NR)	NR (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
Other antidiabetic medication used Sample size	n = 386 ; % = 95.5	n = 386 ; % = 95.8	n = 382 ; % = 94.8
Biguanides Sample size	n = 370 ; % = 91.6	n = 379 ; % = 94	n = 362 ; % = 89.8
Sulfonlyurea Sample size	n = 110 ; % = 27.2	n = 99 ; % = 24.6	n = 99 ; % = 24.6
SGLT2 inhibitor Sample size	n = 99 ; % = 24.5	n = 96 ; % = 23.8	n = 105 ; % = 26.1
Thiazolidinedione Sample size	n = 19 ; % = 4.7	n = 16 ; % = 4	n = 19 ; % = 4.7
DPP-4 inhibitor Sample size	n = 2 ; % = 0.5	n = 3 ; % = 0.7	n = 1 ; % = 0.2
Alpha glucosidase inhibitors Sample size	n = 1 ; % = 0.2	n = 1 ; % = 0.2	n = 0 ; % = 0
GLP-1 agonist Sample size	n = 0 ; % = 0	n = 1 ; % = 0.2	n = 0 ; % = 0

Characteristic	Semaglutide 2.4mg (N = 404)	Semaglutide 1.0mg (N = 403)	Placebo (N = 403)
Fast-acting insulin or insulin analogues Sample size	n = 0 ; % = 0	n = 0 ; % = 0	n = 1 ; % = 0.2
Other Sample size	n = 1 ; % = 0.2	n = 0 ; % = 0	n = 0 ; % = 0
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

26. Davies, 2013

Bibliographic Reference	Davies, M.; Heller, S.; Sreenan, S.; Sapin, H.; Adetunji, O.; Tahbaz, A.; Vora, J.; Once-weekly exenatide versus once- or twice-daily insulin detemir: randomized, open-label, clinical trial of efficacy and safety in patients with type 2 diabetes treated with metformin alone or in combination with sulfonylureas; Diabetes Care; 2013; vol. 36 (no. 5); 1368-76

26.1. 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	NCT01003184
Study type	Randomised controlled trial (RCT)
Study location	UK
Study setting	Hospital
Study dates	10/2009 - 12/2011
Sources of funding	Eli Lilly and Company and Amylin Pharmaceutical, LLC
Inclusion criteria	• At least 18 years of age with type 2 diabetes • HbA1C levels ≥7.1 to ≤10.0% (≥54 to ≤86 mmol/mol) despite the use of oral antidiabetics • BMI of 25 kg/m2 to 45 kg/m2 • Stable weight (≤5% variability) for 3 months • Required to be using a stable dose of metformin (≥ 1,000 mg/day) alone or in combination with stable dose of sulfonylurea (as a separate formulation) for at least 3 months

Exclusion criteria	• Women of childbearing potential were ineligible unless using a reliable form of contraception throughout the study. • Patients were excluded if they had a clinically significant medical condition that could preclude safe participation in this study, had more than three major hypoglycemic episodes in the past 6 months, or had been treated with a drug that promotes weight loss within 3 months of screening. • Lipid-lowering and antihypertensive medications were allowed with appropriate dose adjustments.
Recruitment / selection of participants	A total of 325 participants were screened; 222 of these were randomized to treatments, 216 received at least one dose of study drug and 191 completed the study to week 26.
Intervention(s)	Exenatide 2mg subcutaneous injection once weekly.
Cointervention	All patients received metformin and a large proportion received sulfonylurea (around 70%). A small proportion received sulfonamide/urea derivatives (around 2%). Of the exenatide-treated patients, 80% of patients decreased sulfonylurea therapy by end point, 4% discontinued, 15% had no change, and 1% increased sulfonylurea therapy. Oral metformin use was continued unchanged.
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	People at higher risk of developing cardiovascular disease

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	Insulin detemir administered once or twice daily subcutaneously.
Number of participants	N=222
Duration of follow-up	26 weeks
Indirectness	No additional information.
Method of analysis	ITT
Additional comments	

26.2. Study arms

26.2.1. Exenatide 2mg once weekly (N = 111)

Administered by subcutaneous injection

26.2.2. Insulin detemir titrated (2.0 IU/day to 62.0 IU/day) (N = 105)

Administered by subcutaneous injection once daily or twice daily

26.3. Characteristics

26.3.1. Study-level characteristics

Characteristic	Study (N = 222)
Blood pressure-lowering medication used No of events	n = 162 ; % = 73
Statins/lipid-lowering medication used No of events	n = 184 ; % = 83

26.3.2. Arm-level characteristics

Characteristic	Exenatide 2mg once weekly (N = 111)	Insulin detemir titrated (2.0 IU/day to 62.0 IU/day) (N = 105)
% Male No of events	n = 71 ; % = 64	n = 72 ; % = 69
Mean age (SD) No of events	n = 59 ; % = 10	n = 58 ; % = 10
White No of events	n = 104 ; % = 94	n = 102 ; % = 97
Asian No of events	n = 6 ; % = 5	n = 3 ; % = 3
Black/African-American No of events	n = 1 ; % = 1	n = 0 ; % = 0
Comorbidities Nominal	NR	NR

Characteristic	Exenatide 2mg once weekly (N = 111)	Insulin detemir titrated (2.0 IU/day to 62.0 IU/day) (N = 105)
Presence of frailty Nominal	NR	NR
Time since type 2 diabetes diagnosed Mean (SD)	8 (6)	7 (5)
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 No of events	n = 111 ; % = 100	n = 105 ; % = 100
Sulphonylurea No of events	n = 78 ; % = 70	n = 76 ; % = 72
Sulphonamide/urea derivatives No of events	n = 1 ; % = 1	n = 3 ; % = 3
Other treatment being received Nominal	NR	NR

27. Davies, 2017

Bibliographic Reference	Davies, M.; Pieber, T. R.; Hartoft-Nielsen, M. L.; Hansen, O. K. H.; Jabbour, S.; Rosenstock, J.; Effect of Oral Semaglutide Compared With Placebo and Subcutaneous Semaglutide on Glycemic Control in Patients With Type 2 Diabetes: a Randomized Clinical Trial; JAMA; 2017; vol. 318 (no. 15); 1460-1470

27.1. 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	NCT01923181
Study type	Randomised controlled trial (RCT)
Study location	Multicentre in 14 countries
Study setting	hospital clinics, general practices, and clinical research centres
Study dates	December 2013 and December 2014
Inclusion criteria	Male or female, age ≥ 18 years at the time of signing inform consent; BMI ≥25 and <40 kg/m2; Subjects diagnosed with T2D treated with diet and exercise and/or who have been on a stable dose of metformin for at least 30 days prior to screening; HbA1c 7.0-9.5% (53-80 mmol/mol) (both inclusive)
Exclusion criteria	Treatment with selected oral medications with a narrow therapeutic window History of pancreatitis Chronic malabsorption History of inflammatory bowel disease Treatment with glucose lowering agent(s) other than metformin as stated in the inclusion criteria in a period of 90 days before the screening visit Personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia syndrome type 2

Recruitment / selection of participants	NR
Intervention(s)	7 oral arms: 5 dosages of daily oral semaglutide (2.5, 5, 10, 20, and 40 mg) and a slow escalation and fast escalation dose escalation regimen for the highest dose (40 mg) of oral semaglutide 1 S.c. arm: once-weekly subcutaneous semaglutide
Cointervention	add-on to previous metformin therapy or as monotherapy in the case where the subject is treated with diet and exercise alone. Metformin use over 80% in all arms.
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	eGFR ≥30mL/min/1.73m2
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Population subgroups	NA
Comparator	placebo
Number of participants	632
Duration of follow-up	26 weeks
Indirectness	None
Method of analysis	Modified ITT
Additional comments	all randomized patients during the treatment period who did not receive rescue medication. Adverse events that occurred during the 26-week trial period from all exposed patients, with onset on or after the first day of treatment (including 5-week follow-up plus a visit window of 5 days), with or without rescue medication, are reported. missing data were imputed from a repeated measures model with treatment, stratum, country, and baseline value all nested within visit

27.2. Study arms

27.2.1. Placebo (N = 71)

Placebo tablets once-daily

27.2.2. Semaglutide 2.5mg (N = 70)

Semaglutide tablets once-daily: 2.5 mg

27.2.3. Semaglutide 5mg (N = 70)

Semaglutide tablets once-daily: 2.5 mg for 4 weeks, then 5.0 mg for 22 weeks

27.2.4. Semaglutide 10mg (N = 69)

Semaglutide tablets once-daily: 5.0 mg for 4 weeks, then 10 mg for 22 weeks

27.2.5. Semaglutide 20mg (N = 70)

Semaglutide tablets once-daily: 5.0 mg for 4 weeks, then 10 mg for 4 weeks, then 20 mg for 18 weeks

27.2.6. Semaglutide 40mg standard (N = 71)

Semaglutide (standard escalation) tablets once-daily: 5.0 mg for 4 weeks, then 10 mg for 4 weeks, then 20 mg for 4 weeks, then 40 mg for 14 weeks

27.2.7. Semaglutide 40mg slow (N = 70)

Semaglutide (slow escalation) tablets once-daily: 5.0 mg for 8 weeks, then 10 mg for 8 weeks, then 20 mg for 8 weeks, then 40 mg for 2 weeks

27.2.8. Semaglutide 40mg fast (N = 70)

Semaglutide (fast escalation) tablets once-daily: 5.0 mg for 2 weeks, then 10 mg for 2 weeks, then 20 mg for 2 weeks, then 40 mg for 20 weeks

27.2.9. Semaglutide SC 1mg (N = 69)

Semaglutide injections once-weekly: 0.25 mg for 4 weeks, then 0.50 mg for 4 weeks, then 1.0 mg for 18 weeks

27.3. Characteristics

27.3.1. Arm-level characteristics

Characteristic	Placebo (N = 71)	Semaglutide 2.5mg (N = 70)	Semaglutide 5mg (N = 70)	Semaglutide 10mg (N = 69)	Semaglutide 20mg (N = 70)	Semaglutide 40mg standard (N = 71)	Semaglutide 40mg slow (N = 70)	Semaglutide 40mg fast (N = 70)	Semaglutide SC 1mg (N = 69)
% Male (%) Nominal	56.3	64.3	67.1	62.3	62.9	60.6	58.6	62.9	69.6
Mean age (SD) Mean (SD)	58.9 (10.3)	56.7 (9.9)	55.7 (11)	56.5 (10.1)	58.3 (10.4)	56.5 (10.2)	57.1 (10.5)	57.7 (10.8)	56.8 (11.8)
White Nominal	80.3	81.4	90	82.6	84.3	88.7	77.1	84.3	78.3
Black or African American Nominal	8.5	8.6	2.9	10.1	4.7	5.6	10	10	5.8
Asian Nominal	9.9	10	5.7	5.8	5.7	4.2	10	5.7	14.5
American Indian or Alaska Native Nominal	1.4	0	0	0	2.9	0	0	0	0
Other Nominal	0	0	1.4	1.4	1.4	1.4	2.9	0	1.4
Comorbidities Nominal	NR	NR	NR	NR	NR	NR	NR	NR	NR
Presence of frailty Nominal	NR	NR	NR	NR	NR	NR	NR	NR	NR

Characteristic	Placebo (N = 71)	Semaglutide 2.5mg (N = 70)	Semaglutide 5mg (N = 70)	Semaglutide 10mg (N = 69)	Semaglutide 20mg (N = 70)	Semaglutide 40mg standard (N = 71)	Semaglutide 40mg slow (N = 70)	Semaglutide 40mg fast (N = 70)	Semaglutide SC 1mg (N = 69)
Time since type 2 diabetes diagnosed Mean (SD)	6.7 (5.1)	6.1 (6)	5.3 (4.7)	5.8 (4.8)	7 (5.3)	7.7 (5.9)	6.6 (4.9)	5.6 (4.7)	5.6 (5)
Cardiovascular risk factors Nominal	NR	NR	NR	NR	NR	NR	NR	NR	NR
Presence of severe mental illness Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
People with significant cognitive impairment Nominal	NR	NR	NR	NR	NR	NR	NR	NR	NR
People with a learning disability Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Number of people with obesity Nominal	NR	NR	NR	NR	NR	NR	NR	NR	NR

Characteristic	Placebo (N = 71)	Semaglutide 2.5mg (N = 70)	Semaglutide 5mg (N = 70)	Semaglutide 10mg (N = 69)	Semaglutide 20mg (N = 70)	Semaglutide 40mg standard (N = 71)	Semaglutide 40mg slow (N = 70)	Semaglutide 40mg fast (N = 70)	Semaglutide SC 1mg (N = 69)
Metformin use Sample size	n = 58 ; % = 81.7	n = 61 ; % = 87.1	n = 60 ; % = 85.7	n = 58 ; % = 84.1	n = 58 ; % = 84.3	n = 61 ; % = 85.9	n = 60 ; % = 85.7	n = 60 ; % = 85.7	n = 58 ; % = 84.1
Blood pressure-lowering medication used Nominal	NR	NR	NR	NR	NR	*empty data*	*empty data*	NR	NR
Statins/lipid-lowering medication used Nominal	NR	NR	NR	NR	NR	NR	NR	NR	NR

28. Davies, 2011

Bibliographic Reference	Davies, M; Pratley, R; Hammer, M; Thomsen, A B; Cuddihy, R; Liraglutide improves treatment satisfaction in people with Type 2 diabetes compared with sitagliptin, each as an add on to metformin.; Diabetic medicine : a journal of the British Diabetic Association; 2011; vol. 28 (no. 3); 333-7

28.1. 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.

29. de Jager, 2014

Bibliographic Reference	de Jager, J; Kooy, A; Schalkwijk, C; van der Kolk, J; Lehert, P; Bets, D; Wulffele, M G; Donker, A J; Stehouwer, C D A; Long-term effects of metformin on endothelial function in type 2 diabetes: a randomized controlled trial.; Journal of internal medicine; 2014; vol. 275 (no. 1); 59-70

29.1. Study details

Secondary publication of another included study- see primary study for details	Kooy A, de Jager J, Lehert P, Bets D, Wulffelé MG, Donker AJ, Stehouwer CD. Long-term effects of metformin on metabolism and microvascular and macrovascular disease in patients with type 2 diabetes mellitus. Arch Intern Med. 2009 Mar 23;169(6):616-25. doi: 10.1001/archinternmed.2009.20. PMID: 19307526.

30. DeFronzo, 2012

Bibliographic Reference	DeFronzo, R. A.; Burant, C. F.; Fleck, P.; Wilson, C.; Mekki, Q.; Pratley, R. E.; Efficacy and tolerability of the DPP-4 inhibitor alogliptin combined with pioglitazone, in metformin-treated patients with type 2 diabetes; J Clin Endocrinol Metab; 2012; vol. 97 (no. 5); 1615-22

30.1. 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	NCT00328627
Study type	Randomised controlled trial (RCT)
Study location	327 sites in 20 countries
Study setting	NR
Study dates	NR
Sources of funding	Supported by Takeda Global Research & Development Center, Takeda Pharmaceuticals North America, Inc.
Inclusion criteria	Male and female subjects [age, 18 to 80 yr; body mass index (BMI), 23 to 45 kg/m2; fasting C-peptide, ≥0.26 nmol/liter] with diagnosed type 2 diabetes inadequately controlled by metformin monotherapy (stable metformin dose ≥1500 mg/d for ≥2 months). Females of childbearing potential were required to use medically approved birth control methods. Systolic/diastolic blood pressure no greater than 160/100 mm Hg, hemoglobin of at least 12 g/dl for men and at least 10 g/dl for women, alanine aminotransferase no more than 2.5 times the upper limit of normal, TSH no greater than the upper limit of normal, serum creatinine below 133 µmol/litre (for men) or below 124 µmol/litre (for women), and the willingness and ability to perform self-monitoring of blood glucose (BG).

	After the run-in/stabilization period, subjects were required to have an HbA1c of 7.5 to 10%, inclusive, and fasting plasma glucose (FPG) no greater than 16.7 mmol/litre.
Exclusion criteria	Subjects taking any antidiabetic medication other than metformin. Oral or systemically injected glucocorticoids or weight-loss drugs within 3 months of randomization, urine albumin/creatinine ratio greater than 113 mg/mmol, history of laser treatment for proliferative retinopathy within 6 months, treated diabetic gastroparesis, history of New York Heart Association Class III or IV heart failure, cardiac surgery, or myocardial infarction within 6 months.
Recruitment / selection of participants	NR
Intervention(s)	Trial has 12 treatment arms placebo, alogliptin at doses of 12.5 or 25 mg qd (A12.5 and A25), pioglitazone at doses of 15, 30, or 45 mg qd (P15, P30, and P45), the combinations of alogliptin 12.5 mg with 15, 30, or 45 mg pioglitazone (A12.5+P15, A12.5+P30, and A12.5+P45) and alogliptin 25 mg with 15, 30, or 45 mg pioglitazone (A25+P15, A25+P30, and A25+P45). Results only available for the following arms combined which have been extracted as combined arms (no results available for placebo or Alogliptin alone): Pioglitazone (15mg, 30mg, 45mg) Alogliptin 12.5mg + Pioglitazone (15mg, 30mg, 45mg) Alogliptin 25mg + Pioglitazone (15mg, 30mg, 45mg)
Cointervention	Stabilised dose of metformin. 2-wk pre-screening period, during which the metformin dose was increased to 1500 mg/d if tolerated. An optional 12-wk titration period ensued. During the run-in/stabilization period, eligible subjects were switched (open label) from their own metformin medication to an equivalent dose of immediate-release metformin formulation.
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear Excluded "history of New York Heart Association Class III or IV heart failure in past 6 months", otherwise unclear. No information in baseline characteristics
Strata 2: People with atherosclerotic cardiovascular disease	Not stated/unclear Excluded "history of myocardial infarction within 6 months", otherwise unclear. No information in baseline characteristics
Strata 3: People with type 2	Not stated/unclear Not an inclusion/exclusion criteria. No information in baseline characteristics

diabetes mellitus and chronic kidney disease	
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	Not stated/unclear
Subgroup 1: People with moderate or severe frailty	Not stated/unclear
Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear
Subgroup 3: People with non-alcoholic fatty liver disease	Not stated/unclear
Subgroup 4: People with obesity	Not stated/unclear
Subgroup 5: eGFR category at baseline	Not stated/unclear
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Population subgroups	NR
Comparator	NA
Number of participants	1554 randomised in total to all 12 arms. 1168 of those for the arms extracted here.
Duration of follow-up	26 weeks

Indirectness	None
Method of analysis	Modified ITT
Additional comments	Analyses were performed with the full analysis set, defined as all randomized patients who received at least one dose of double-blind study drug and who had a baseline assessment (defined as the last value before the first dose of study medication) and at least one postbaseline assessment, with last observation carried forward at the time of rescue therapy or at the time the subject was lost to follow-up.

30.2. Study arms

30.2.1. Pioglitazone (N = 388)

3 separate arms in trial but results are combined. Pioglitazone 15mg, 30mg, or 45mg, all plus alogliptin placebo.

30.2.2. Alogliptin 12.5mg + Pioglitazone (N = 390)

3 separate arms in trial but results are combined. Pioglitazone 15mg, 30mg, or 45mg, all plus alogliptin 12.5mg.

30.2.3. Alogliptin 25mg + Pioglitazone (N = 390)

3 separate arms in trial but results are combined. Pioglitazone 15mg, 30mg, or 45mg, all plus alogliptin 25mg.

30.3. Characteristics

30.3.1. Arm-level characteristics

Characteristic	Pioglitazone (N = 388)	Alogliptin 12.5mg + Pioglitazone (N = 390)	Alogliptin 25mg + Pioglitazone (N = 390)
% Male Nominal	177	174	168
Mean age (SD) Mean (SD)	54.9 (9.57)	54.2 (9.62)	54.5 (9.28)
Ethnicity (%)	NA	NA	NA

Characteristic	Pioglitazone (N = 388)	Alogliptin 12.5mg + Pioglitazone (N = 390)	Alogliptin 25mg + Pioglitazone (N = 390)
Nominal			
Comorbidities Nominal	NR	NR	NR
Presence of frailty Nominal	NR	NR	NR
Time since type 2 diabetes diagnosed Mean (SD)	6.33 (5.58)	6.17 (5.31)	6.57 (5.52)
Cardiovascular risk factors Nominal	NR	NR	NR
Smoking status Nominal	NR	NR	NR
Alcohol consumption Mean (SD)	NR (NR)	NR (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
Other antidiabetic medication used Nominal	NA	NA	NA

Characteristic	Pioglitazone (N = 388)	Alogliptin 12.5mg + Pioglitazone (N = 390)	Alogliptin 25mg + Pioglitazone (N = 390)
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

31. DeFronzo, 2009

Bibliographic Reference	DeFronzo, R. A.; Hissa, M. N.; Garber, A. J.; Luiz Gross, J.; Yuyan Duan, R.; Ravichandran, S.; Chen, R. S.; The efficacy and safety of saxagliptin when added to metformin therapy in patients with inadequately controlled type 2 diabetes with metformin alone; Diabetes Care; 2009; vol. 32 (no. 9); 1649-55

31.1. 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	NCT00121667. CV181-014
Study location	US
Study setting	NR
Study dates	NR
Sources of funding	sponsored and monitored by Bristol-Myers Squibb and AstraZeneca
Inclusion criteria	Inadequate glycemic control (A1C ≥7.0 and ≤10.0%) taking a stable dose of metformin (≥1,500 but not >2,550 mg/ day) for at least 8 weeks before screening, fasting C-peptide concentration ≥1.0 ng/ ml, age 18–77 years, and BMI ≤40 kg/m2
Exclusion criteria	One or more of the following: symptoms of poorly controlled diabetes, a history of diabetic ketoacidosis or hyperosmolar nonketotic coma, use of any other antihyperglycemic medication (8 weeks before) or insulin (1 year before), a cardiovascular event within 6 months before study entry or New York Heart Association stage III/IV congestive heart failure and/or known left ventricular ejection fraction ≤40%, chronic or repeated intermittent corticosteroid treatment, a history of alcohol or drug abuse within the previous year, treatment with potent systemic cytochrome P450 3A4

	inhibitors or inducers, active liver disease and/or clinically significant abnormalities on screening tests of hepatic, renal, endocrine, metabolic, or hematologic function, or assessment of an immunocompromised state. Women who were pregnant or breastfeeding
Recruitment / selection of participants	NR
Intervention(s)	Saxagliptin
Cointervention	Metformin (open-label metformin at their pre-study dose)
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear Excluded "New York Heart Association stage III/IV congestive heart failure and/or known left ventricular ejection fraction 40%", otherwise unclear. No information in baseline characteristics
Strata 2: People with atherosclerotic cardiovascular disease	Not stated/unclear Excluded ", a cardiovascular event within 6 months before study entry", prior to this unclear. No information in baseline characteristics
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear Not an inclusion/exclusion criteria. No information in baseline characteristics
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	Not stated/unclear
Subgroup 1: People with moderate or severe frailty	Not stated/unclear
Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear

Subgroup 3: People with non-alcoholic fatty liver disease	Not stated/unclear
Subgroup 4: People with obesity	Not stated/unclear
Subgroup 5: eGFR category at baseline	Not stated/unclear
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Population subgroups	NR
Comparator	Placebo
Number of participants	743
Duration of follow-up	24 weeks
Indirectness	None
Method of analysis	Modified ITT
Additional comments	Efficacy analyses were performed on the randomly assigned patient population, consisting of randomly assigned patients who received at least one dose of study medication and had a baseline and at least one postbaseline measurement. Last observation carried forward methodology was used to handle missing data. Safety analyses were performed on the treated patient population, consisting of randomly assigned patients who received at least one dose of study medication.

31.2. Study arms

31.2.1. Placebo (N = 179)

Placebo in addition to their lead-in dose of open-label metformin. 2-week, single-blind, dietary and exercise placebo lead-in period and received open-label metformin at their pre-study dose

31.2.2. Saxagliptin 2.5mg (N = 192)

Saxagliptin 2.5mg in addition to their lead-in dose of open-label metformin. . 2-week, single-blind, dietary and exercise placebo lead-in period and received open-label metformin at their pre-study dose

31.2.3. Saxagliptin 5mg (N = 191)

Saxagliptin 5mg in addition to their lead-in dose of open-label metformin. 2-week, single-blind, dietary and exercise placebo lead-in period and received open-label metformin at their pre-study dose

31.2.4. Saxagliptin 10mg (N = 181)

Saxagliptin 10mg in addition to their lead-in dose of open-label metformin. 2-week, single-blind, dietary and exercise placebo lead-in period and received open-label metformin at their pre-study dose

31.3. Characteristics

31.3.1. Arm-level characteristics

Characteristic	Placebo (N = 179)	Saxagliptin 2.5mg (N = 192)	Saxagliptin 5mg (N = 191)	Saxagliptin 10mg (N = 181)
% Male Sample size	n = 96 ; % = 53.6	n = 83 ; % = 43.2	n = 103 ; % = 53.9	n = 95 ; % = 52.5
Mean age (SD) Mean (SD)	54.8 (10.2)	54.7 (10.1)	54.7 (9.6)	54.2 (10.1)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
Caucasian Sample size	n = 150 ; % = 83.8	n = 153 ; % = 79.7	n = 159 ; % = 83.2	n = 144 ; % = 79.6
African-American Sample size	n = 7 ; % = 3.9	n = 8 ; % = 4.2	n = 11 ; % = 5.8	n = 14 ; % = 7.7
Asian Sample size	n = 4 ; % = 2.2	n = 8 ; % = 4.2	n = 3 ; % = 1.6	n = 5 ; % = 2.8

Characteristic	Placebo (N = 179)	Saxagliptin 2.5mg (N = 192)	Saxagliptin 5mg (N = 191)	Saxagliptin 10mg (N = 181)
Other Sample size	n = 18 ; % = 10.1	n = 23 ; % = 12	n = 18 ; % = 9.4	n = 18 ; % = 9.9
Comorbidities Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Presence of frailty Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Time since type 2 diabetes diagnosed Mean (SD)	6.7 (5.6)	6.7 (5.6)	6.4 (4.7)	6.3 (4.4)
Cardiovascular risk factors Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Smoking status Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Alcohol consumption Mean (SE)	NR (NR)	NR (NR)	NR (NR)	NR (NR)
Presence of severe mental illness Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
People with significant cognitive impairment Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
People with a learning disability Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Number of people with obesity Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Other antidiabetic medication used Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA

Characteristic	Placebo (N = 179)	Saxagliptin 2.5mg (N = 192)	Saxagliptin 5mg (N = 191)	Saxagliptin 10mg (N = 181)
Metformin Sample size	n = 179 ; % = 100	n = 192 ; % = 100	n = 191 ; % = 100	n = 181 ; % = 100
Blood pressure-lowering medication used Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Statins/lipid-lowering medication used Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Other treatment being received Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR

32. DeFronzo, 2015

Bibliographic Reference	DeFronzo, R. A.; Lewin, A.; Patel, S.; Liu, D.; Kaste, R.; Woerle, H. J.; Broedl, U. C.; Combination of empagliflozin and linagliptin as second-line therapy in subjects with type 2 diabetes inadequately controlled on metformin; Diabetes Care; 2015; vol. 38 (no. 3); 384-93

32.1. 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	NCT01422876
Study type	Randomised controlled trial (RCT)
Study location	22 countries US Argentina Australia Brazil Bulgaria Canada Colombia Denmark Estonia

	Hungary Italy Lebanon Malaysia Mexico Peru Philippines Poland Romania Russia Spain Sweden Taiwan
Study setting	No additional information.
Study dates	08/2011 - 09/2013
Sources of funding	Boehringer Ingelheim and Eli Lilly and Company
Inclusion criteria	Subjects aged ≥18 years with BMI ≤45 kg/m2 and HbA1c >7 to ≤10.5% (>53 to ≤91 mmol/mol) at screening who had been treated with metformin immediate release (≥1,500 mg/day, maximum tolerated dose, or maximum dose according to local label) at an unchanged dose for ≥12 weeks prior to randomisation and were on a diet and exercise regimen.
Exclusion criteria	Uncontrolled hyperglycemia (glucose level >240 mg/dL after an overnight fast confirmed by a second measurement during placebo run-in); treatment with any antidiabetes drug except metformin within 12 weeks prior to randomisation; estimated glomerular filtration rate (eGFR) ,60 mL/min/1.73 m2 using the Modification of Diet in Renal Disease (MDRD) equation; acute coronary syndrome, stroke, or transient ischemic attack within 3 months prior to consent; bariatric surgery in the last 2 years; investigational drug intake within 1 month prior to consent; and treatment with anti-obesity drugs within 3 months prior to consent.
Recruitment / selection of participants	Patients taking metformin were randomised 1:1:1:1:1 to receive empagliflozin 25 mg/linagliptin 5 mg as a fixed-dose combination tablet, empagliflozin 10 mg/linagliptin 5 mg fixed-dose combination tablet, empagliflozin 25 mg, empagliflozin 10 mg, or linagliptin 5 mg for 52 weeks as add-on to metformin at an unchanged dose.

Intervention(s)	• Empagliflozin 25 mg/linagliptin 5 mg fixed-dose combination taken once daily in the morning. • Empagliflozin 10 mg/linagliptin 5 mg fixed-dose combination taken once daily in the morning. Administered orally.
Cointervention	Metformin ≥ 1,500 mg/daily, maximum tolerated dose, or maximum dose according local label. The dose had to be unchanged ≥12 weeks prior to randomisation. Administered orally.
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 prior to 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 "eGFR<60 mL/min/1.73 m2", otherwise unclear. Baseline characteristics give breakdown by eGFR but not CKD diagnosis.
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	Not stated/unclear
Subgroup 1: People with moderate or severe frailty	Not stated/unclear

Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear
Subgroup 3: People with non-alcoholic fatty liver disease	Not stated/unclear
Subgroup 4: People with obesity	Not stated/unclear
Subgroup 5: eGFR category at baseline	eGFR ≥30mL/min/1.73m2
Subgroup 6: Albuminuria category at baseline	A2 (ACR 30-300 mg/g or 3-30mg/mmol)
Population subgroups	
Comparator	Empagliflozin 25 mg once daily Empagliflozin 25 mg once daily Linagliptin 5 mg once daily Administered orally in the morning.
Number of participants	N=686
Duration of follow-up	52-week
Indirectness	No additional information.
Method of analysis	Modified ITT
Additional comments	Efficacy analysis and safety analysis included those who were treated with ≥1 dose of study drug.

32.2. Study arms

32.2.1. Empagliflozin 2g/linagliptin 5mg (N = 134)

Administered orally in the morning

32.2.2. Empagliflozin 10 mg/linagliptin 5 mg (N = 135)

Administered orally in the morning

32.2.3. Empagliflozin 25 mg (N = 140)

Administered orally in the morning

32.2.4. Empagliflozin 10 mg (N = 137)

Administered orally in the morning

32.2.5. Linagliptin 5 mg (N = 128)

Administered orally in the morning

32.3. Characteristics

32.3.1. Arm-level characteristics

Characteristic	Empagliflozin 2g/linagliptin 5mg (N = 134)	Empagliflozin 10 mg/linagliptin 5 mg (N = 135)	Empagliflozin 25 mg (N = 140)	Empagliflozin 10 mg (N = 137)	Linagliptin 5 mg (N = 128)
% Male No of events	n = 72 ; % = 53.7	n = 83 ; % = 61.5	n = 65 ; % = 46.4	n = 78 ; % = 56.9	n = 64 ; % = 50
Mean age (SD) (years) Mean (SD)	57.1 (10.2)	56.2 (10.3)	55.5 (10)	56.1 (10.5)	56.2 (10)
White No of events	n = 97 ; % = 72.4	n = 102 ; % = 75.6	n = 100 ; % = 71.4	n = 104 ; % = 75.9	n = 96 ; % = 75

Characteristic	Empagliflozin 2g/linagliptin 5mg (N = 134)	Empagliflozin 10 mg/linagliptin 5 mg (N = 135)	Empagliflozin 25 mg (N = 140)	Empagliflozin 10 mg (N = 137)	Linagliptin 5 mg (N = 128)
Asian No of events	n = 22 ; % = 16.4	n = 18 ; % = 13.3	n = 20 ; % = 14.3	n = 19 ; % = 13.9	n = 14 ; % = 10.9
Other No of events	n = 15 ; % = 11.2	n = 15 ; % = 11.1	n = 20 ; % = 14.3	n = 14 ; % = 10.2	n = 18 ; % = 14
Comorbidities Nominal	NR	NR	NR	NR	NR
Presence of frailty Nominal	NR	NR	NR	NR	NR
≤ 1 years No of events	n = 10 ; % = 7.5	n = 19 ; % = 14.1	n = 10 ; % = 7.1	n = 13 ; % = 9.5	n = 10 ; % = 7.8
> 1 to 5 years No of events	n = 46 ; % = 34.3	n = 49 ; % = 36.3	n = 50 ; % = 35.7	n = 51 ; % = 37.2	n = 44 ; % = 34.4
>5 to 10 years No of events	n = 46 ; % = 34.3	n = 41 ; % = 30.4	n = 50 ; % = 35.7	n = 39 ; % = 28.5	n = 42 ; % = 32.8
>10 years No of events	n = 32 ; % = 23.9	n = 26 ; % = 19.3	n = 30 ; % = 21.4	n = 34 ; % = 24.8	n = 32 ; % = 25
HbA1c (%) Mean (SD)	7.9 (0.79)	7.95 (0.8)	8.02 (0.83)	8 (0.93)	8.02 (0.9)
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

Characteristic	Empagliflozin 2g/linagliptin 5mg (N = 134)	Empagliflozin 10 mg/linagliptin 5 mg (N = 135)	Empagliflozin 25 mg (N = 140)	Empagliflozin 10 mg (N = 137)	Linagliptin 5 mg (N = 128)
People with significant cognitive impairment Nominal	NR	NR	NR	NR	NR
People with a learning disability Nominal	NR	NR	NR	NR	NR
Number of people with obesity Nominal	NR	NR	NR	NR	NR
Metformin No of events	n = 134 ; % = 100	n = 135 ; % = 100	n = 140 ; % = 100	n = 137 ; % = 100	n = 128 ; % = 100
Statins/lipid-lowering medication used Nominal	NR	NR	NR	NR	NR
Other treatment being received Nominal	NR	NR	NR	NR	NR

33. DeFronzo, 2005

Bibliographic Reference	DeFronzo, R. A.; Ratner, R. E.; Han, J.; Kim, D. D.; Fineman, M. S.; Baron, A. D.; Effects of exenatide (exendin-4) on glycemic control and weight over 30 weeks in metformin-treated patients with type 2; Diabetes Care; 2005; vol. 28 (no. 5); 1092-100

33.1. Study details

Secondary publication of another included study- see primary study for details	NA
Trial name / registration number	NR
Study type	Randomised controlled trial (RCT)
Study location	82 sites in the U.S.
Study setting	NR
Study dates	January 2002 to June 2003
Sources of funding	Supported by Amylin Pharmaceuticals, San Diego, California, and Eli Lilly, Indianapolis, Indiana
Inclusion criteria	19–78 years of age with type 2 diabetes treated with metformin monotherapy; screening fasting plasma glucose concentration of <13.3 mmol/l (<240 mg/dl), BMI of 27–45 kg/ m2 , and HbA1c of 7.1–11.0%; metformin dose was ≥1,500 mg/day for 3 months before screening; weight stable (+/-10%) for 3 months before screening with no clinically significant (for a type 2 diabetes population) abnormal laboratory test values (>25% outside normal laboratory values). Female subjects were postmenopausal, surgically sterile, or using contraceptives for 3 months before screening and continuing throughout the study.
Exclusion criteria	Use of sulfonylureas, meglitinides, thiazolidinediones, alpha-glucosidase inhibitors, exogenous insulin therapy, weight loss drugs, corticosteroids, drugs known to affect gastrointestinal motility, transplantation medications, or any investigational drug, or evidence of clinically significant comorbid conditions for 3 months before screening.
Recruitment / selection of participants	NR

Intervention(s)	Exenatide 20mcg daily Exenatide 10mcg daily
Cointervention	Metformin. All subjects continued their current regimen of metformin treatment (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 mellitus and chronic kidney disease	Not stated/unclear Not an inclusion/exclusion criteria. No information in baseline characteristics.
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	Not stated/unclear
Subgroup 1: People with moderate or severe frailty	Not stated/unclear
Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear
Subgroup 3: People with non-alcoholic fatty liver disease	Not stated/unclear

Subgroup 4: People with obesity	Not stated/unclear
Subgroup 5: eGFR category at baseline	Not stated/unclear
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Population subgroups	NR
Comparator	Placebo (matched placebo was used for each dose arm (with volume equivalents), however, placebo group all analysed together.
Number of participants	336
Duration of follow-up	30 week trial (4 week lead in period, 26 week treatment period)
Indirectness	None
Method of analysis	Modified ITT
Additional comments	The intent-to-treat population was defined as all randomized subjects who received at least one injection of medication starting from the evening of day 1. All efficacy and safety analyses were performed on the intent-to-treat population. For intent-to-treat subjects, missing data (including missing values at intermediate visits) were imputed from scheduled visits using the last-observation carried-forward method. Complete data available for 91 (80.5%), 90 (81.8%) and 89 (78.8%) in 20mcg, 10mcg and placebo, respectively.

33.2. Study arms

33.2.1. Exenatide 20mcg daily (N = 113)

Exenatide 20mcg (10mcg twice daily). 4-week, single-blind, lead-in period with subcutaneous injection of placebo twice daily. Acclimation period (4 weeks) at a lower exenatide fixed dose (5 g twice daily). Study medication was self-injected subcutaneously in the abdomen within 15 min before meals in the morning and evening. Any subject with either an HbA1c change of +1.5% from baseline at any clinic visit or an HbA1c ≥11.5% at week 18 or 24 could be terminated from the study for safety reasons at the investigator’s discretion (loss of glucose control).

33.2.2. Exenatide 10mcg daily (N = 110)

Exenatide 10mcg (5mcg twice daily). 4-week, single-blind, lead-in period with subcutaneous injection of placebo twice daily. Acclimation period (4 weeks) at exenatide fixed dose (5 g twice daily). Study medication was self-injected subcutaneously in the abdomen within 15 min before meals in the morning and evening. Any subject with either an HbA1c change of +1.5% from baseline at any clinic visit or an HbA1c ≥11.5% at week 18 or 24 could be terminated from the study for safety reasons at the investigator's discretion (loss of glucose control).

33.2.3. Placebo (N = 113)

Volumes of placebo equivalent to those administered to each dose arm. 4-week, single-blind, lead-in period with subcutaneous injection of placebo twice daily. Study medication was self-injected subcutaneously in the abdomen within 15 min before meals in the morning and evening. Any subject with either an HbA1c change of +1.5% from baseline at any clinic visit or an HbA1c ≥11.5% at week 18 or 24 could be terminated from the study for safety reasons at the investigator's discretion (loss of glucose control).

33.3. Characteristics

33.3.1. Arm-level characteristics

Characteristic	Exenatide 20mcg daily (N = 113)	Exenatide 10mcg daily (N = 110)	Placebo (N = 113)
% Male Sample size	n = 68 ; % = 60.2	n = 57 ; % = 51.8	n = 67 ; % = 59.3
Mean age (SD) Mean (SD)	52 (11)	53 (11)	54 (9)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
Caucasian Sample size	n = 90 ; % = 79.6	n = 85 ; % = 77.3	n = 82 ; % = 72.6
Black Sample size	n = 10 ; % = 8.8	n = 12 ; % = 10.9	n = 15 ; % = 13.3
Hispanic Sample size	n = 9 ; % = 8	n = 8 ; % = 7.3	n = 12 ; % = 10.6

Characteristic	Exenatide 20mcg daily (N = 113)	Exenatide 10mcg daily (N = 110)	Placebo (N = 113)
Other Sample size	n = 4 ; % = 3.5	n = 5 ; % = 4.6	n = 4 ; % = 3.5
Comorbidities Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Presence of frailty Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Time since type 2 diabetes diagnosed Mean (SD)	4.9 (4.7)	6.2 (5.9)	6.6 (6.1)
Cardiovascular risk factors Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Smoking status Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Alcohol consumption Mean (SD)	NR (NR)	NR (NR)	NR (NR)
Presence of severe mental illness Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
People with significant cognitive impairment Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
People with a learning disability Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Number of people with obesity Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Other antidiabetic medication used Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA
Metformin Sample size	n = 113 ; % = 100	n = 110 ; % = 100	n = 113 ; % = 100

Characteristic	Exenatide 20mcg daily (N = 113)	Exenatide 10mcg daily (N = 110)	Placebo (N = 113)
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

34. Del Prato, 2014

Bibliographic Reference	Del Prato, S.; Camisasca, R.; Wilson, C.; Fleck, P.; Durability of the efficacy and safety of alogliptin compared with glipizide in type 2 diabetes mellitus: a 2-year study; Diabetes Obes Metab; 2014; vol. 16 (no. 12); 1239-46

34.1. 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	NCT00856284
Study type	Randomised controlled trial (RCT)
Study location	310 study sites in North and South America, Europe, Asia, South Africa and Australia/New Zealand
Study setting	NR
Study dates	NR
Sources of funding	Takeda Pharmaceuticals International, Inc.
Inclusion criteria	adults aged 18–80 years with a historical diagnosis of T2DM, body mass index ≥23 and ≤45 kg/m2 (if Asian, ≥20 and ≤35 kg/m2), and inadequate glycaemic control defined in one of two ways: (i) glycated haemoglobin (HbA1c) level 7.0–9.0% with fasting plasma glucose (FPG) <15.3 mmol/l on stable metformin (≥1500 mg or maximum tolerated dose [MTD]), or (ii) HbA1c of 7.5–10% on metformin <1500 mg without documented MTD, with HbA1c values 7.0–9.0% and FPG <15.3 mmol/l after metformin stabilization (≥1500 mg or MTD) for 8 weeks.
Exclusion criteria	treatment with other antidiabetic agents within the previous 2 months; systolic blood pressure ≥150 mm Hg and/or diastolic blood pressure ≥90 mm Hg; history of cancer (other than squamous cell or basal cell

	carcinoma of the skin in full remission for ≥5 years); New York Heart Association Class III–IV heart failure; receiving alogliptin in a previous investigational study; and history of coronary angioplasty, coronary stent placement, coronary bypass surgery, myocardial infarction, stroke or transient ischaemic attack in the previous 3 months.
Recruitment / selection of participants	NR
Intervention(s)	Alogliptin Glipizide
Cointervention	Metformin: open-label metformin ≥1500 mg once daily or MTD Schedule A (patients with HbA1c 7.0–9.0% on stable metformin at ≥1500 mg or MTD) consisted of screening (up to 2 weeks), stabilization (4 weeks), treatment (104 weeks) and follow-up (2 weeks) and schedule B (patients with HbA1c 7.5–10.0% on metformin <1500 mg and below MTD) consisted of pre-screening (up to 2 weeks), titration (to metformin ≥1500 mg or MTD, 8 weeks), screening (up to 1 week), stabilization (4 weeks), treatment (104 weeks) and follow-up (2 weeks).
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear Excluded "New York Heart Association Class III–IV heart failure", otherwise unclear. No information in baseline characteristics
Strata 2: People with atherosclerotic cardiovascular disease	Not stated/unclear Excluded "history of coronary angioplasty, coronary stent placement, coronary bypass surgery, myocardial infarction, stroke or transient ischaemic attack in the previous 3 months", prior unclear. No information in baseline characteristics
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear Not an inclusion/exclusion criteria. No information in baseline characteristics
Strata 4: People with type 2 diabetes mellitus and high	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 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	NR
Comparator	NA
Number of participants	2639
Duration of follow-up	104 weeks
Indirectness	None
Method of analysis	Modified ITT
Additional comments	full analysis set included all patients receiving study medication with a baseline and at least one post-baseline assessment. The per-protocol set included all patients in the full analysis set with no major protocol violations. The safety set used for safety endpoints included all patients who took at least one dose of study medication. Missing values were extrapolated using the last observation carried forward Unable to extract weight outcome as unclear n numbers in the full analysis set for the variable of weight in order to calculate SDs.

34.2. Study arms

34.2.1. Alogliptin 12.5 mg (N = 880)

Alogliptin 12.5 mg once daily

34.2.2. Alogliptin 25 mg (N = 885)

Alogliptin 25 mg once daily

34.2.3. Glipizide (N = 874)

Glipizide 5 mg once daily with titration up to 20 mg once daily up to week 20 as needed, based on the predefined hyperglycaemia criteria (FPG ≥13.9 mmol/l, confirmed by a repeat test within 7 days) underwent dose titration of glipizide or matching placebo from 5 to ≤20 mg once daily in 5-mg increments over 4-week intervals. After week 20, the dose of glipizide (or matching placebo) was kept constant.

34.3. Characteristics

34.3.1. Arm-level characteristics

Characteristic	Alogliptin 12.5 mg (N = 880)	Alogliptin 25 mg (N = 885)	Glipizide (N = 874)
% Male Sample size	n = 419 ; % = 47.6	n = 452 ; % = 51.1	n = 441 ; % = 50.5
Mean age (SD) Mean (SD)	55.2 (9.6)	55.5 (9.81)	55.4 (9.6)
White Sample size	n = 557 ; % = 63.3	n = 555 ; % = 62.7	n = 533 ; % = 61
Asian Sample size	n = 191 ; % = 21.7	n = 207 ; % = 23.4	n = 203 ; % = 23.2
Black or African American Sample size	n = 74 ; % = 8.4	n = 66 ; % = 7.5	n = 81 ; % = 9.3
American Indian or Alaska Native	n = 40 ; % = 4.5	n = 42 ; % = 4.7	n = 36 ; % = 4.1

Characteristic	Alogliptin 12.5 mg (N = 880)	Alogliptin 25 mg (N = 885)	Glipizide (N = 874)
Sample size			
Multiracial or other Sample size	n = 18 ; % = 2	n = 15 ; % = 1.7	n = 21 ; % = 2.4
Comorbidities Nominal	NR	NR	NR
Presence of frailty Nominal	NR	NR	NR
Time since type 2 diabetes diagnosed Mean (SD)	5.7 (5.32)	5.4 (4.73)	5.5 (4.88)
Cardiovascular risk factors Nominal	NR	NR	NR
Smoking status Nominal	NR	NR	NR
Alcohol consumption Mean (SD)	NR (NR)	NR (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
Metformin dose Mean (SD)	1825.2 (405.59)	1837.2 (373.06)	1823.4 (390.63)
Blood pressure-lowering medication used	NR	NR	NR

Characteristic	Alogliptin 12.5 mg (N = 880)	Alogliptin 25 mg (N = 885)	Glipizide (N = 874)
Nominal			
Statins/lipid-lowering medication used Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Other treatment being received Nominal	NR	NR	NR

35. Del Prato, 2021

Bibliographic Reference	Del Prato, S.; Kahn, S. E.; Pavo, I.; Weerakkody, G. J.; Yang, Z.; Doupis, J.; Aizenberg, D.; Wynne, A. G.; Riesmeyer, J. S.; Heine, R. J.; et, al.; Tirzepatide versus insulin glargine in type 2 diabetes and increased cardiovascular risk (SURPASS-4): a randomised, open-label, parallel-group, multicentre, phase 3 trial; Lancet; 2021; vol. 398 (no. 10313); 1811-1824

35.1. 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	Heerspink, Hiddo J L, Sattar, Naveed, Pavo, Imre et al. (2022) Effects of tirzepatide versus insulin glargine on kidney outcomes in type 2 diabetes in the SURPASS-4 trial: post-hoc analysis of an open-label, randomised, phase 3 trial. The lancet. Diabetes & endocrinology 10(11): 774-785
Trial name / registration number	NCT03730662
Study type	Randomised controlled trial (RCT)
Study location	Multicentre trial (14 countries, 5 continents).
Study setting	Outpatient follow-up.
Study dates	November 20th 2018 to April 22nd 2021.
Sources of funding	Funded by Eli Lilly and Company. Authors received grants and honoraria from a variety of pharmaceutical companies.
Inclusion criteria	Adults (aged at least 18 years) with type 2 diabetes inadequately controlled (HbA1c 7.5-10.5%) with any of three oral glucose-lowering medications (i.e. metformin, sulfonylurea or SGLT-2 inhibitor either alone or in combination; BMI of 25kg/m2 or more; stable weight (no more than 5% fluctuation in either direction) during the previous 3 months; increased risk of cardiovascular events (defined as coronary, peripheral arterial or cerebrovascular disease or aged 50 years or older with either history of CKD and an eGFR <60mL/min/1.73m2 or history of congestive heart failure NYHA class II-III).

Exclusion criteria	Type 1 diabetes; history of pancreatitis; proliferative diabetic retinopathy or maculopathy or non-proliferative diabetic retinopathy that requires acute treatment; history of ketoacidosis or hyperosmolar state/coma; 1 or more episode of severe hypoglycaemia and/or 1 or more episode of hypoglycaemia unawareness within the 6 months prior to visit 1; known clinically significant gastric emptying abnormality, have undergone gastric bypass surgery or restrictive bariatric surgery, or chronically take drugs that affect GI motility; NYHA class IV congestive heart failure; CV conditions within 2 months of visit 1: acute MI, cerebrovascular accident, hospitalisation for heart failure; acute or chronic hepatitis, symptoms of any liver disease, ALT >3.0 times the upper limit of normal (people with NAFLD are eligible if their ALT level if <3.0 times the upper limit of normal); significant, uncontrolled endocrine abnormality; family or personal history of medullary thyroid carcinoma or Multiple Endocrine Neoplasia syndrome type 2; raised serum calcitonin level; evidence of significant, active autoimmune abnormality that requires treatment with glucocorticoids in the next 12 months; known or suspected hypersensitivity to trial products; transplanted organ or awaiting transplant; history of an active or untreated malignancy or in remission from a clinically significant malignancy for less than 5 years; history of any other condition (such as known drug, alcohol abuse or psychiatric disorder) that in the opinion of the investigator may preclude the person from following and completing the protocol); haematological condition that may interfere with HbA1c treatment; history of insulin treatment except for treatment of gestational diabetes or acute treatment for less than 14 days; chronic systemic glucocorticoid therapy for at least 2 weeks within 1 week of visit 1; any drugs that promote weight loss within 3 months prior to visit 1; participation in other trials.
Recruitment / selection of participants	No additional information.
Intervention(s)	Tirzepatide N=997 3 arms combined: Tirzepatide 5mg (n=329), tirzepatide 10mg (n=330), tirzepatide 15mg (n=338). Tirzepatide given as a once-per-week subcutaneous injection with a prefilled syringe. Initiated at 2.5mg once per week, increased by 2.5mg every 4 weeks until the randomised dose was achieved and maintained for the study duration.
Cointervention	Concomitant therapy: People remained on their background glucose-lowering medications throughout the study. These medications could be reduced or discontinued due to the occurrence of hypoglycaemia. Additional medications could be used as rescue therapy. GLP-1 receptor agonists, DPP-4 inhibitors and pramlintide were not allowed.
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear Stated people with heart failure were included in the inclusion criteria, but not explicit about how many people were included.
Strata 2: People with	People with atherosclerotic cardiovascular diseases

atherosclerotic cardiovascular disease	Inclusion criteria "increased risk of cardiovascular events, defined as known coronary, peripheral arterial, or cerebrovascular disease, OR aged 50 years or older with risk factors". Baseline characteristics show 87% had a history of CVD.
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear Stated people with CKD were included in the inclusion criteria, but not explicit about how many people were included.
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	Not stated/unclear
Subgroup 1: People with moderate or severe frailty	Not stated/unclear
Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear
Subgroup 3: People with non-alcoholic fatty liver disease	Not stated/unclear
Subgroup 4: People with obesity	Not stated/unclear
Subgroup 5: eGFR category at baseline	Not stated/unclear
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Population subgroups	No additional information.

Comparator	Insulin N=1005 Insulin glargine once a day via subcutaneous injection with a prefilled pen containing 3mL typically before bedtime. Initiated at 10 units/day, titrated up to a fasting blood glucose of less than 100mg/dL. Dose adjustments were made based on the median value of the last three self-monitored fasting blood glucose values.
Number of participants	2002
Duration of follow-up	104 weeks.
Indirectness	No additional information.
Method of analysis	Modified ITT
Additional comments	No additional information.

35.2. Study arms

35.2.1. Tirzepatide (N = 997)

3 arms combined: Tirzepatide 5mg (n=329), tirzepatide 10mg (n=330), tirzepatide 15mg (n=338). Tirzepatide given as a once-per-week subcutaneous injection with a prefilled syringe. Initiated at 2.5mg once per week, increased by 2.5mg every 4 weeks until the randomised dose was achieved and maintained for the study duration. Concomitant therapy: People remained on their background glucose-lowering medications throughout the study. These medications could be reduced or discontinued due to the occurrence of hypoglycaemia. Additional medications could be used as rescue therapy. GLP-1 receptor agonists, DPP-4 inhibitors and pramlintide were not allowed.

35.2.2. Insulin (N = 1005)

Insulin glargine once a day via subcutaneous injection with a prefilled pen containing 3mL typically before bedtime. Initiated at 10 units/day, titrated up to a fasting blood glucose of less than 100mg/dL. Dose adjustments were made based on the median value of the last three self-monitored fasting blood glucose values. Concomitant therapy: People remained on their background glucose-lowering medications throughout the study. These medications could be reduced or discontinued due to the occurrence of hypoglycaemia. Additional medications could be used as rescue therapy. GLP-1 receptor agonists, DPP-4 inhibitors and pramlintide were not allowed.

35.3. Characteristics

35.3.1. Arm-level characteristics

Characteristic	Tirzepatide (N = 997)	Insulin (N = 1005)
% Male Sample size	n = 610 ; % = 61	n = 636 ; % = 64
Mean age (SD) (years) Mean (SD)	63.4 (8.6)	63.8 (8.5)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA
Asian Sample size	n = 39 ; % = 4	n = 31 ; % = 3
Black or African American Sample size	n = 41 ; % = 4	n = 32 ; % = 3
White Sample size	n = 804 ; % = 81	n = 825 ; % = 83
Comorbidities Sample size	n = NA ; % = NA	n = NA ; % = NA
Documented coronary artery disease Sample size	n = 425 ; % = 43	n = 455 ; % = 45
Myocardial infarction Sample size	n = 302 ; % = 30	n = 344 ; % = 34
Coronary revascularisation procedure Sample size	n = 315 ; % = 32	n = 329 ; % = 33
Hospitalisation for unstable angina Sample size	n = 73 ; % = 7	n = 91 ; % = 9
Hospitalisation for heart failure Sample size	n = 72 ; % = 7	n = 68 ; % = 7
Stroke Sample size	n = 116 ; % = 12	n = 125 ; % = 12
Transient ischaemic attack	n = 45 ; % = 5	n = 53 ; % = 5

Characteristic	Tirzepatide (N = 997)	Insulin (N = 1005)
Sample size		
Peripheral artery disease Sample size	n = 304 ; % = 31	n = 302 ; % = 30
Presence of frailty Sample size	n = NA ; % = NA	n = NA ; % = NA
Time since type 2 diabetes diagnosed Median (IQR)	10.4 (5.5 to 15.7)	10.7 (6.3 to 16.5)
Smoking status Sample size	n = NR ; % = NR	n = NR ; % = NR
Alcohol consumption Sample size	n = NR ; % = NR	n = NR ; % = NR
Presence of severe mental illness Sample size	n = NR ; % = NR	n = NR ; % = NR
People with significant cognitive impairment Sample size	n = NR ; % = NR	n = NR ; % = NR
People with a learning disability Sample size	n = NR ; % = NR	n = NR ; % = NR
Number of people with obesity Sample size	n = NR ; % = NR	n = NR ; % = NR
Other antidiabetic medication used Sample size	n = NA ; % = NA	n = NA ; % = NA
SGLT2 inhibitor use Sample size	n = 245 ; % = 25	n = 256 ; % = 26
Sulfonylurea use Sample size	n = 549 ; % = 55	n = 537 ; % = 54
Metformin use Sample size	n = 939 ; % = 94	n = 954 ; % = 95
Blood pressure-lowering medication used Sample size	n = 925 ; % = 93	n = 930 ; % = 93

Characteristic	Tirzepatide (N = 997)	Insulin (N = 1005)
Statins/lipid-lowering medication used Sample size	n = 820 ; % = 82	n = 818 ; % = 82
Other treatment being received Anti-platelets Sample size	n = 685 ; % = 69	n = 704 ; % = 70

36. Del Prato, 2015

Bibliographic Reference	Del Prato, S; Nauck, M; Duran-Garcia, S; Maffei, L; Rohwedder, K; Theuerkauf, A; Parikh, S; Long-term glycaemic response and tolerability of dapagliflozin versus a sulphonylurea as add-on therapy to metformin in patients with type 2 diabetes: 4-year data.; Diabetes, obesity & metabolism; 2015; vol. 17 (no. 6); 581-590

36.1. Study details

Secondary publication of another included study- see primary study for details	Parent study: Nauck et al. (2011). Dapagliflozin versus glipizide as add-on therapy in patients with type 2 diabetes who have inadequate glycemic control with metformin: a randomized, 52-week, double-blind, active-controlled noninferiority trial. Diabetes Care; 2011; vol. 34 (no. 9); 2015-22.
Other publications associated with this study included in review	NA
Trial name / registration number	NCT00660907

37. DePaoli, 2014

Bibliographic Reference	DePaoli, Alex M; Higgins, Linda S; Henry, Robert R; Mantzoros, Christos; Dunn, Fredrick L; Can a selective PPARgamma modulator improve glycemic control in patients with type 2 diabetes with fewer side effects compared with pioglitazone?.; Diabetes care; 2014; vol. 37 (no. 7); 1918-23

37.1. 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	NCT00631007
Study type	Randomised controlled trial (RCT)
Study location	
Study setting	NR
Study dates	NR
Sources of funding	Study was funded by InteKrin Therapeutics, Inc.
Inclusion criteria	Poorly controlled T2D on sulfonylurea or sulfonylurea plus metformin. Males or females 30–75 years old with T2D ≥6 months on a stable dose (≥3 months) of sulfonylurea with or without metformin, HbA1c 7.5–10%, and FPG <240 mg/dL
Exclusion criteria	Had significant concomitant disease (e.g., CHF, ischemic heart disease, cardiac electrophysiology abnormalities, renal impairment, liver disease, uncontrolled hypertension, prior malignancy, or morbid obesity)

Recruitment / selection of participants	Eligible subjects after a 2-week screening/lead-in period
Intervention(s)	Pioglitazone was the active comparator in a trial assessing the efficacy of a non-protocol intervention (INT131 besylate)
Cointervention	Sulfonylurea or sulfonylurea plus metformin
Strata 1: People with type 2 diabetes mellitus and heart failure	People without heart failure Excluded CHF
Strata 2: People with atherosclerotic cardiovascular disease	Not stated/unclear Excluded "ischemic heart disease", otherwise unclear. No information in baseline characteristics.
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear Excluded "renal impairment", otherwise unclear. No information in baseline characteristics.
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	Not stated/unclear
Subgroup 1: People with moderate or severe frailty	Not stated/unclear
Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear
Subgroup 3: People with non-alcoholic	Not stated/unclear

fatty liver disease	
Subgroup 4: People with obesity	Not stated/unclear
Subgroup 5: eGFR category at baseline	Not stated/unclear
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Population subgroups	NR
Comparator	Placebo
Number of participants	367 in whole trial (121 in Pioglitazone and placebo arms)
Duration of follow-up	24 weeks
Indirectness	None
Method of analysis	Per protocol
Additional comments	Per-protocol (271/367) - all subjects in the ITT population who completed the 24-week double-blind treatment period without any major deviations from the protocol requirements as determined by a blinded data review prior to database lock. The safety population (366/367) was defined as all randomized subjects who received at least one dose of study drug.

37.2. Study arms

37.2.1. Pioglitazone (N = 60)

45 mg pioglitazone HCl

37.2.2. Placebo (N = 61)

37.3. Characteristics

37.3.1. Arm-level characteristics

Characteristic	Pioglitazone (N = 60)	Placebo (N = 61)
% Male Nominal	28	33
Mean age (SD) Mean (SD)	55.8 (10.4)	55.3 (10.9)
Ethnicity Nominal	NA	NA
White Nominal	47	50
Black Nominal	9	6
Hispanic Nominal	28	31
Comorbidities Nominal	NR	NR
Presence of frailty Sample size	n = NR ; % = NR	n = NR ; % = NR
Time since type 2 diabetes diagnosed Mean (SD)	8.2 (6.1)	8.9 (6.1)
Cardiovascular risk factors Nominal	NR	NR
Smoking status Nominal	NR	NR
Alcohol consumption Mean (SD)	NR (NR)	NR (NR)
Presence of severe mental illness Nominal	NR	NR
People with significant cognitive impairment	NR	NR

Characteristic	Pioglitazone (N = 60)	Placebo (N = 61)
Nominal		
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
Sulfonlyurea Sample size	n = 60 ; % = 100	n = 61 ; % = 100
Metformin Sample size	n = 48 ; % = 80	n = 49 ; % = 80.3
Blood pressure-lowering medication used Nominal	NR	NR
Statins/lipid-lowering medication used Nominal	NR	NR
Other treatment being received Nominal	NR	NR

38. Derosa, 2014

Bibliographic Reference	Derosa, G.; Bonaventura, A.; Bianchi, L.; Romano, D.; Fogari, E.; D'Angelo, A.; Maffioli, P.; Vildagliptin compared to glimepiride on post-prandial lipemia and on insulin resistance in type 2 diabetic patients; Metabolism; 2014; vol. 63 (no. 7); 957-967

38.1. Study details

Secondary publication of another included study- see primary study for details	N/A
Other publications associated with this study included in review	Derosa, G, Bonaventura, A, Bianchi, L et al. (2014) Comparison of vildagliptin and glimepiride: effects on glycaemic control, fat tolerance and inflammatory markers in people with type 2 diabetes. Diabetic medicine : a journal of the British Diabetic Association 31(12): 1515-23
Trial name / registration number	NR
Study type	Randomised controlled trial (RCT)
Study location	Italy
Study setting	Department of Internal Medicine and Therapeutics, University of Pavia
Study dates	NR
Sources of funding	NR
Inclusion criteria	• Type 2 diabetic patients according to the ESC (European Society of Cardiology) and EASD (European Association for the Study of Diabetes) Guidelines criteria [26] • Aged ≥ 18 years • Inadequately controlled type 2 diabetes mellitus [glycated haemoglobin (HbA1c) between 7.0% and 9.0%] in therapy with metformin at the maximum tolerated dose.
Exclusion criteria	• History of ketoacidosis or had unstable or rapidly progressive diabetic retinopathy, nephropathy, or neuropathy

	• Impaired hepatic function (defined as plasma aminotransferase and/or gamma glutamyl transferase level higher than the upper limit of normal [ULN] for age and sex) • Impaired renal function (defined as serum creatinine level higher than the ULN for age and sex) • Severe anaemia • Patients taking statins or drugs affecting lipid profile (to avoid interference with OFL) • Patients could not start statins or drugs affecting lipid profile for the entire duration of the study • Patients with serious cardiovascular disease (CVD) (e.g., New York Heart Association class I–IV congestive heart failure or a history of myocardial infarction or stroke) or cerebrovascular conditions within 6 months before study enrolment • Patients with a history of pancreatitis • Women who were pregnant or breastfeeding or of childbearing potential and not taking adequate contraceptive precautions
Recruitment / selection of participants	Suitable patients were identified from a review of case notes and/or computerized clinic registers and were contacted by the investigators in person or by telephone.
Intervention(s)	• Vildagliptin 50 mg twice a day + one dummy tablet to maintain double-blind study design • Glimepiride 2 mg three times a day
Cointervention	• Metformin including 1-month run-in period in which metformin dose was maintained stable • Controlled-energy diet (nearly 600 kcal daily deficit) based on American Heart Association (AHA) recommendations • Standard diet advice given by a dietitian and/or specialist doctor • Individuals were encouraged to increase their physical activity
Strata 1: People with type 2 diabetes mellitus and heart failure	People without heart failure Excluded "New York Heart Association class I-IV congestive heart failure"
Strata 2: People with atherosclerotic cardiovascular disease	Not stated/unclear Excluded "serious CVD or cerebrovascular conditions within 6 months before study enrolment", otherwise unclear. No information in baseline characteristics.
Strata 3: People with type 2 diabetes mellitus and	Not stated/unclear Excluded "impaired renal function (defined as serum creatinine level higher than the upper limit of normal for age and sex)", otherwise unclear. No information in baseline characteristics.

chronic kidney disease	
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	Not stated/unclear
Subgroup 1: People with moderate or severe frailty	Not stated/unclear
Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear
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	NR
Comparator	N/A
Number of participants	178 participants were enrolled in the study and 167 were randomised. 11 participants in the glimepiride group and 3 participants in the vildagliptin group did not complete the study.
Duration of follow-up	3 and 6 months

Indirectness	Directly applicable
Method of analysis	ITT An intention-to-treat analysis was conducted in patients who had received ≥ 1 dose of study medication and had a subsequent efficacy observation. Intervention effects were adjusted for additional potential confounders (sex, smoking status) using analysis of covariance (ANCOVA). ANOVA was also used to assess the significance within and between groups. The statistical significance of the independent effects of treatments on the other variables was determined using ANCOVA taking the baseline level of each parameter as a covariate.
Additional comments	Considering a clinically significant difference of at least 10% compared to the baseline and an error of 0.05, the actual sample size was reported to be adequate to obtain a power higher than 0.80 for all measured variables.

38.2. Study arms

38.2.1. Glimepiride (N = 81)

38.2.2. Vildagliptin (N = 86)

38.3. Characteristics

38.3.1. Arm-level characteristics

Characteristic	Glimepiride (N = 81)	Vildagliptin (N = 86)
% Male Percentage calculated by analyst Sample size	n = 40 ; % = 49.4	n = 42 ; % = 48.8
Mean age (SD) (years) Mean (SD)	57.2 (9)	59.8 (9.9)
Ethnicity Caucasian Sample size	n = 81 ; % = 100	n = 86 ; % = 100
Comorbidities Nominal	NR	NR

Characteristic	Glimepiride (N = 81)	Vildagliptin (N = 86)
Presence of frailty Nominal	NR	NR
Time since type 2 diabetes diagnosed (Months) Mean (SD)	6.8 (3.6)	6.9 (4.7)
Cardiovascular risk factors Nominal	NR	NR
Smoking status Percentages calculated by analyst Sample size	n = 23 ; % = 28.4	n = 25 ; % = 29.1
Male Sample size	n = 12 ; % = 30	n = 14 ; % = 33.3
Female Sample size	n = 11 ; % = 26.8	n = 11 ; % = 25
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	Glimepiride (N = 81)	Vildagliptin (N = 86)
Other treatment being received Nominal	NR	NR

39. Derosa, 2012

Bibliographic Reference	Derosa, G.; Carbone, A.; D'Angelo, A.; Querci, F.; Fogari, E.; Cicero, A. F.; Maffioli, P.; A randomized, double-blind, placebo-controlled trial evaluating sitagliptin action on insulin resistance parameters and beta-cell function; Expert Opin Pharmacother; 2012; vol. 13 (no. 17); 2433-42

39.1. Study details

Secondary publication of another included study- see primary study for details	N/A
Other publications associated with this study included in review	N/A
Trial name / registration number	NR
Study type	Randomised controlled trial (RCT)
Study location	Multicentre study in Italy
Study setting	Department of Internal Medicine and Therapeutics, University of Pavia, Pavia; at the Hospital Center of Diabetes, Sant'Angelo Lodigiano, Lodi; at the Ospedale Pesenti Fenaroli, Alzano Lombardo, Bergamo; and at the Aging and Kidney diseases, "G. Descovich" Atherosclerosis Study Center, University of Bologna, Bologna
Study dates	NR
Sources of funding	• University of Pavia • Sigma-Tau
Inclusion criteria	• Type 2 diabetes according to the ESC Table (European Society of Cardiology) and EASD (European Association for the Study of Diabetes) Guidelines criteria • Aged >18 years • Treatment naïve, and with poor glycaemic control, expressed as glycated hemoglobin (HbA1c) level > 8.0 %,

	• With overweight or slight obesity [body mass index (BMI) >=25 and < 33 kg/m2]
Exclusion criteria	• History of ketoacidosis or had unstable or rapidly progressive diabetic retinopathy, nephropathy, or neuropathy • Impaired hepatic function (defined as plasma aminotransferase and/or gamma glutamyl transferase level higher than the upper limit of normal [ULN] for age and sex), impaired renal function (defined as serum creatinine level higher than the ULN for age and sex), or severe anaemia. • Serious cardiovascular disease (CVD) (e.g., New York Heart Association class I-IV congestive heart failure or a history of myocardial infarction or stroke) or cerebrovascular conditions within 6 months before study enrolment • Women who were pregnant or breastfeeding or of childbearing potential and not taking adequate contraceptive precautions
Recruitment / selection of participants	Suitable participants were identified from reviewing case notes and/or computerized clinic registers and were contacted personally or by telephone. All eligible candidates had to provide signed informed consent before enrolling in the study.
Intervention(s)	Sitagliptin 100 mg once per day
Cointervention	• During a run-in period of 8 ± 2 months before randomisation, participants received unblinded treatment with metformin, which was gradually titrated until a mean dosage of 2500 ± 500 mg/day. • Controlled-energy diet (near 600 kcal daily deficit) based on American Heart Association (AHA) recommendations • Standard diet advice was given by a dietitian and/or specialist doctor • Individuals were encouraged to increase their physical activity
Strata 1: People with type 2 diabetes mellitus and heart failure	People without heart failure Excluded "New York Heart Association class I-IV congestive heart failure"
Strata 2: People with atherosclerotic cardiovascular disease	Not stated/unclear Excluded "serious CVD or cerebrovascular conditions within 6 months before study enrolment", otherwise unclear. No information in baseline characteristics.
Strata 3: People with type 2 diabetes mellitus and	Not stated/unclear Excluded "impaired renal function (defined as serum creatinine level higher than the upper limit of normal for age and sex)", otherwise unclear. No information in baseline characteristics.

chronic kidney disease	
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	Not stated/unclear
Subgroup 1: People with moderate or severe frailty	Not stated/unclear
Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear
Subgroup 3: People with non-alcoholic fatty liver disease	Not stated/unclear
Subgroup 4: People with obesity	Not stated/unclear Inclusion criteria: "in over-weight or slightly obese [body mass index (BMI) ≥ 25 and < 33 kg/m2." No information on number of participants included with obesity.
Subgroup 5: eGFR category at baseline	Not stated/unclear
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Population subgroups	N/A
Comparator	Placebo
Number of participants	181 participants were enrolled in the study, and 178 participants completed the run-in period. There were 12 patients who did not complete the study (3 at randomisation, 5 in the sitagliptin arm, and 4 in the placebo arm).

Duration of follow-up	3, 6, 9 and 12 months
Indirectness	Partially direct - the study recruited participants who were treatment naïve, and participants may have responded sufficiently to metformin alone prior to randomisation to either sitagliptin or placebo
Method of analysis	ITT All patients randomized with at least one post-randomization measure were analysed, i.e., intent-to-treat. Continuous variables were evaluated using analysis of variance (ANOVA) tests. Intervention effects were adjusted for the presence of potential confounding variables using analysis of covariance (ANCOVA).
Additional comments	A sample size of 85 patients per group was required to provide 90% power to detect a significant between-group difference in AIRarg.

39.2. Study arms

39.2.1. Sitagliptin (N = 91)

39.2.2. Placebo (N = 87)

39.3. Characteristics

39.3.1. Arm-level characteristics

Characteristic	Sitagliptin (N = 91)	Placebo (N = 87)
% Male Sample size	n = 42 ; % = 46.2	n = 44 ; % = 50.6
Mean age (SD) Mean (SD)	55.9 (8.8)	54.8 (7.9)
Ethnicity Caucasian Sample size	n = 91 ; % = 100	n = 87 ; % = 100
Comorbidities Nominal	NR	NR

Characteristic	Sitagliptin (N = 91)	Placebo (N = 87)
Presence of frailty Nominal	NR	NR
Time since type 2 diabetes diagnosed (Months) Mean (SD)	5.8 (2.6)	5.4 (2.3)
Cardiovascular risk factors Nominal	NR	NR
Smoking status % calculated by analyst Sample size	n = 22 ; % = 24.2	n = 23 ; % = 26.4
Male Sample size	n = 11 ; % = 26.2	n = 13 ; % = 29.5
Female Sample size	n = 11 ; % = 22.4	n = 10 ; % = 23.3
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
Other treatment being received	NR	NR

Characteristic	Sitagliptin (N = 91)	Placebo (N = 87)
Nominal		

40. Derosa, 2010

Bibliographic Reference	Derosa, G.; Maffioli, P.; Salvadeo, S. A.; Ferrari, I.; Ragonesi, P. D.; Querci, F.; Franzetti, I. G.; Gadaleta, G.; Ciccarelli, L.; Piccinni, M. N.; D'Angelo, A.; Cicero, A. F.; Effects of sitagliptin or metformin added to pioglitazone monotherapy in poorly controlled type 2 diabetes mellitus patients; Metabolism; 2010; vol. 59 (no. 6); 887-95

40.1. 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	NR
Study type	Randomised controlled trial (RCT)
Study location	Multicentre study in Italy
Study setting	Department of Internal Medicine and Therapeutics, University of Pavia, Pavia; the “G Descovich” Atherosclerosis Study Center, Department of Internal Medicine, Aging and Kidney Diseases, University of Bologna, Bologna; the Diabetes Care Unit, S Carlo Hospital, Milano; the Pesenti Fenaroli Hospital, Alzano Lombardo, Bergamo; the Metabolic Unit, Regional Hospital, Varese; the Division of Medicine, Civic Hospital (Cittiglio, Varese; the RSA Don Leone Porta, Milano; and the Fondazione Ospedale della Carità (Casalbuttano, Cremona.
Study dates	NR
Sources of funding	NR
Inclusion criteria	• T2DM according to the European Society of Cardiology and the European Association for the Study of Diabetes guidelines criteria with uncontrolled T2DM (HbA1c>7.5%) in therapy with pioglitazone.

	• Aged >=18 years
Exclusion criteria	• History of ketoacidosis or unstable or rapidly progressive diabetic retinopathy, nephropathy, or neuropathy • Impaired hepatic function • Impaired renal function (defined as serum creatinine level higher than the upper limit of normal for age and sex) • Severe anaemia • Serious cardiovascular disease (e.g., New York Heart Association class I-IV congestive heart failure or a history of myocardial infarction or stroke) or cerebrovascular conditions within 6 months before study enrolment • Women who were pregnant or breastfeeding or of child bearing potential and not taking adequate contraceptive precautions
Recruitment / selection of participants	Suitable patients, who were identified from review of case notes and/or computerized clinic registers, were contacted by the investigators in person or by telephone. All patients provided written informed consent to participate.
Intervention(s)	Sitagliptin 100 mg once a day for 12 months
Cointervention	• Pioglitazone (sitagliptin arm: 30 mg once a day; metformin arm: 15 mg twice a day) • Controlled-energy diet (near 600 kcal daily deficit) based on American Heart Association recommendations • Standard diet advice was given by a dietician and/or specialist physician • Participants were encouraged to increase their physical activity
Strata 1: People with type 2 diabetes mellitus and heart failure	People without heart failure Excluded "New York Heart Association class I-IV congestive heart failure"
Strata 2: People with atherosclerotic cardiovascular disease	Not stated/unclear Excluded "serious CVD or cerebrovascular conditions within 6 months before study enrolment", 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 (defined as serum creatinine level higher than the upper limit of normal for age and sex)", 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 Exclusion criteria: "Serious cardiovascular disease (e.g., New York Heart Association class I-IV congestive heart failure or a history of myocardial infarction or stroke) or cerebrovascular conditions within 6 months before study enrolment"
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	NR
Comparator	Metformin 850 mg twice a day
Number of participants	151 participants were enrolled, and 137 participants completed the study. There were 14 participants who did not complete the study.
Duration of follow-up	3, 6, 9 and 12 months
Indirectness	Directly applicable

Method of analysis	ITT An intention-to-treat analysis was conducted in patients who had received at least 1 dose of study medication and had a subsequent efficacy observation. Intervention effects were adjusted for additional potential confounders using analysis of covariance.
Additional comments	NA

40.2. Study arms

40.2.1. Sitagliptin (N = 75)

40.2.2. Metformin (N = 76)

40.3. Characteristics

40.3.1. Arm-level characteristics

Characteristic	Sitagliptin (N = 75)	Metformin (N = 76)
% Male % calculated by reviewer Sample size	n = 37 ; % = 49.3	n = 39 ; % = 51.3
Mean age (SD) Mean (SD)	57 (5)	58 (6)
Ethnicity White Sample size	n = 75 ; % = 100	n = 76 ; % = 100
Comorbidities Nominal	NR	NR
Presence of frailty Nominal	NR	NR
Time since type 2 diabetes diagnosed Mean (SD)	5 (2)	6 (3)

Characteristic	Sitagliptin (N = 75)	Metformin (N = 76)
Cardiovascular risk factors Nominal	NR	NR
Smoking status % calculated by reviewer Sample size	n = NA	n = NA
Male Sample size	n = 12 ; % = 16	n = 16 ; % = 21.1
Female Sample size	n = 15 ; % = 20	n = 14 ; % = 18.4
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
Statins/lipid-lowering medication used Nominal	NR	NR
Other treatment being received Nominal	NR	NR

41. Derosa, 2011

Bibliographic Reference	Derosa, G.; Putignano, P.; Bossi, A. C.; Bonaventura, A.; Querci, F.; Franzetti, I. G.; Guazzini, B.; Testori, G.; Fogari, E.; Maffioli, P.; Exenatide or glimepiride added to metformin on metabolic control and on insulin resistance in type 2 diabetic patients; Eur J Pharmacol; 2011; vol. 666 (no. 13); 251-6

41.1. 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	NR
Study type	Randomised controlled trial (RCT)
Study location	Multicentre trial in Italy
Study setting	Department of Internal Medicine and Therapeutics, University of Pavia, Pavia; Outpatient Diabetic Clinic, S. Gerardo Hospital, Monza; Metabolic Diseases and Diabetes Unit Treviglio Hospital, Bergamo; Hospital Pesenti Fenaroli, Alzano Lombardo, Bergamo; Metabolic Unit, Regional Hospital, Varese; Hospital of Melegnano, Milano; Diabetes Unit, Fatebenefratelli Hospital, Milano
Study dates	NR
Sources of funding	NR
Inclusion criteria	• Type 2 diabetes according to the ESC (European Society of Cardiology) and EASD (European Association for the Study of Diabetes) Guidelines criteria • Aged 18 years and older

	• Poor glycaemic control, expressed as glycated haemoglobin (HbA1c) level >8.0%, and with overweight [body mass index (BMI)>= 25, and <30 kg/m2 • Participants were taking metformin at various different doses (1000–2000 mg/day) and were intolerant to metformin at the highest dosages (2500–3000 mg/day)
Exclusion criteria	• History of ketoacidosis • Unstable or rapidly progressive diabetic retinopathy, nephropathy, or neuropathy • Impaired hepatic function (defined as plasma aminotransferase and/or gamma-glutamyltransferase level higher than the upper limit of normal [ULN] for age and sex) • Impaired renal function (defined as serum creatinine level higher than the ULN for age and sex) • Severe anaemia • Serious cardiovascular disease (CVD) (e.g., New York Heart Association classes I–IV congestive heart failure or a history of myocardial infarction or stroke) or cerebrovascular conditions within 6 months before study enrolment • Women who were pregnant or breastfeeding or of childbearing potential and not taking adequate contraceptive precautions
Recruitment / selection of participants	Suitable patients, were identified from reviewing case notes and/or computerized clinic registers and were contacted by the investigators in person or by telephone.
Intervention(s)	• Exenatide: exenatide 5 µg twice a day titrated after 1 month to exenatide 10 µg twice a day for 12 months • Glimepiride: glimepiride 1 mg three times a day titrated after 1 month to glimepiride 2 mg three times a day for 12 months
Cointervention	• Metformin at various different doses (1000–2000 mg/day) • Controlled-energy diet (near 600 Kcal daily deficit based on American Heart Association (AHA) recommendations • Standard diet advice was given by a dietitian and/or specialist doctor • Individuals were also encouraged to increase their physical activity
Strata 1: People with type 2 diabetes mellitus and heart failure	People without heart failure Excluded "New York Heart Association class I-IV congestive heart failure"
Strata 2: People with atherosclerotic cardiovascular disease	Not stated/unclear Excluded "serious CVD or cerebrovascular conditions within 6 months before study enrolment", 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 (defined as serum creatinine level higher than the upper limit of normal for age and sex)", 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	People who do not have obesity Participants with overweight [body mass index (BMI)>= 25, and <30 kg/m2
Subgroup 5: eGFR category at baseline	Not stated/unclear
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Population subgroups	NR
Comparator	N/A

Number of participants	111 participants were enrolled, and 101 participants completed the study. 10 participants did not complete the study, including 5 participants in the exenatide group and 5 participants in the glimepiride group.
Duration of follow-up	3, 6, 9, and 12 months
Indirectness	Directly applicable
Method of analysis	ITT An intention-to-treat analysis was conducted in patients who had received one or more doses of study medication, did not show any acute adverse reactions, and had a subsequent efficacy observation. Continuous variables were tested using a two-way repeated measures analysis of variance (ANOVA). Intervention effects were adjusted for additional potential confounders using analysis of covariance.
Additional comments	Every patient who had received at least one dose of the study medication underwent a tolerability observation to exclude the presence of acute adverse reactions.

41.2. Study arms

41.2.1. Exenatide (N = 57)

41.2.2. Glimepiride (N = 54)

41.3. Characteristics

41.3.1. Arm-level characteristics

Characteristic	Exenatide (N = 57)	Glimepiride (N = 54)
% Male % calculated by analyst Sample size	n = 28 ; % = 49	n = 26 ; % = 48
Mean age (SD) Mean (SD)	56 (7)	55 (6)
Ethnicity Caucasian Sample size	n = 57 ; % = 100	n = 54 ; % = 100

Characteristic	Exenatide (N = 57)	Glimepiride (N = 54)
Comorbidities Nominal	NR	NR
Presence of frailty Nominal	NR	NR
Time since type 2 diabetes diagnosed Nominal	NR	NR
Cardiovascular risk factors Nominal	NR	NR
Smoking status % calculated by analyst Sample size	n = 27 ; % = 47.4	n = 23 ; % = 42.6
Male Sample size	n = 12 ; % = 21.1	n = 11 ; % = 20.4
Female Sample size	n = 15 ; % = 26.3	n = 12 ; % = 22.2
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	Exenatide (N = 57)	Glimepiride (N = 54)
Nominal		
Other treatment being received Nominal	NR	NR

42. Derosa, 2012

Bibliographic Reference	Derosa, G.; Ragonesi, P. D.; Carbone, A.; Fogari, E.; Bianchi, L.; Bonaventura, A.; Romano, D.; Cicero, A. F. G.; Maffioli, P.; Vildagliptin added to metformin on beta-cell function after a euglycemic hyperinsulinemic and hyperglycemic clamp in type 2 diabetes patients; Diabetes Technol Ther; 2012; vol. 14 (no. 6); 475-84

42.1. Study details

Secondary publication of another included study- see primary study for details	Derosa, Giuseppe, Ragonesi, Pietro D, Carbone, Anna et al. (2012) Vildagliptin action on some adipocytokine levels in type 2 diabetic patients: a 12-month, placebo-controlled study. Expert opinion on pharmacotherapy 13(18): 2581-91
Other publications associated with this study included in review	
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear Excluded "New York Heart Association class I-IV congestive heart failure"
Strata 2: People with atherosclerotic cardiovascular disease	Not stated/unclear Excluded "serious CVD or cerebrovascular conditions within 6 months before study enrolment", 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 (defined as serum creatinine level higher than the upper limit of normal for age and sex)", otherwise unclear. No information in baseline characteristics.

42.2. Study arms

42.2.1. Vildagliptin (N = 84)

42.2.2. Placebo (N = 83)

43. Derosa, 2014

Bibliographic Reference	Derosa, G.; Ragonesi, P. D.; Fogari, E.; Cicero, A. F. G.; Bianchi, L.; Bonaventura, A.; Romano, D.; Maffioli, P.; Sitagliptin added to previously taken antidiabetic agents on insulin resistance and lipid profile: A 2-year study evaluation; Fundam Clin Pharmacol; 2014; vol. 28 (no. 2); 221-229

43.1. 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	NR
Study type	Randomised controlled trial (RCT)
Study location	Multicentre trial in Italy
Study setting	Department of Internal Medicine and Therapeutics, University of Pavia, Pavia; at the Diabetes Care Unit, S. Carlo Hospital, Milano; and at the 'G. Descovich' Atherosclerosis Study Center, Department of Internal Medicine, Aging and Kidney diseases, University of Bologna, Bologna
Study dates	NR
Sources of funding	NR
Inclusion criteria	• Patients with type 2 diabetes according to the ESC (European Society of Cardiology) and EASD Guidelines criteria • Aged ≥18 years • Uncontrolled type 2 diabetes mellitus (HbA1c > 7.0%) in therapy with different antidiabetic drugs from at least 6 months
Exclusion criteria	• History of ketoacidosis or had unstable or rapidly progressive diabetic retinopathy, nephropathy, or neuropathy and impaired

	hepatic function (defined as plasma amino transferase and/or gamma-glutamyltransferase level higher than the upper limit of normal [ULN] for age and sex) • Impaired renal function (defined as serum creatinine level higher than the ULN for age and sex) • Severe anemia • Patients with serious cardiovascular disease (CVD, e.g. New York Heart Association class III–IV congestive heart failure or a history of myocardial infarction or stroke) or cerebrovascular conditions within 6 months before study enrolment • Women who were pregnant or breastfeeding or of childbearing potential and not taking adequate contraceptive precautions
Recruitment / selection of participants	Suitable patients were identified from review of case notes and/or computerized clinic registers, and were contacted by the investigators in person or by telephone.
Intervention(s)	Sitagliptin 100 mg once daily
Cointervention	• Participants were already following a controlled-energy diet (near 600 Kcal daily deficit based on American Heart Association (AHA) recommendations • Standard diet advice was given by a dietitian and/or specialist doctor • Individuals were also encouraged to increase their physical activity
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear Excluded "New York Heart Association class III-IV congestive heart failure", otherwise unclear.
Strata 2: People with atherosclerotic cardiovascular disease	Not stated/unclear Excluded "serious CVD or cerebrovascular conditions within 6 months before study enrolment", 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 (defined as serum creatinine level higher than the upper limit of normal for age and sex)", otherwise unclear. No information in baseline characteristics.
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	N/A
Comparator	Placebo
Number of participants	205 participants were enrolled in the study and 197 participants completed the study. 7 participants in the placebo arm and 1 participant in the sitagliptin arm did not complete the study.
Duration of follow-up	6, 12, 18, and 24 months
Indirectness	Directly applicable
Method of analysis	ITT An intention-to-treat analysis was conducted in patients who had received 1 dose of study medication and had a subsequent efficacy observation. Continuous variables were compared by analysis of variance (ANOVA). Intervention effects were adjusted for additional potential confounders using analysis of covariance (ANCOVA). ANOVA was also used to assess

	the significance within and between groups. The statistical significance of the independent effects of treatments on the other variables was determined using ANCOVA.
Additional comments	N/A

43.2. Study arms

43.2.1. Sitagliptin (N = 102)

43.2.2. Placebo (N = 103)

43.3. Characteristics

43.3.1. Study-level characteristics

Characteristic	**Study (N = 205)**
Mean age (SD) Nominal	NR
Ethnicity Caucasian Sample size	n = 205 ; % = 100
Comorbidities Nominal	NR
Presence of frailty Nominal	NR
Time since type 2 diabetes diagnosed Nominal	NR
Cardiovascular risk factors Nominal	NR
Smoking status Nominal	NR

Characteristic	Study (N = 205)
Alcohol consumption Nominal	NR
Presence of severe mental illness Nominal	NR
People with significant cognitive impairment Nominal	NR
People with a learning disability Nominal	NR
Number of people with obesity Nominal	NR
Other antidiabetic medication used Sample size	n = NA
Sulfonlyureas - all Sample size	n = 52 ; % = 25.4
Sulfonlyureas - Glyburide % as a proportion of all sulfonylureas Sample size	n = 4 ; % = 7.7
Sulfonlyureas - Glimepiride % as a proportion of all sulfonylureas Sample size	n = 30 ; % = 57.7
Sulfonlyureas - Gliclazide % as a proportion of all sulfonylureas Sample size	n = 18 ; % = 34.6
Glinides - all Sample size	n = 38 ; % = 18.5
Glinides - Repaglinide % as a proportion of all glinides Sample size	n = 38 ; % = 100
Alpha-glucosidase inhibitor - all Sample size	n = 28 ; % = 13.6

Characteristic	Study (N = 205)
Acarbose % as a proportion of alpha-glucosidase inhibitors Sample size	n = 28 ; % = 100
Thiazolidinediones - all Sample size	n = 42 ; % = 20.5
Pioglitazone % as a proportion of thiazolidinediones Sample size	n = 38 ; % = 90.5
Rosiglitazone % as a proportion of thiazolidinediones Sample size	n = 4 ; % = 9.5
Blood pressure-lowering medication used Nominal	NR
Statins/lipid-lowering medication used Sample size	n = 185 ; % = 90.2
Fluvastatin Sample size	n = 10 ; % = 5.4
Simvastatin Sample size	n = 64 ; % = 34.6
Atorvastatin Sample size	n = 80 ; % = 43.2
Rosuvastatin Sample size	n = 31 ; % = 16.8
Other treatment being received Nominal	NR

43.3.2. Arm-level characteristics

Characteristic	Sitagliptin (N = 102)	Placebo (N = 103)
% Male Sample size	n = 50 ; % = 49	n = 50 ; % = 48.5

44. Derosa, 2014

Bibliographic Reference	Derosa, G; Bonaventura, A; Bianchi, L; Romano, D; Fogari, E; D'Angelo, A; Maffioli, P; Comparison of vildagliptin and glimepiride: effects on glycaemic control, fat tolerance and inflammatory markers in people with type 2 diabetes.; Diabetic medicine : a journal of the British Diabetic Association; 2014; vol. 31 (no. 12); 1515-23

44.1. Study details

Secondary publication of another included study- see primary study for details	Derosa, G., Bonaventura, A., Bianchi, L. et al. (2014) Vildagliptin compared to glimepiride on post-prandial lipemia and on insulin resistance in type 2 diabetic patients. Metabolism 63(7): 957-967 This paper was retracted as it is a dual publication of the above parent paper. Kept this paper included as the baseline medication usage was reported here.
Strata 1: People with type 2 diabetes mellitus and heart failure	People without heart failure Excluded "New York Heart Association class I–IV congestive heart failure".
Strata 2: People with atherosclerotic cardiovascular disease	Not stated/unclear Excluded "CVD within 6 months", prior 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.

45. Derosa, 2012

Bibliographic Reference	Derosa, G; Franzetti, I G; Querci, F; Carbone, A; Ciccarelli, L; Piccinni, M N; Fogari, E; Maffioli, P; Exenatide plus metformin compared with metformin alone on beta-cell function in patients with Type 2 diabetes.; Diabetic medicine : a journal of the British Diabetic Association; 2012; vol. 29 (no. 12); 1515-23

45.1. Study details

Secondary publication of another included study- see primary study for details	NR
Other publications associated with this study included in review	Derosa, G., Cicero, A. F. G., Franzetti, I. G. et al. (2013) Effects of exenatide and metformin in combination on some adipocytokine levels: A comparison with metformin monotherapy. Can J Physiol Pharmacol 91(9): 724-732 Derosa, Giuseppe, Franzetti, Ivano G, Querci, Fabrizio et al. (2013) Variation in inflammatory markers and glycemic parameters after 12 months of exenatide plus metformin treatment compared with metformin alone: a randomized placebo-controlled trial. Pharmacotherapy 33(8): 817-26
Trial name / registration number	NR
Study type	Randomised controlled trial (RCT)
Study location	Multicentre study in Italy
Study setting	Department of Internal Medicine and Therapeutics, University of Pavia, Metabolic Unit, Regional Hospital, Varese, Ospedale Pesenti Fenaroli, Alzano Lombardo, Bergamo, Hospital Centre of Diabetes, Sant'Angelo Lodigiano, Lodi, RSA Villa Mafalda, Borgo San Siro, Pavia, and Fondazione Ospedale della Carita`, Casalbuttano, Cremona.
Study dates	NR
Sources of funding	None

Inclusion criteria	• Type 2 diabetes according to the European Society of Cardiology and European Association for the Study of Diabetes Guidelines criteria • Aged > 18 years • Naive and with poor glycaemic control, expressed as glycated haemoglobin ((HbA1c) level > 64 mmol/mol (8.0%), but <97 mmol /mol (11%) • With overweight (BMI >= 25 and < 30 kg /m2).
Exclusion criteria	• History of ketoacidosis • Rapidly progressive diabetic retinopathy • Nephropathy (defined by onset of albumin excretion >300 mg/24 h or albumin excretion rate >200 ug/min over a 6-month period) • Neuropathy • Impaired hepatic function • Impaired renal function (defined as serum creatinine level higher than the upper limit of normal for age and sex) • Severe anaemia • Serious cardiovascular disease, or New York Heart Association class I–IV congestive heart failure • History of myocardial infarction or stroke or cerebrovascular conditions (ischaemic stroke, haemorrhagic stroke, or transient ischemic attack) within 6 months before study enrolment • Women who were pregnant, or breastfeeding or of childbearing potential and not taking adequate contraceptive precautions
Recruitment / selection of participants	Suitable subjects, and/ identified from review of case notes or computerized clinic registers, were contacted personally or by telephone. All eligible candidates had to provide signed, informed consent before enrolling in the study.
Intervention(s)	Exenatide (5 ug twice a day for the first 4 weeks and forced titration to 10 ug twice a day thereafter) for 12 months. [Treatment was injected in the upper arm, thigh or abdomen within 60 min before morning and evening meals. Throughout the study, patients were instructed to take their first dose of new medication on the day after they were given the study medication.]
Cointervention	• Prior to randomisation to exenatide or placebo, participants completed an unblinded 8±2 month run-in period where they were treated with metformin gradually titrated to a mean dosage of 2500 ± 500 mg/day. • At baseline subjects began a controlled-energy diet (near 600 Kcal daily deficit) based on American Heart Association recommendation. • Standard diet advice was given by a dietitian and/or specialist doctor. A dietitian and/or specialist doctor periodically provided instruction on dietary intake, recording procedures as part of a behaviour modification programme and then later used the subject's food diaries for counselling.

	• Individuals were also encouraged to increase their physical activity by walking briskly for 20–30 min, three to five times per week, or by cycling.
Strata 1: People with type 2 diabetes mellitus and heart failure	People without heart failure People with "New York Heart Association class I–IV congestive heart failure" were excluded
Strata 2: People with atherosclerotic cardiovascular disease	Not stated/unclear Exclusion criteria include "serious cardiovascular disease" and "history of myocardial infarction or stroke or cerebrovascular conditions (ischaemic stroke, haemorrhagic stroke, or transient ischemic attack) within 6 months before study enrolment"
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear Excluded "impaired renal function (defined as serum creatinine level higher than the ULN for age and gender)", 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	People who do not have obesity Participants with BMI >= 25 and < 30 kg /m2 were included.
Subgroup 5: eGFR category at baseline	Not stated/unclear
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Population subgroups	NR
Comparator	Placebo of equivalent volume to the intervention. [Treatment was injected in the upper arm, thigh or abdomen within 60 min before morning and evening meals. Throughout the study, patients were instructed to take their first dose of new medication on the day after they were given the study medication.]
Number of participants	174 participants were enrolled and 171 participants completed the run-in period. 11 participants did not complete the study (5 participants in the exenatide group, 3 participants in the placebo group, and 3 participants at randomisation).
Duration of follow-up	3, 6, 9 and 12 months
Indirectness	Partially direct - participants were treatment naive prior to initiation of the metformin run-in period, and the population included participants that may have responded adequately to metformin alone.
Method of analysis	ITT All patients randomized with at least one post-randomization measure were analysed (i.e. intent-to-treat). Continuous variables were evaluated using tests. Intervention effects were adjusted ANOVA for the presence of potential confounding variables using analysis of covariance (ANCOVA).
Additional comments	A sample size of 85 patients per group was required to provide 90% power to detect a significant between-group difference in arginine-stimulated C-peptide secretion

45.2. Study arms

45.2.1. Exenatide (N = 86)

45.2.2. Placebo (N = 85)

45.3. Characteristics

45.3.1. Arm-level characteristics

Characteristic	Exenatide (N = 86)	Placebo (N = 85)
% Male % calculated by analyst Sample size	n = 43 ; % = 50	n = 41 ; % = 45.8
Mean age (SD) Mean (SD)	57.3 (7.7)	56.7 (7.3)
Ethnicity Caucasian Sample size	n = 86 ; % = 100	n = 85 ; % = 100
Comorbidities Sample size	n = 79 ; % = 91.9	n = 77 ; % = 90.6
Hypertension Sample size	n = 51 ; % = 64.5	n = 48 ; % = 62.3
Hypercholesterolaemia Sample size	n = 49 ; % = 62	n = 53 ; % = 68.8
Hypertriglycaeridaemia Sample size	n = 21 ; % = 26.6	n = 19 ; % = 24.7
Combined dyslipidaemia Sample size	n = 15 ; % = 19	n = 12 ; % = 15.6
Coronary heart disease Sample size	n = 4 ; % = 5.1	n = 5 ; % = 6.5
Transient ischaemic attack Sample size	n = 1 ; % = 1.3	n = 2 ; % = 2.6
Stroke Sample size	n = 0 ; % = 0	n = 1 ; % = 1.3

Characteristic	Exenatide (N = 86)	Placebo (N = 85)
Presence of frailty Nominal	NR	NR
Time since type 2 diabetes diagnosed (Months) Mean (SD)	7.6 (2.8)	7.8 (3.1)
Smoking status Sample size	n = NR	n = NR
Male Sample size	n = 16 ; % = 18.6	n = 12 ; % = 14.1
Female Sample size	n = 12 ; % = 14	n = 11 ; % = 16.9
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	NA	NA
Blood pressure-lowering medication used Sample size	n = NR	n = NR
Angiotensin-converting enzyme inhibitor Sample size	n = 18 ; % = 22.8	n = 20 ; % = 26
Angiotensin receptor blockers Sample size	n = 28 ; % = 35.4	n = 25 ; % = 32.5
Calcium-antagonists Sample size	n = 25 ; % = 31.6	n = 27 ; % = 35.1

Characteristic	Exenatide (N = 86)	Placebo (N = 85)
b-Blockers Sample size	n = 7 ; % = 8.9	n = 9 ; % = 11.7
Diuretics Sample size	n = 23 ; % = 29.1	n = 21 ; % = 27.3
Statins/lipid-lowering medication used Sample size	n = NR	n = NR
Statins Sample size	n = 66 ; % = 83.5	n = 63 ; % = 81.8
Fibrates Sample size	n = 14 ; % = 17.7	n = 15 ; % = 19.5
Other treatment being received Sample size	n = NR	n = NR
Omega-3 Sample size	n = 10 ; % = 12.6	n = 9 ; % = 11.7
Acetylsalicylic acid Sample size	n = 13 ; % = 16.5	n = 12 ; % = 15.6
Ticlopidine Sample size	n = 1 ; % = 1.3	n = 1 ; % = 1.3
Clopidogrel Sample size	n = 0 ; % = 0	n = 2 ; % = 2.6

46. Derosa, 2010

Bibliographic Reference	Derosa, G; Maffioli, P; Ferrari, I; Mereu, R; Ragonesi, P D; Querci, F; Franzetti, I G; Gadaleta, G; Ciccarelli, L; Piccinni, M N; D'Angelo, A; Salvadeo, S A T; Effects of one year treatment of vildagliptin added to pioglitazone or glimepiride in poorly controlled type 2 diabetic patients.; Hormone and metabolic research = Hormon- und Stoffwechselforschung = Hormones et metabolisme; 2010; vol. 42 (no. 9); 663-9

46.1. 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	NR
Study type	Randomised controlled trial (RCT)
Study location	Multicentre study in Italy
Study setting	Internal Medicine and Therapeutics Department at the University of Pavia; in the Diabetes Care Unit at S. Carlo Hospital, Milano; the Pesenti Fenaroli Hospital, Alzano Lombardo, Bergamo, Italy; the Metabolic Unit of Regional Hospital, Varese; the Medical Division of Civic Hospital, Cittiglio, Varese; the RSA Don Leone Porta, Milano; in Fondazione Ospedale della Carit à, Casalbuttano, Cremona)
Study dates	NR
Sources of funding	NR
Inclusion criteria	• Type 2 diabetic patients according to the ESC (European Society of Cardiology) and EASD (European Association for the Study of Diabetes) Guidelines criteria with uncontrolled T2DM [glycated hemoglobin (HbA1c) > 7.5 %]

	• Patients aged >=18 years
Exclusion criteria	• History of ketoacidosis • Unstable or rapidly progressive diabetic retinopathy • Nephropathy • Neuropathy • Impaired hepatic • Renal function • Severe anaemia • Patients with serious cardiovascular disease (CVD) (e.g., New York Heart Association class I – IV congestive heart failure or a history of myocardial infarction or stroke) or past incidences of cerebrovascular conditions within 6 months of study enrolment. • Women who were pregnant or breastfeeding or who might become pregnant (due to inadequate contraceptive precautions).
Recruitment / selection of participants	All patients provided written informed consent to participate.
Intervention(s)	Pioglitazone 30 mg once a day
Cointervention	• Vildagliptin 50 mg twice per day • Controlled-energy diet (near 600 kcal daily deficit) based on American Heart Association (AHA) recommendations • Standard diet advice was given by a dietitian and/or specialist doctor • Participants were encouraged to increase their physical activity
Strata 1: People with type 2 diabetes mellitus and heart failure	People without heart failure Excluded "New York Heart Association class I – IV congestive heart failure"
Strata 2: People with atherosclerotic cardiovascular disease	Not stated/unclear Excluded "serious cardiovascular disease (CVD) (e.g., a history of myocardial infarction or stroke) or past incidences of cerebrovascular conditions within 6 months", other categories within the review protocol unclear. No information in baseline characteristics.
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear Excluded "; impaired hepatic or renal function", otherwise unclear. No information in baseline characteristics.

Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	Not stated/unclear Exclusion criteria: "Patients with serious cardiovascular disease (CVD) (e.g., New York Heart Association class I – IV congestive heart failure or a history of myocardial infarction or stroke) or past incidences of cerebrovascular conditions within 6 months of study enrolment."
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	NR
Comparator	Glimepiride 2 mg 3 times per day
Number of participants	168 participants were enrolled in the study, and 155 participants completed the study. 13 participants did not complete the study.
Duration of follow-up	3, 6, 9, 12 months
Indirectness	Directly applicable

Method of analysis	ITT An intention-to-treat analysis was conducted in patients who had received >= 1 dose of study medication and had a subsequent efficacy observation. Continuous variables were evaluated using analysis of variance (ANOVA) tests. Intervention effects were adjusted for the presence of potential confounding variables using analysis of covariance (ANCOVA).
Additional comments	• Report states "All patients were found to be not well controlled with diet, physical activity, and pioglitazone at dosage of 30 mg / day or glimepiride at dosage of 6 mg / day."

46.2. Study arms

46.2.1. Pioglitazone + vildagliptin (N = 83)

46.2.2. Glimepiride + vildagliptin (N = 85)

46.3. Characteristics

46.3.1. Arm-level characteristics

Characteristic	Pioglitazone + vildagliptin (N = 83)	Glimepiride + vildagliptin (N = 85)
% Male % calculated by reviewer Sample size	n = 42 ; % = 50.6	n = 42 ; % = 49.4
Mean age (SD) Mean (SD)	59 (6)	58 (5)
Ethnicity Caucasian Sample size	n = 83 ; % = 100	n = 85 ; % = 100
Comorbidities Nominal	NR	NR
Presence of frailty Nominal	NR	NR

Characteristic	Pioglitazone + vildagliptin (N = 83)	Glimepiride + vildagliptin (N = 85)
Time since type 2 diabetes diagnosed Mean (SD)	7 (3)	6 (2)
Cardiovascular risk factors Nominal	NR	NR
Smoking status % calculated by analyst Sample size	n = NR	n = NR
Male Sample size	n = 15 ; % = 18.1	n = 17 ; % = 0.2
Female Sample size	n = 16 ; % = 19.3	n = 18 ; % = 21.2
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	Pioglitazone + vildagliptin (N = 83)	Glimepiride + vildagliptin (N = 85)
Nominal		
Other treatment being received Nominal	NR	NR

47. Derosa, 2012

Bibliographic Reference	Derosa, Giuseppe; Ragonesi, Pietro D; Carbone, Anna; Fogari, Elena; D'Angelo, Angela; Cicero, Arrigo F G; Maffioli, Pamela; Vildagliptin action on some adipocytokine levels in type 2 diabetic patients: a 12-month, placebo-controlled study.; Expert opinion on pharmacotherapy; 2012; vol. 13 (no. 18); 2581-91

47.1. Study details

Secondary publication of another included study- see primary study for details	NR
Other publications associated with this study included in review	Derosa, G., Ragonesi, P. D., Carbone, A. et al. (2012) Vildagliptin added to metformin on beta-cell function after a euglycemic hyperinsulinemic and hyperglycemic clamp in type 2 diabetes patients. Diabetes Technol Ther 14(6): 475-84
Trial name / registration number	NR
Study type	Randomised controlled trial (RCT)
Study location	Multicentre study conducted in Italy
Study setting	Department of Internal Medicine and Therapeutics, University of Pavia; the Diabetes Care Unit, S. Carlo Hospital, Milano; the Hospital Center of Diabetes, Sant'Angelo Lodigiano, LODI; the Aging and Kidney diseases, "G. Descovich" Atherosclerosis Study Center, University of Bologna
Study dates	NR
Sources of funding	NR
Inclusion criteria	• Patients had known type 2 diabetes for 6 months • Naive to treatment • Poor glycaemic control, expressed as HbA1c level > 63.9 mmol/mol, but < 96.7 mmol/mol • Overweight (BMI >=25, and < 30 kg/m2)

Exclusion criteria	• History of ketoacidosis • Rapidly progressive diabetic retinopathy • Nephropathy (defined by onset of albumin excretion > 300 mg/24 h or albumin excretion rate > 200 ug/min over a six-month period), • Neuropathy • Impaired hepatic function • Impaired renal function (defined as serum creatinine level higher than the ULN for age and gender) • Severe anemia • Serious cardiovascular disease (CVD) or New York Heart Association class III-IV congestive heart failure • History of myocardial infarction or stroke or cerebrovascular conditions (ischemic stroke, haemorrhagic stroke, or transient ischemic attack) within 6 months before study enrolment • Women who were pregnant or breastfeeding or of childbearing potential and not taking adequate contraceptive precautions were also excluded.
Recruitment / selection of participants	Suitable subjects, identified from review of case notes and/or computerized clinic registers were contacted personally or by telephone. All eligible candidates had to provide signed informed consent before enrolling in the study.
Intervention(s)	Vildagliptin 50 mg twice daily for 12 months
Cointervention	• Participants completed a run-in period with metformin treatment for 8 ± 2 months before beginning treatment with vildagliptin or placebo. Treatment with metformin was unblinded and was gradually titrated until a mean dosage of 2500 ± 500 mg/day was reached. • Participants began a controlled-energy diet (near 600 Kcal daily deficit) based on American Heart Association (AHA) recommendations. • Standard diet advice was given by a dietitian and/or a specialist doctor. The dietitian and/or specialist doctor periodically provided instruction on dietary intake recording procedures as part of a behaviour-modification program and then later used the subject's food diaries for counselling. • Individuals were also encouraged to increase their physical activity
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear Excluded "New York Heart Association class III-IV congestive heart failure" otherwise unclear. No information in baseline characteristics.
Strata 2: People with atherosclerotic cardiovascular disease	Not stated/unclear Excluded "serious cardiovascular disease (CVD), or a history of myocardial infarction or stroke or cerebrovascular conditions (ischemic stroke, hemorrhagic stroke, or transient ischemic attack) within 6 months

	before study enrolment", prior 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 (defined as serum creatinine level higher than the ULN for age and gender)", 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	People who do not have obesity Inclusion criteria: overweight (BMI >=25, and < 30 kg/m2)
Subgroup 5: eGFR category at baseline	Not stated/unclear
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Population subgroups	N/A
Comparator	Placebo

Number of participants	171 participants were enrolled in the study and 167 participants were randomised. 11 patients did not complete the study (4, 3, and 4 participants at randomisation, in the vildagliptin arm, and placebo arm respectively.
Duration of follow-up	3, 6, 9, and 12 months
Indirectness	Partially direct - participants were treatment naive prior to initiation of the metformin run-in period, and the population included participants that may have responded adequately to metformin alone.
Method of analysis	ITT All patients randomized with at least one post-randomization measure were analysed. Continuous variables were evaluated using analysis of variance (ANOVA) tests. Intervention effects were adjusted for the presence of potential confounding variables such as BMI, exercise, HbA1c using analysis of covariance (ANCOVA).
Additional comments	A sample size of 85 patients per group was required to provide 90% power to detect a significant between-group difference in AIRarg.

47.2. Study arms

47.2.1. Vildagliptin (N = 84)

47.2.2. Placebo (N = 83)

47.3. Characteristics

47.3.1. Arm-level characteristics

Characteristic	Vildagliptin (N = 84)	Placebo (N = 83)
% Male % calculated by analyst Sample size	n = 42 ; % = 35.28	n = 43 ; % = 51.81
Mean age (SD) Mean (SD)	54.2 (8.3)	52.4 (7.1)
Ethnicity Caucasian	n = 84 ; % = 100	n = 83 ; % = 100

Characteristic	Vildagliptin (N = 84)	Placebo (N = 83)
Sample size		
Comorbidities Nominal	NR	NR
Presence of frailty Nominal	NR	NR
Time since type 2 diabetes diagnosed Mean (SD)	6.1 (3.7)	6.3 (3.9)
Cardiovascular risk factors Nominal	NR	NR
Smoking status % calculated by analyst Sample size	n = NR	n = NR
Male Sample size	n = 8 ; % = 19.05	n = 11 ; % = 25.58
Female Sample size	n = 11 ; % = 26.19	n = 10 ; % = 25
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
Other antidiabetic medication used Nominal	NA	NA
Blood pressure-lowering medication used Nominal	NR	NR
Statins/lipid-lowering medication used Nominal	NR	NR

Characteristic	Vildagliptin (N = 84)	Placebo (N = 83)
Other treatment being received Nominal	NR	NR

48. Diamant, 2010

Bibliographic Reference	Diamant, M.; Gaal, L.; Stranks, S.; Northrup, J.; Cao, D.; Taylor, K.; Trautmann, M.; Once weekly exenatide compared with insulin glargine titrated to target in patients with type 2 diabetes (DURATION-3): an open-label randomised trial; Lancet; 2010; vol. 375 (no. 9733); 2234-43

48.1. Study details

Secondary publication of another included study- see primary study for details	
Other publications associated with this study included in review	Diamant M, Van Gaal L, Guerci B, Stranks S, Han J, Malloy J, Boardman MK, Trautmann ME. Exenatide once weekly versus insulin glargine for type 2 diabetes (DURATION-3): 3-year results of an open-label randomised trial. Lancet Diabetes Endocrinol. 2014 Jun;2(6):464-73 Diamant M, Van Gaal L, Stranks S, Guerci B, MacConell L, Haber H, Scism-Bacon J, Trautmann M. Safety and efficacy of once-weekly exenatide compared with insulin glargine titrated to target in patients with type 2 diabetes over 84 weeks. Diabetes Care. 2012 Apr;35(4):683-9.
Trial name / registration number	NCT00641056
Study type	Randomised controlled trial (RCT)
Study location	Multicentre trial. 72 sites across the USE, Puerto Rico, the European Union, Russia, Australia, Korea, Taiwan and Mexico
Study setting	NR
Study dates	May 2008 to January 2012
Sources of funding	Amlyn Pharmaceuticals Inc and Eli Lilly and Company. Authors have received grants and honoraria from multiple pharmaceutical companies.
Inclusion criteria	Patients with type 2 diabetes aged 18 years or older (no upper limit specified) with suboptimum glycaemic control despite maximum tolerated doses of metformin or combined metformin and sulphonylurea treatment for 3 months or longer. HbA1c concentration between 7.1% and 11.0%

	inclusive, BMI between 25 kg/m2 (23 kg/m2 in participants from South Korea and Taiwan) and 45 kg/m2 and a stable bodyweight for 3 months or more. Patients must have been treated with a stable dose of 1500 mg or more per day for 8 or more weeks of screening
Exclusion criteria	More than 3 episodes of major hypoglycaemia within 6 months of screening; treatment within 4 weeks of screening with systemic glucocorticoids; and treatment for longer than 2 weeks with insulin, thiazolidinediones, alpha-glucosidase inhibitors, meglitinides, exenatide twice-a-day formulation, dipeptidyl peptidae-4 inhibitors or pramlintide acetate within 3 months of screening.
Recruitment / selection of participants	Participants were recruited according to standard local practices.
Intervention(s)	Exenatide (n=233). 2mg dose injected into abdominal subcutaneous tissue once a week
Cointervention	Concomitant therapy. People remained on metformin or metformin and sulphonylurea. Those patients receiving metformin and sulphonylurea with confirmed hypoglycaemia were recommended to reduce sulphonylurea dose.
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear Not an inclusion/exclusion criteria. No information in baseline characteristics.
Strata 2: People with atherosclerotic cardiovascular disease	Not stated/unclear Not an inclusion/exclusion criteria. No information in baseline characteristics.
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear Not an inclusion/exclusion criteria. No information in baseline characteristics.
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	Not stated/unclear

Subgroup 1: People with moderate or severe frailty	Not stated/unclear
Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear
Subgroup 3: People with non-alcoholic fatty liver disease	Not stated/unclear
Subgroup 4: People with obesity	Not stated/unclear
Subgroup 5: eGFR category at baseline	Not stated/unclear
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Population subgroups	No additional information
Comparator	Insulin glargine (n=223) Initial treatment with 10 IU per day with adjustment to doses to achieve a target glucose of 4.0 - 5.5 mmol/L . Daily injections to be carried out at same time each day, preferably at bedtime
Number of participants	456
Duration of follow-up	3 years
Indirectness	No additional information
Method of analysis	Modified ITT

48.2. Study arms

48.2.1. Exenatide (N = 233)

Once weekly 2mg injection of exenatide. Continuation of stable dosing of metformin or metformin +sulphonylurea. Recommendation of reduction in sulphonylurea if patient taking metformin and sulphonylurea had confirmed hypoglycaemia.

48.2.2. Insulin glargine (N = 223)

Initial 10 IU per day of insulin glargine, and then adjusted the dose to achieve a target glucose of 4.0 - 5.5 mmol/L. Insulin glargine injected at the same time every day, preferably at bedtime with continuation of metformin or metformin + sulphonylurea.

48.3. Characteristics

48.3.1. Arm-level characteristics

Characteristic	Exenatide (N = 233)	Insulin glargine (N = 223)
% Male Sample size	n = 120 ; % = 52	n = 123 ; % = 55
Mean age (SD) (Years (mean, SD)) Mean (SD)	58 (10)	58 (9)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA
African-American Sample size	n = 2 ; % = 1	n = 1 ; % = 0.04
White Sample size	n = 190 ; % = 82	n = 189 ; % = 85
Asian Sample size	n = 13 ; % = 6	n = 14 ; % = 6
Hispanic Sample size	n = 28 ; % = 12	n = 19 ; % = 9
Presence of frailty Sample size	n = NR ; % = NR	n = NR ; % = NR

Characteristic	Exenatide (N = 233)	Insulin glargine (N = 223)
Time since type 2 diabetes diagnosed (Years (mean, SD)) Mean (SD)	8 (6)	7.8 (6)
Blood pressure Sample size	n = NR ; % = NR	n = NR ; % = NR
Smoking status Sample size	n = NR ; % = NR	n = NR ; % = NR
Alcohol consumption Sample size	n = NR ; % = NR	n = NR ; % = NR
Presence of severe mental illness Sample size	n = NR ; % = NR	n = NR ; % = NR
People with significant cognitive impairment Sample size	n = NR ; % = NR	n = NR ; % = NR
People with a learning disability Sample size	n = NR ; % = NR	n = NR ; % = NR
Number of people with obesity Sample size	n = NR ; % = NR	n = NR ; % = NR
Other antidiabetic medication used Sample size	n = NA ; % = NA	n = NA ; % = NA
Metformin use Sample size	n = 164 ; % = 70	n = 157 ; % = 70
Metformin + Sulfonylurea use Sample size	n = 69 ; % = 30	n = 66 ; % = 30
Statins/lipid-lowering medication used Sample size	n = NR ; % = NR	n = NR ; % = NR

49. Diamant, 2014

Bibliographic Reference	Diamant, M.; Nauck, M. A.; Shaginian, R.; Malone, J. K.; Cleall, S.; Reaney, M.; de Vries, D.; Hoogwerf, B. J.; MacConell, L.; Wolffenbuttel, B. H.; Glucagon-like peptide 1 receptor agonist or bolus insulin with optimized basal insulin in type 2 diabetes; Diabetes Care; 2014; vol. 37 (no. 10); 2763-73

49.1. 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	NCT00960661
Study type	Randomised controlled trial (RCT)
Study location	108 centres in 17 countries
Study setting	NR
Study dates	September 2009 to August 2012
Sources of funding	Study was part of the Eli Lilly and Company / Amlyn Pharmaceuticals Alliance and the Bristol-Myers Squibb / AstraZeneca Alliance. Authors received grants and honoraria from a number of different pharmaceutical companies.
Inclusion criteria	18 years and older with type 2 diabetes treated with insulin glargine and metformin +/- sulfonylurea with HbA1c of 7.0% to 10.0% and BMI of 25.0 kg/m2 (23.0 kg/m2 for South Korean participants) to 45.0 kg/m2
Exclusion criteria	1. Are currently taking oral antidiabetes medication that is not described in inclusion criteria and not allowed with concurrent use of insulin per local product label.

	2. Have taken more than 1 week within 1 month prior to visit 1 any glucose-lowering medications not included in inclusion criteria (for example, those not approved for use with insulin, rosiglitazone, rimonabant, acarbose, miglitol, pramlintide, repaglinide, nateglinide or dipeptidyl peptidase-4 inhibitors, or pioglitazone) either alone or in combination formulations, or have used a drug for weight loss (for example, prescription drugs such as orlistat, sibutramine, phenylpropanolamine, rimonabant, or similar over-the-counter medications). 3. Have taken any insulin other than glargine within the 3 months prior to visit 1 for more than 1 week. 4. Are receiving chronic (lasting longer than 2 weeks) systemic glucocorticoid therapy (excluding topical, intraocular, and inhaled preparations) within 4 weeks prior to visit 1. 5. Have had a clinically significant history of cardiac disease with functional status that is Class III or IV (New York Heart Association Class III or IV) or considered by the investigator to be exclusionary. 6. Have had more than 1 episode of major hypoglycaemia, as defined in the Abbreviations and Definitions section, within 6 months prior to visit 1. 7. Female patients with a positive pregnancy test and/or intending to become pregnant or sexually active and not using birth control throughout the study to prevent pregnancy. 8. Women who are breastfeeding. 9. Have any of the following concomitant diseases: presence of clinically significant hematologic, oncologic, renal (or have creatinine clearance below 30 ml/min), cardiac, hepatic or gastrointestinal disease or any other serious disease considered by the investigator to be exclusionary. 10. Have fasting triglyceride levels >500 mg/dL (>5.64 mmol/L). 11. Have a history of renal transplantation or are currently receiving renal dialysis. 12. Have a history of confirmed pancreatitis. 13. Have an active or untreated malignancy or have been in remission from clinically significant malignancy (other than basal cell or squamous cell skin cancer, in situ carcinomas of the cervix, or in situ prostate cancer) for less than 5 years. 14. Have contraindication or known hypersensitivity or allergy to exenatide or to any of the product components (including prior withdrawal of exenatide therapy after experiencing adverse events). 15. Have had a blood transfusion or severe blood loss within 3 months prior to visit 1 or have known hemoglobinopathy, hemolytic anemia, or

	sickle cell anemia, or any other condition known to interfere with the glycated hemoglobin methodology. 16. Have any other condition (including known drug or alcohol abuse or psychiatric disorder) that precludes the patient from following and completing the protocol, according to the investigator's judgment. 17. Are currently enrolled in, or discontinued within the last 30 days from, a clinical trial involving an off-label use of an investigational drug or device (other than the study drug/device used in this study), or concurrently enrolled in any other type of medical research judged not to be scientifically or medically compatible with this study. 18. Are investigator site personnel directly affiliated with this study and/or their immediate families. Immediate family is defined as a spouse, parent, child, or sibling, whether biological or legally adopted. 19. Are employed by Eli Lilly and Company or Amylin Pharmaceuticals, Inc. (Amylin). 20. Have previously completed or been withdrawn from this study after enrolment. 21. If on metformin and have contraindication to metformin use, including known metabolic or lactic acidosis, or any condition associated with hypoperfusion, hypoxemia, dehydration, or sepsis. 22. Have had a radiologic contrast study performed within 48 hours prior to visit 1. 23. Have any exclusion required by local law.
Recruitment / selection of participants	No further information
Intervention(s)	Exenatide (n=247) 5 mcg twice daily per injection for the first 4 weeks and 10 mcg per injection thereafter before the two largest meals. Dose reduction permitted based on tolerability
Cointervention	Concomitant therapy: patients continued on glucose lowering medications (metformin and glargine) throughout the study
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear Excluded "New York Heart Association Class III or IV", otherwise unclear. No information in baseline characteristics.
Strata 2: People with	Not stated/unclear

atherosclerotic cardiovascular disease	Not an inclusion/exclusion criteria. No information in baseline characteristics.
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear Not an inclusion/exclusion criteria. No information in baseline characteristics.
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	Not stated/unclear
Subgroup 1: People with moderate or severe frailty	Not stated/unclear
Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear
Subgroup 3: People with non-alcoholic fatty liver disease	Not stated/unclear
Subgroup 4: People with obesity	Not stated/unclear
Subgroup 5: eGFR category at baseline	Not stated/unclear
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Population subgroups	No additional information

Comparator	Insulin lispro (n=263) three daily injections of lispro to maintain pre-meal glucose of 5.6 - 6.0 mmol/L
Number of participants	627
Duration of follow-up	30 weeks
Indirectness	No additional information
Method of analysis	ITT
Additional comments	The primary objective of the study was to compare the difference in HbA1c change from randomization to 30 weeks between exenatide or lispro added to glargine in the per-protocol (PP) population. Noninferiority was assessed using an HbA1c margin of 0.4%. If this objective was met, a second noninferiority comparison would be conducted with an HbA1c margin of 0.3%. If noninferiority was established using this stricter margin, superiority would be tested in the intent-to-treat (ITT) population

49.2. Study arms

49.2.1. Exenatide (N = 315)

Trial name / registration number	NCT00960661
Subgroup 4: People with obesity	Mixed population

Injection of exenatide before the two largest meals, with at least 6 h between dosing. Regimen was 5 mg twice daily per injection for the first 4 weeks and 10 mg per injection thereafter. Exenatide dose reduction was allowed based on tolerability. At study entry, all patients continue metformin and discontinue sulfonylurea. During the 12-week basal insulin optimisation phase, bedtime glargine titrated to fasting glucose of 5.6 mmol/L or lower without hypoglycaemia (glucose <3.0 mmol/L) based on self monitored blood glucose and dosing aid. At randomisation (0 week) daily glargine reduced by 10% or more in patients with HbA1c of 8% (64 mmol/mol) or less.

49.2.2. Insulin lispro (N = 312)

Three daily injections of lispro before mealtimes to maintain pre-meal glucose of 5.6 – 6.0 mmol/L. At study entry, all patients continue metformin and discontinue

sulfonylurea. During the 12-week basal insulin optimisation phase, bedtime glargine titrated to fasting glucose of 5.6 mmol/L or lower without hypoglycaemia (glucose <3.0 mmol/L) based on self monitored blood glucose and dosing aid. At randomisation (0 week) daily glargine reduced by one-half or one-third, at the investigator's discretion. The reduced amount replaced with three doses of lispro injected before meals to maintain the same total insulin dose. Thereafter, glargine was titrated as in the 12 week optimisation-phase (study entry) and lispro was titrated based on self-monitored premeal glucose values.

49.3. Characteristics

49.3.1. Arm-level characteristics

Characteristic	Exenatide (N = 315)	Insulin lispro (N = 312)
% Male Exenatide sample size n = 247, Insulin lispro n = 263 Sample size	n = 128 ; % = 52	n = 133 ; % = 51
Mean age (SD) (Years (mean, SD)) Exenatide sample size n = 247, Insulin lispro n = 263 Mean (SD)	59.5 (9.6)	59.4 (9.3)
Ethnicity Exenatide sample size n = 247, Insulin lispro n = 263 Sample size	n = NA ; % = NA	n = NA ; % = NA
White Sample size	n = 222 ; % = 90	n = 229 ; % = 87
Asian Sample size	n = 11 ; % = 5	n = 14 ; % = 5
African American Sample size	n = 2 ; % = 0.8	n = 1 ; % = 0.4
American-Indian/Alaska Native Sample size	n = 12 ; % = 5	n = 18 ; % = 7
Presence of frailty Sample size	n = NR ; % = NR	n = NR ; % = NR

Characteristic	Exenatide (N = 315)	Insulin lispro (N = 312)
Time since type 2 diabetes diagnosed Exenatide sample size n = 247, Insulin lispro n = 263 Mean (SD)	NR (NR)	NR (NR)
Time since type 2 diabetes diagnosed Exenatide sample size n = 247, Insulin lispro n = 263 Median (IQR)	12 (8 to 17)	11 (8 to 15)
Smoking status Sample size	n = NR ; % = NR	n = NR ; % = NR
Alcohol consumption Sample size	n = NR ; % = NR	n = NR ; % = NR
Presence of severe mental illness Sample size	n = NR ; % = NR	n = NR ; % = NR
People with significant cognitive impairment Sample size	n = NR ; % = NR	n = NR ; % = NR
People with a learning disability Sample size	n = NR ; % = NR	n = NR ; % = NR
Number of people with obesity Sample size	n = NR ; % = NR	n = NR ; % = NR
Other antidiabetic medication used Sample size	n = NA ; % = NA	n = NA ; % = NA
Metformin Exenatide sample size n = 247, Insulin lispro n = 263 Sample size	n = 247 ; % = 100	n = 263 ; % = 100
Insulin glargine Exenatide sample size n = 247, Insulin lispro n = 263 Sample size	n = 247 ; % = 100	n = 263 ; % = 100
Blood pressure-lowering medication used Sample size	n = NR ; % = NR	n = NR ; % = NR

Characteristic	Exenatide (N = 315)	Insulin lispro (N = 312)
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

50. Diamant, 2014

Bibliographic Reference	Diamant, Michaela; Van Gaal, Luc; Guerci, Bruno; Stranks, Stephen; Han, Jenny; Malloy, Jaret; Boardman, Marilyn K; Trautmann, Michael E; Exenatide once weekly versus insulin glargine for type 2 diabetes (DURATION-3): 3-year results of an open-label randomised trial.; The lancet. Diabetes & endocrinology; 2014; vol. 2 (no. 6); 464-73

50.1. Study details

Secondary publication of another included study- see primary study for details	Parent study Diamant M, Van Gaal L, Stranks S, Northrup J, Cao D, Taylor K, Trautmann M. Once weekly exenatide compared with insulin glargine titrated to target in patients with type 2 diabetes (DURATION-3): an open-label randomised trial. Lancet. 2010 Jun 26;375(9733):2234-43.
Other publications associated with this study included in review	Other study Diamant M, Van Gaal L, Stranks S, Guerci B, MacConell L, Haber H, Scism-Bacon J, Trautmann M. Safety and efficacy of once-weekly exenatide compared with insulin glargine titrated to target in patients with type 2 diabetes over 84 weeks. Diabetes Care. 2012 Apr;35(4):683-9.

51. Diamant, 2012

Bibliographic Reference	Diamant, Michaela; Van Gaal, Luc; Stranks, Stephen; Guerci, Bruno; MacConell, Leigh; Haber, Harry; Scism-Bacon, Jamie; Trautmann, Michael; Safety and efficacy of once-weekly exenatide compared with insulin glargine titrated to target in patients with type 2 diabetes over 84 weeks.; Diabetes care; 2012; vol. 35 (no. 4); 683-9

51.1. Study details

Secondary publication of another included study- see primary study for details	Parent study Diamont 2010

52. Dobs, 2013

Bibliographic Reference	Dobs, A. S.; Goldstein, B. J.; Aschner, P.; Horton, E. S.; Umpierrez, G. E.; Duran, L.; Hill, J. S.; Chen, Y.; Golm, G. T.; Langdon, R. B.; Williams-Herman, D. E.; Kaufman, K. D.; Amatruda, J. M.; Ferreira, J. C.; Efficacy and safety of sitagliptin added to ongoing metformin and rosiglitazone combination therapy in a randomized placebo-controlled 54-week trial in patients with type 2 diabetes; J Diabetes; 2013; vol. 5 (no. 1); 68-79

52.1. Study details

Trial name / registration number	NCT00350779
Study type	Randomised controlled trial (RCT)
Study location	41 sites across North and South America, Europe and Asia
Study setting	No additional information
Study dates	29 August 2006 to 27 May 2008
Sources of funding	Study sponsored by Merck Sharp and Dohme Corp. Numerous authors are current or former employees of Merk Sharp and Dohme Corp.
Inclusion criteria	Participants of either sex, aged 18–78 years, and had T2D being actively treated either with metformin plus a PPARc agonist, metformin plus a sulfonylurea, or a sulfonylurea plus a PPARc agonist. Concurrent treatment was permitted with generally stable doses of medications taken for birth control, hormone replacement, hypertension, thyroid disease, and hyperlipidemia
Exclusion criteria	Active liver disease or abnormal liver function tests (>2 x upper limit of normal), congestive heart failure (requiring pharmacological therapy or New York Heart Association Class II–IV), type 1 diabetes, were pregnant or breastfeeding, or had received insulin or the GLP-1 mimetic exenatide within the prior 3 months. Concurrent treatment with other antihyperglycemic medications was prohibited.
Intervention(s)	Sitagliptin (n=181) 100 mg / day taken as one tablet prior to the morning meal
Cointervention	Concomitant therapy: Metformin (≥1500 mg/day up to to 2550 mg/day) + rosiglitazone (≥4 mg/day up to 8 mg/day)
Strata 1: People with type 2	People without heart failure

diabetes mellitus and heart failure	
Strata 2: People with atherosclerotic cardiovascular disease	Not stated/unclear Not an inclusion/exclusion criteria. No information in baseline characteristics.
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	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	Not stated/unclear

category at baseline	
Population subgroups	No additional information
Comparator	Placebo (n=97) Placebo administered as one tablet per day taken before the morning meal
Number of participants	278
Duration of follow-up	54 weeks
Indirectness	No additional information
Method of analysis	Not stated/unclear
Additional comments	Efficacy outcomes were analysed using populations defined for each endpoint as the set of all randomized patients who received at least one dose of study medication and for whom a baseline measurement and at least one post-randomization measurement of the respective endpoint were available. An analysis of covariance (ANCOVA) model was used to compare least squares mean (LS mean) changes from baseline in continuous efficacy parameters in the two treatment groups. In this model, baseline value was a continuous covariate and treatment allocation and pharmacotherapy status at the time of screening were included as factors. Missing data were imputed using the method of last observation carried forward. To control the type 1 error rate for multiple comparisons at the primary time point (Week 18), an ordered testing strategy was used for the key efficacy endpoints (HbA1c, then 2-h PMG, then FPG) whereby a subsequent endpoint was not tested unless success was achieved (P < 0.05) in the test of the preceding endpoint.

52.2. Study arms

52.2.1. Sitagliptin (N = 181)

Randomization to treatment was preceded by discontinuation of sulfonylureas and a dose-adjustment period for metformin and/or rosiglitazone of up to 8 weeks, a dose-stable period of 6–12 weeks, and a single-blind placebo run-in period of 2 weeks. During the dose-adjustment period, daily doses of metformin and rosiglitazone were increased to the maximum levels that were tolerated (up to 2550 mg/day metformin and 8 mg/day rosiglitazone). The duration of the dose stable period was 6 weeks for patients who presented at screening with HbA1c ≥7.5% and ≤11.0% while receiving metformin ≥1500 mg/day plus either rosiglitazone ≥4 mg/day or pioglitazone ≥30 mg/day, and 8–12 weeks for patients requiring up-titration of metformin or rosiglitazone. Patients taking pioglitazone were switched to doses of rosiglitazone

that were considered clinically equivalent (i.e. 30 mg pioglitazone was replaced by 4 mg rosiglitazone, and 45 mg pioglitazone was replaced by 8 mg rosiglitazone). Upon conclusion of the dose-stable period, eligible patients entered the placebo run-in period. 100 mg/day sitagliptin doses were administered in the form of one tablet taken once daily before the morning meal. Patients who did not meet progressively stricter glycemic criteria were provided glycemic rescue therapy with open-label glipizide or an alternative sulfonylurea.

52.2.2. Placebo (N = 97)

Randomization to treatment was preceded by discontinuation of sulfonylureas and a dose-adjustment period for metformin and/or rosiglitazone of up to 8 weeks, a dose-stable period of 6–12 weeks, and a single-blind placebo run-in period of 2 weeks. During the dose-adjustment period, daily doses of metformin and rosiglitazone were increased to the maximum levels that were tolerated (up to 2550 mg/day metformin and 8 mg/day rosiglitazone). The duration of the dose stable period was 6 weeks for patients who presented at screening with HbA1c ≥7.5% and ≤11.0% while receiving metformin ≥1500 mg/day plus either rosiglitazone ≥4 mg/day or pioglitazone ≥30 mg/day, and 8–12 weeks for patients requiring up-titration of metformin or rosiglitazone. Patients taking pioglitazone were switched to doses of rosiglitazone that were considered clinically equivalent (i.e. 30 mg pioglitazone was replaced by 4 mg rosiglitazone, and 45 mg pioglitazone was replaced by 8 mg rosiglitazone). Upon conclusion of the dose-stable period, eligible patients entered the two placebo run-in period. The placebo was administered in the form of one tablet taken once daily before the morning meal. Patients who did not meet progressively stricter glycemic criteria were provided glycemic rescue therapy with open-label glipizide or an alternative sulfonylurea.

52.3. Characteristics

52.3.1. Arm-level characteristics

Characteristic	Sitagliptin (N = 181)	Placebo (N = 97)
% Male Sitagliptin n = 170, Placebo n = 92 Sample size	n = 96 ; % = 66	n = 55 ; % = 60
Mean age (SD) (Years (mean, SD)) Sitagliptin n = 170, Placebo n = 92 Mean (SD)	54.4 (8.8)	54.8 (9.5)
Ethnicity Sitagliptin n = 170, Placebo n = 92 Sample size	n = NA ; % = NA	n = NA ; % = NA

Characteristic	Sitagliptin (N = 181)	Placebo (N = 97)
White Sample size	n = 82 ; % = 48	n = 51 ; % = 55
Asian Sample size	n = 58 ; % = 34	n = 24 ; % = 26
Hispanic Sample size	n = 13 ; % = 8	n = 10 ; % = 11
Black Sample size	n = 7 ; % = 4	n = 3 ; % = 3
Other Sample size	n = 10 ; % = 6	n = 4 ; % = 4
Comorbidities Sitagliptin n = 170, Placebo n = 92 Sample size	n = NR ; % = NR	n = NR ; % = NR
Presence of frailty Sitagliptin n = 170, Placebo n = 92 Sample size	n = NR ; % = NR	n = NR ; % = NR
Time since type 2 diabetes diagnosed (Years (mean, SD)) Sitagliptin n = 170, Placebo n = 92 Mean (SD)	9.3 (5.9)	9.4 (6.8)
Smoking status Sitagliptin n = 170, Placebo n = 92 Sample size	n = NR ; % = NR	n = NR ; % = NR
Alcohol consumption Sitagliptin n = 170, Placebo n = 92 Sample size	n = NR ; % = NR	n = NR ; % = NR
Presence of severe mental illness Sitagliptin n = 170, Placebo n = 92 Sample size	n = NR ; % = NR	n = NR ; % = NR
People with significant cognitive impairment Sitagliptin n = 170, Placebo n = 92 Sample size	n = NR ; % = NR	n = NR ; % = NR

Characteristic	Sitagliptin (N = 181)	Placebo (N = 97)
People with a learning disability Sitagliptin n = 170, Placebo n = 92 Sample size	n = NR ; % = NR	n = NR ; % = NR
Number of people with obesity Sitagliptin n = 170, Placebo n = 92 Sample size	n = NR ; % = NR	n = NR ; % = NR

53. Dorkhan, 2009

Bibliographic Reference	Dorkhan, M.; Dencker, M.; Stagmo, M.; Groop, L.; Effect of pioglitazone versus insulin glargine on cardiac size, function, and measures of fluid retention in patients with type 2 diabetes; Cardiovasc Diabetol; 2009; vol. 8; 15

53.1. Study details

Study type	Randomised controlled trial (RCT)
Study location	NR
Study dates	NR
Sources of funding	Study was in part financially supported by grants from Sanofi-Aventis, The Crafoord Foundation, and The Swedish Heart and Lung Association. Authors declare various honoraria's with Eli Lilly and Sanofi-Aventis. One author owns shares and stock options in Novo Nordisk A/S.
Inclusion criteria	Patients with T2D and inadequate glycaemic control were included. Inadequate glycaemic control was defined as treatment with metformin and sulfonylurea/meglitinide in doses > 50% of maximum recommended doses and HbA1c > 6.2% measured with Mono-S method (= 7% National Glycohemoglobin Standardisation Program, NGSP).
Exclusion criteria	Patients with known heart failure or clinical signs of heart failure (New York Heart Association class II–IV), patients with significant valvular dysfunction (defined as more than mild regurgitation or presence of valvular stenosis), reduced ejection fraction EF (< 50%) or inappropriate acoustic window were excluded.
Intervention(s)	Pioglitazone (n=15) Pioglitazone increased to 45 mg/day after 16 weeks if HbA1c > 6.2%
Cointervention	Metformin plus sulfonylurea / meglinitide.
Strata 1: People with type 2 diabetes mellitus and heart failure	People without heart failure Excluded "Patients with known heart failure or clinical signs of heart failure (New York Heart Association class II–IV) were excluded".
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 glargine (n=15) Up-titrated to achieve fasting plasma glucose < 6 mmol/L
Number of participants	30

Duration of follow-up	26 weeks
Method of analysis	Not stated/unclear

53.2. Study arms

53.2.1. Pioglitazone (N = 15)

Pioglitazone for 26 weeks increased to 45 mg/day after 16 weeks if HbA1c > 6.2%. Concomitant therapy: patients receiving metformin and sulfonylurea / meglinitide

53.2.2. Insulin glargine (N = 15)

Insulin glargine up-titrated over 26 weeks to achieve fasting plasma glucose < 6 mmol/L. Concomitant therapy: patients receiving metformin and sulfonylurea / meglinitide

53.3. Characteristics

53.3.1. Arm-level characteristics

Characteristic	Pioglitazone (N = 15)	Insulin glargine (N = 15)
% Male Sample size	n = 11 ; % = 73	n = 9 ; % = 60
Mean age (SD) Mean (SD)	60.8 (7.1)	61.5 (8.2)
Ethnicity Sample size	n = NR ; % = NR	n = NR ; % = NR
Time since type 2 diabetes diagnosed (Years (mean, SD)) Mean (SD)	11.1 (6)	9.5 (7.5)
Smoking status Sample size	n = NR ; % = NR	n = NR ; % = NR
Alcohol consumption	n = NR ; % = NR	n = NR ; % = NR

Characteristic	Pioglitazone (N = 15)	Insulin glargine (N = 15)
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
Number of people with obesity Sample size	n = NR ; % = NR	n = NR ; % = NR
Metformin use Sample size	n = 15 ; % = 100	n = 15 ; % = 100
Sulfonylurea / meglinitide Sample size	n = 15 ; % = 100	n = 15 ; % = 100

54. Dormandy John, 2005

Bibliographic Reference	Dormandy John, A; Charbonnel, Bernard; Eckland David J, A; Erdmann, Erland; Massi-Benedetti, Massimo; Moules Ian, K; Skene Allan, M; Tan Meng, H; Lefebvre Pierre, J; Murray Gordon, D; Standl, Eberhard; Wilcox Robert, G; Wilhelmsen, Lars; Betteridge, John; Birkeland, Kare; Golay, Alain; Heine Robert, J; Koranyi, Laszlo; Laakso, Markku; Mokan, Marian; Norkus, Antanas; Pirags, Valdis; Podar, Toomas; Scheen, Andre; Scherbaum, Werner; Schernthaner, Guntram; Schmitz, Ole; Skrha, Jan; Smith, Ulf; Taton, Jan; PROactive, Investigators; Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitAzone Clinical Trial In macroVascular Events): a randomised controlled trial.; Lancet (London, England); 2005; vol. 366 (no. 9493); 1279-89

54.1. Study details

Secondary publication of another included study- see primary study for details	This is a secondary study of the PROactive trial – see Wilcox 2008 for further details Wilcox, Robert, Kupfer, Stuart, Erdmann, Erland (2008) Effects of pioglitazone on major adverse cardiovascular events in high-risk patients with type 2 diabetes: Results from PROspective pioglitAzone Clinical Trial In macro Vascular Events (PROactive 10). American heart journal 155 (4): 712-7
Other publications associated with this study included in review	NA
Trial name / registration number	PROactive trial. Clinicaltrial.gov = NCT00174993
Study location	
Inclusion criteria	Adults (aged 35-75, inclusive) with type 2 diabetes and with an established history of macrovascular disease; Type 2 diabetes was defined as: haemoglobin A1c level above the upper limit of normal; i.e., the local equivalent of 6.5% for a DCCT traceable assay; An established history of macrovascular disease was defined as having one or more of the following: MI, stroke, percutaneous coronary intervention (PCI), or coronary artery bypass graft (CABG) ≥6 months before entering the study; ACS ≥3 months before entering the study; Objective evidence of coronary artery disease (positive exercise test or scintigraphy, or angiography showing at least one lesion >50% stenosis); Peripheral arterial obstructive disease of the leg (previous leg amputation above the ankle, or intermittent claudication with an ankle or toe brachial pressure index >0.9).

Exclusion criteria	People with Type 1 diabetes; were taking only insulin; had planned coronary or peripheral revascularisation; had New York Heart Association class II heart failure or above; had ischaemic ulcers, gangrene, or rest pain in the leg; had haemodialysis; or had greater than 2•5 times the upper limit of normal concentrations of alanine aminotransferase.
Recruitment / selection of participants	Not specified; patents were recruited to the PROspective pioglitAzone Clinical Trial In macro Vascular Events (PROactive) trial
Intervention(s)	Pioglitazone (Dose was force-titrated from 15 to 45 mg/d during the first 2 months, depending upon tolerability)
Strata 2: People with atherosclerotic cardiovascular disease	People with atherosclerotic cardiovascular diseases
Indirectness	None - Study population, intervention, and comparator meets review protocol
Method of analysis	ITT
Additional comments	Kaplan-Meier estimates of the 3-year event rates were calculated; Time-to-event analyses were carried out by fitting proportional hazards survival models with “treatment” as the only covariate, and estimated hazard ratios (HRs) and 95% CIs were calculated. Linear models or logistic regression models were used for other endpoints

54.2. Study arms

54.2.1. Pioglitazone (N = 2605)

54.2.2. Placebo (N = 2633)

54.3. Characteristics

54.3.1. Arm-level characteristics

Characteristic	Pioglitazone (N = 2605)	Placebo (N = 2633)
% Male Sample size	n = 1735 ; % = 67	n = 1726 ; % = 66

Characteristic	Pioglitazone (N = 2605)	Placebo (N = 2633)
Mean age (SD) (years) Mean (SD)	61.9 (7.6)	61.6 (7.8)
Ethnicity males Sample size	n = 2564 ; % = 98	n = 2600 ; % = 99
Time since type 2 diabetes diagnosed (years) Median (IQR)	8 (4 to 13)	8 (4 to 14)
Systolic blood pressure Mean (SD)	144 (18)	143 (18)
Diastolic blood pressure Mean (SD)	83 (10)	83 (9)
Current smoker Sample size	n = 340 ; % = 13	n = 381 ; % = 14
Past smoker Sample size	n = 1199 ; % = 46	n = 1159 ; % = 44
BMI (kg/m²) Mean (SD)	307 (47)	31 (4.8)
LDL-cholesterol Median (IQR)	2.9 (2.3 to 3.5)	2.9 (2.3 to 0.35)
HDL cholesterol Median (IQR)	1.1 (0.9 to 1.3)	1.1 (0.9 to 1.3)
Triglycerides Median (IQR)	79 (68 to 92)	79 (68 to 92.5)
Other antidiabetic medication used Sample size	n = 2496 ; % = 96	n = 2528 ; % = 96
Metformin Sample size	n = 253 ; % = 10	n = 261 ; % = 10
Sulphonylureas only Sample size	n = 508 ; % = 20	n = 493 ; % = 19

Characteristic	Pioglitazone (N = 2605)	Placebo (N = 2633)
Metformin + sulphonylureas Sample size	n = 654 ; % = 25	n = 660 ; % = 25
Insulin Sample size	n = 5 ; % = 0.2	n = 8 ; % = 0.3
Insulin + metformin Sample size	n = 456 ; % = 18	n = 475 ; % = 18
Insulin + sulphonylureas Sample size	n = 209 ; % = 8	n = 219 ; % = 8
Insulin + metformin + sulphonylureas Sample size	n = 105 ; % = 4	n = 107 ; % = 4
Other combination Sample size	n = 306 ; % = 12	n = 305 ; % = 12
Beta blocker Sample size	n = 1423 ; % = 55	n = 1434 ; % = 54
ACE inhibitor Sample size	n = 1630 ; % = 63	n = 1658 ; % = 63
Angiotensin II antagonists Sample size	n = 170 ; % = 7	n = 184 ; % = 7
Calcium channel blockers Sample size	n = 892 ; % = 34	n = 964 ; % = 37
Nitrates Sample size	n = 1018 ; % = 39	n = 1045 ; % = 40
Thiazides Sample size	n = 401 ; % = 15	n = 430 ; % = 16
Loop diuretics Sample size	n = 372 ; % = 14	n = 378 ; % = 14
Statins Sample size	n = 1108 ; % = 43	n = 1137 ; % = 43
Fibrates	n = 264 ; % = 10	n = 294 ; % = 11

Characteristic	Pioglitazone (N = 2605)	Placebo (N = 2633)
Sample size		
Antiplatelet medications does not reports the names Sample size	n = 2221 ; % = 85	n = 2175 ; % = 83
Aspirin Sample size	n = 1942 ; % = 75	n = 1888 ; % = 72
History of hypertension Sample size	n = 1947 ; % = 75	n = 2005 ; % = 76
History of microvascular diseases retinopathy, nephropathy, neuropathy Sample size	n = 1113 ; % = 43	n = 1076 ; % = 41
HBA1C (Percentage) Median (IQR)	7.8 (7 to 8.9)	7.9 (7.1 to 8.9)
Creatinine (micromol/L) Median (IQR)	79 (68 to 92)	79 (68 to 92.5)

55. Douek, 2005

Bibliographic Reference	Douek, I. F.; Allen, S. E.; Ewings, P.; Gale, E. A.; Bingley, P. J.; Continuing metformin when starting insulin in patients with Type 2 diabetes: a double-blind randomized placebo-controlled trial; Diabetic Med; 2005; vol. 22 (no. 5); 634-40

55.1. Study details

Study type	Randomised controlled trial (RCT)
Study location	Five hospitals in southwest England
Study dates	NR
Sources of funding	Supported by the Special Trustees for the United Bristol Hospitals and the NHS Executive Southwest. Lipha Pharmaceuticals donated trial medication.
Inclusion criteria	Patients with Type 2 diabetes referred to one of five hospitals in southwest England for conversion to insulin between 1999 and 2002 because of unsatisfactory glycaemic control, a duration of diabetes of at least 2 years and aged 75 years or less.
Exclusion criteria	Individuals known to be intolerant of metformin, those due to start nocturnal insulin alone and women who were breastfeeding, pregnant or planning a pregnancy. Other exclusion criteria related to the risk of lactic acidosis including; chronic renal impairment measured by an estimated creatinine clearance of < 65 ml/min using the Cockcroft Gault equation, cardiac failure not adequately controlled on minimal doses of diuretic and ACE inhibitor or equivalent, significant pulmonary disease with reduction in exercise tolerance to less than one flight of stairs, extensive vascular disease, or known liver disease, alcohol dependence or liver enzyme measurements more than twice the upper limit of the normal range
Recruitment / selection of participants	Recruited from hospital diabetes clinics
Intervention(s)	Metformin (n=92) Titrated up to 2g per day or maximum tolerated dose given in two divided doses for 12 months. Participants were asked to stop all previous oral anti-hyperglycaemic medication and received education, dietary advice, insulin therapy and follow-up according to the normal practice of the local clinicians. Patients followed a protocol for gradual introduction of the trial medication to a maximum dose of 1 g twice a day over a 4-week period. Those who experienced gastrointestinal side-effects were advised to revert

	to the highest tolerated dose and to remain on this until the end of the study.
Cointervention	Insulin No standard management protocol for the adjustment of insulin was specified. Participants were in regular contact with their diabetes team, by visits or telephone consultation or both, when they were given advice about insulin dose changes and methods to improve control. All teams worked to targets of pre-meal capillary blood glucose readings below 7 mmol/l without debilitating hypoglycaemia and HbA1c levels below 7%.
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear Excluded ";cardiac failure not adequately controlled on minimal doses of diuretic and ACE inhibitor or equivalent", otherwise unclear. No information in baseline characteristics
Strata 2: People with atherosclerotic cardiovascular disease	Not stated/unclear Excluded "extensive vascular disease", otherwise unclear. No information in baseline characteristics
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear Excluded "chronic renal impairment measured by an estimated creatinine clearance of < 65 ml/min using the Cockcroft Gault equation", 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	
Comparator	Placebo (n=1) Placebo given twice daily for 12 months
Number of participants	183
Duration of follow-up	12 months
Indirectness	No additional information
Method of analysis	ITT
Additional comments	Analyses were conducted on an ITT wherever data were available.

55.2. Study arms

55.2.1. Metformin (N = 92)

Participants received metformin to a target dose of 2 g a day or maximum tolerated dose given in two divided doses. Participants underwent a gradual introduction of metformin to maximum dose of 1 g twice a day over a 4 week period. Those who experienced gastrointestinal side effects were advised to revert to the highest tolerated dose and to remain on this until the end of the study. No standard management protocol for the adjustment of insulin was specified. Participants were in

regular contact with their diabetes team when given advice about insulin dose changes and methods to improve control. All teams worked to target of pre-meal capillary blood glucose targets <7 mmol/L without debilitating hypoglycaemia and HbA1c levels <7%.

55.2.2. Placebo (N = 91)

Patients received placebo daily in two divided doses. No standard management protocol for the adjustment of insulin was specified. Participants were in regular contact with their diabetes team when given advice about insulin dose changes and methods to improve control. All teams worked to target of pre-meal capillary blood glucose targets <7 mmol/L without debilitating hypoglycaemia and HbA1c levels <7%.

55.3. Characteristics

55.3.1. Arm-level characteristics

Characteristic	Metformin (N = 92)	Placebo (N = 91)
% Male Sample size	n = 62 ; % = 67	n = 57 ; % = 63
Mean age (SD) (Years (mean, SD)) Mean (SD)	58 (8.9)	58 (7.7)
Ethnicity Sample size	n = NR ; % = NR	n = NR ; % = NR
Time since type 2 diabetes diagnosed (Years (mean, SD)) Mean (SD)	9 (5.2)	10 (5.2)
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

Characteristic	Metformin (N = 92)	Placebo (N = 91)
People with a learning disability Sample size	n = NR ; % = NR	n = NR ; % = NR
Number of people with obesity Sample size	n = NR ; % = NR	n = NR ; % = NR
Other antidiabetic medication used Sample size	n = NA ; % = NA	n = NA ; % = NA
Insulin use Sample size	n = 92 ; % = 100	n = 91 ; % = 100

56. Dungan, 2016

Bibliographic Reference	Dungan, K. M.; Weitgasser, R.; Perez Manghi, F.; Pintilei, E.; Fahrbach, J. L.; Jiang, H. H.; Shell, J.; Robertson, K. E.; A 24-week study to evaluate the efficacy and safety of once-weekly dulaglutide added on to glimepiride in type 2 diabetes (AWARD-8); Diabetes Obes Metab; 2016; vol. 18 (no. 5); 475-482

56.1. Study details

Trial name / registration number	NCT01769378 AWARD-8
Study type	Randomised controlled trial (RCT)
Study location	NR
Study setting	NR
Study dates	NR
Sources of funding	Funded by Eli Lilly and Company. First author declares funding and honoraria from multiple pharmaceutcal companies
Inclusion criteria	Adult men and women (aged ≥18 years) with BMI ≤45 kg/m2 with T2D not optimally controlled [HbA1c ≥7.5 and ≤9.5% (≥58 and ≤80 mmol/mol)] with diet and exercise on a stable dose of sulphonylurea that was at least 50% of the maximum dose per country-specific label for at least 3 months before screening.
Exclusion criteria	Patients treated with any other antihyperglycaemic medication (including insulin) less than 3 months before screening were excluded from the study, as were patients with a history of pancreatitis, signs or symptoms of liver disease, impaired renal function (estimated glomerular filtration rate <30 ml/min/1.73m2) elevated serum calcitonin concentration (20 ng/L) or recent history of severs hypoglycaemia
Intervention(s)	Dulaglutide (n=240) 1.5 mg administered as a weekly subcutaneous injection for 24 weeks
Cointervention	Concomitant therapy: During a two week lead-in period, participants either continued their pre-study dose of glimepiride or replaced their previous sulphonylurea with an approximately equivalent dose of glimepiride. Participants maintained their lead-in glimepiride dose throughout the study, but the dose could be reduced, followed by discontinuation, in the case of hypoglycaemia or for an AE. Patients with severe, persistent hyperglycaemia could either increase the glimepiride dose or initiate additional glycaemic rescue therapy

Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear Not an inclusion/exclusion criteria. No information in baseline characteristics.
Strata 2: People with atherosclerotic cardiovascular disease	Not stated/unclear Not an inclusion/exclusion criteria. No information in baseline characteristics.
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear Excluded "impaired renal function (estimated glomerular filtration rate <30 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=60) Placebo administered once weekly as a subcutaneous injection for 24 weeks
Number of participants	300
Duration of follow-up	24 weeks
Indirectness	No additional information
Method of analysis	ITT
Additional comments	Efficacy and safety analyses were performed using the intention-to-treat population, defined as all randomized patients who took ≥1 dose of study medication. Efficacy and hypoglycaemia measurements were censored after therapeutic intervention for persistent hyperglycaemia (post-rescue). A mixed-model for repeated measures (MMRM) was used as the primary analysis model, with treatment, country, visit and treatment-by-visit as fixed effects, baseline as a covariate, and patient as a random effect. The secondary analysis for the primary endpoint was analysis of covariance (ANCOVA) for change in HbA1c from baseline to endpoint, with country and treatment as fixed effects and baseline as a covariate. Body weight was analysed using MMRM and ANCOVA and adjusted for baseline values. MMRM was used for analyses of other continuous measures. The chi-squared test was used for categorical measures. The percentages of patients achieving HbA1c targets [last observed carried forward (LOCF)] were analysed using a logistic regression model for repeated measures with factors of treatment, country, baseline HbA1c, visit and visit-by-treatment interaction. Hypoglycaemia rate was analysed using a generalized linear model with negative binomial distribution

56.2. Study arms

56.2.1. Dulaglutide (N = 240)

Dulaglutide 1.5 mg initiated administered once weekly as a subcutaneous injection in patients with T2D who had inadequate glycaemic control with sulphonylurea monotherapy. During the 2 week lead-in period, participants either continued their pre-study dose of glimepiride or replaced their previous sulphonylurea with an approximately equivalent dose of glimepiride. Participants maintained their lead-in glimepiride dose throughout the study, but the dose could be reduced, followed by discontinuation, in the case of hypoglycaemia or for an AE. Patients with severe, persistent hyperglycaemia could either increase the glimepiride dose or initiate additional glycaemic rescue therapy.

56.2.2. Placebo (N = 60)

Placebo administered once weekly as a subcutaneous injection in patients with T2D who had inadequate glycaemic control with Sulphonylurea monotherapy. During the 2 week lead-in period, participants either continued their pre-study dose of glimepiride or replaced their previous sulphonylurea with an approximately equivalent dose of glimepiride. Participants maintained their lead-in glimepiride dose throughout the study, but the dose could be reduced, followed by discontinuation, in the case of hypoglycaemia or for an AE. Patients with severe, persistent hyperglycaemia could either increase the glimepiride dose or initiate additional glycaemic rescue therapy.

56.3. Characteristics

56.3.1. Arm-level characteristics

Characteristic	Dulaglutide (N = 240)	Placebo (N = 60)
% Male Dulaglutide n = 239, Placebo n = 60 Sample size	n = 104 ; % = 43.5	n = 28 ; % = 46.7
Mean age (SD) (Years (mean, SD)) Dulaglutide n = 239, Placebo n = 60 Mean (SD)	57.7 (10.2)	58.2 (7.4)
Ethnicity Dulaglutide n = 239, Placebo n = 60 Sample size	n = NA ; % = NA	n = NA ; % = NA
American-Indian/Alaska Native Sample size	n = 21 ; % = 8.8	n = 5 ; % = 8.3
Asian Sample size	n = 3 ; % = 1.3	n = 2 ; % = 3.3

Characteristic	Dulaglutide (N = 240)	Placebo (N = 60)
Black or African American Sample size	n = 7 ; % = 2.9	n = 4 ; % = 6.7
Multiple Sample size	n = 6 ; % = 2.5	n = 2 ; % = 3.3
White Sample size	n = 202 ; % = 84.5	n = 47 ; % = 78.3
Hispanic or Latino Sample size	n = 112 ; % = 46.9	n = 27 ; % = 45
Not hispanic or latino Sample size	n = 127 ; % = 53.1	n = 33 ; % = 55
Presence of frailty Dulaglutide n = 239, Placebo n = 60 Sample size	n = NR ; % = NR	n = NR ; % = NR
Time since type 2 diabetes diagnosed (Years (mean, SD)) Dulaglutide n = 239, Placebo n = 60 Mean (SD)	7.8 (5.3)	6.8 (3.8)
Smoking status Dulaglutide n = 239, Placebo n = 60 Sample size	n = NR ; % = NR	n = NR ; % = NR
Alcohol consumption Dulaglutide n = 239, Placebo n = 60 Sample size	n = NR ; % = NR	n = NR ; % = NR
Presence of severe mental illness Dulaglutide n = 239, Placebo n = 60 Sample size	n = NR ; % = NR	n = NR ; % = NR
People with significant cognitive impairment Dulaglutide n = 239, Placebo n = 60 Sample size	n = NR ; % = NR	n = NR ; % = NR
People with a learning disability Dulaglutide n = 239, Placebo n = 60 Sample size	n = NR ; % = NR	n = NR ; % = NR

Characteristic	Dulaglutide (N = 240)	Placebo (N = 60)
Number of people with obesity Dulaglutide n = 239, Placebo n = 60 Sample size	n = NR ; % = NR	n = NR ; % = NR
Other antidiabetic medication used Dulaglutide n = 239, Placebo n = 60 Sample size	n = NA ; % = NA	n = NA ; % = NA
Glimepiride use Sample size	n = 239 ; % = 100	n = 60 ; % = 100

57. Dungan, 2014

Bibliographic Reference	Dungan, Kathleen M; Povedano, Santiago Tofe; Forst, Thomas; Gonzalez, Jose G Gonzalez; Atisso, Charles; Sealls, Whitney; Fahrbach, Jessie L; Once-weekly dulaglutide versus once-daily liraglutide in metformin-treated patients with type 2 diabetes (AWARD-6): a randomised, open-label, phase 3, non-inferiority trial.; Lancet (London, England); 2014; vol. 384 (no. 9951); 1349-57

57.1. Study details

Trial name / registration number	NCT01624259
Study type	Randomised controlled trial (RCT)
Study location	62 sites in 9 countries
Study setting	No additional information
Study dates	20 June 2012 to 25 November 2013
Sources of funding	Sponsored by Eli Lilly and Company. Authors state numerous grants and honoraria from multiple pharmaceutical companies.
Inclusion criteria	Patients are eligible to be included in the study only if they meet all of the following criteria at Visit 1: 1. Have type 2 diabetes based on WHO diagnostic criteria 2. Are not optimally controlled on diet and exercise and a dose of metformin that is at least 1500 mg/day and has been at a stable dose for at least 3 months prior to Visit 1 3. Have an HbA1c value of ≥7·0% (≥53 mmol/mol) to ≤10·0% (≤86 mmol/mol), as determined by the central laboratory draw performed at Visit 1 4. Accept continued treatment with metformin throughout the trial, as required per protocol 5. Are able and willing to administer once daily or once weekly injections 6. Are men or nonpregnant women who are ≥18 years of age 7. Have a stable weight (±5%) for at least 3 months prior to Visit 1

	8. Have a body mass index (BMI) that is ≤45 kg/m2 9. Are, in the investigator's opinion, well-motivated, capable, and willing to: • Perform SMPG testing • Learn how to self-inject treatment, as required for this protocol (visually impaired persons who are not able to perform the injections must have the assistance of a sighted individual trained to inject the study drug; persons with physical limitations who are not able to perform the injections must have the assistance of an individual trained to inject the study drug) • Maintain a study diary, as required for this protocol 10. Are females of childbearing potential (a woman will be considered of childbearing potential if she is not surgically sterilized and between menarche and 1-year postmenopausal [2-years postmenopausal if <50 years of age]) who must: • Test negative for pregnancy at Visit 1, based on a serum pregnancy test • Agree to use a reliable method of birth control; partner with vasectomy; or abstinence if consistent with lifestyle) during the study, and for 1 month following the last dose of study drug • Not be breastfeeding 11. Have given written informed consent to participate in this study in accordance with local regulations and the ethical review board (ERB) governing the study site.
Exclusion criteria	Patients will be excluded from the study if they meet any of the following criteria at Visit 1: 1. Have type 1 diabetes mellitus 2. Have been treated with ANY other antihyperglycemic medications (other than metformin) at the time of Visit 1 or within the 3 months prior to Visit 1 3. Have used insulin therapy (outside of pregnancy) any time in the past 2 years, except for short-term treatment of acute conditions, and up to a maximum of 4 weeks; any insulin use within 3 months prior to Visit 1 is exclusionary 4. Have a history of ≥1 episodes of ketoacidosis or hyperosmolar state/coma 5. Have been treated with drugs that promote weight loss within 3 months of Visit 1

	6. Are receiving chronic (>14 days) systemic glucocorticoid therapy (excluding topical, intraocular, intranasal, or inhaled preparations) or have received such therapy within the 4 weeks immediately prior to Visit 1 7. Have had any of the following CV conditions within 2 months prior to Visit 1: acute myocardial infarction, New York Heart Association (NYHA) Class III or Class IV heart failure, or cerebrovascular accident (stroke) 8. Have a known clinically significant gastric emptying abnormality (eg, severe diabetic gastroparesis or gastric outlet obstruction) or have undergone gastric bypass (bariatric) surgery or restrictive bariatric surgery 9. Have acute or chronic hepatitis, signs and symptoms of any other liver disease, or alanine transaminase (ALT) level ≥3 times the upper limit of the reference range, as determined by the central laboratory (patients with nonalcoholic fatty liver disease are eligible) at Visit 1 10. Have a history of chronic pancreatitis or acute idiopathic pancreatitis, or were diagnosed with any type of acute pancreatitis within the 3-month period prior to Visit 1 11. Have a serum creatinine ≥1·5 mg/dL (male) or ≥1·4 mg/dL (female), or a creatinine clearance <60 mL/minute as determined by the central laboratory at Visit 1 12. Have evidence of a significant, uncontrolled endocrine abnormality (eg, thyrotoxicosis, adrenal crisis), in the opinion of the investigator 13. Have any 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 (this exclusion includes those patients with a family history of MEN 2A or 2B, whose family history for the syndrome is RET negative; the only exception for this exclusion will be for patients whose family members with MEN 2A or 2B have a known RET

	mutation and the potential patient for the study is negative for that RET mutation) 14. Have any self or family history of medullary C-cell hyperplasia, focal hyperplasia, carcinoma (including sporadic, familial or part of MEN 2A or 2B syndrome) 15. Have a serum calcitonin ≥20 pg/mL as determined by the central laboratory at Visit 1 16. Have evidence of a significant, active autoimmune abnormality (eg, lupus, rheumatoid arthritis) 17. Have any other condition not listed in this section (eg, hypersensitivity) that is a contraindication for the use of dulaglutide, metformin or liraglutide 18. Have a history of a transplanted organ (corneal transplantation [keratoplasty] is allowed) 19. Have a history of an active or untreated malignancy, or are in remission from a clinically significant malignancy (other than basal or squamous cell skin cancer, in situ carcinomas of the cervix, or in situ prostate cancer) during the last 5 years prior to Visit 1 20. Have a history of any other condition (such as known drug or alcohol abuse or a psychiatric disorder) which, in the opinion of the investigator, may preclude the patient from following and completing the protocol 21. Have any hematological condition that may interfere with HbA1c measurement (e.g., hemolytic anemias, sickle-cell disease) 22. Are investigator site personnel directly affiliated with this study and/or their immediate families. Immediate family is defined as a spouse, parent, child, or sibling, whether biological or legally adopted 23. Are Lilly employees 24. Are currently enrolled in, or discontinued within the last 30 days from, a clinical trial involving an off-label use of an investigational drug or device (other than the study drug/device used in this study), or concurrently enrolled in any

	other type of medical research judged not to be scientifically or medically compatible with this study 25. Have previously screen failed, discontinued, completed or withdrawn from this study or have been randomised in any other clinical trial of dulaglutide
Intervention(s)	Dulaglutide (n=299) 1.5 mg once weekly dose via a pre-filled syringe to be self-administered.
Cointervention	Concomitant therapy: Patients continued metformin therapy greater than 1500 mg/day up to the highest dose allowed per local label throughout the study. Patients with severe, persistent hyperglycaemia during the study could initiate additional glycaemic rescue therapy according to prespecified criteria. The antihyperglycaemic intervention was determined by the investigator; use of other non-study GLP-1 receptor agonists or inhibitors of dipeptidyl peptidase-4 was not permitted.
Strata 1: People with type 2 diabetes mellitus and heart failure	People without heart failure
Strata 2: People with atherosclerotic cardiovascular disease	Not stated/unclear Excluded "recent cardiovascular event", prior unclear. No information in baseline characteristics.
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear Not an inclusion/exclusion criteria. No information in baseline characteristics.
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	Not stated/unclear
Subgroup 1: People with moderate or severe frailty	Not stated/unclear

Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear
Subgroup 3: People with non-alcoholic fatty liver disease	Not stated/unclear
Subgroup 4: People with obesity	Not stated/unclear
Subgroup 5: eGFR category at baseline	Not stated/unclear
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Comparator	Liraglutide (n=300) Liraglutide was up-titrated from 0.6 mg/day in week 1, to 1.2 mg/day in week 2 and then to 1.8 mg/day in week 3 using a prefilled pen to be self administered.
Number of participants	599
Duration of follow-up	26 weeks
Indirectness	No additional information
Method of analysis	ITT
Additional comments	Efficacy and safety analyses were done with the intention-to-treat population (all randomly assigned patients who took one or more doses of study drug). For efficacy and hypoglycaemia measures, only data obtained before rescue drugs were given were used. The primary efficacy analysis used a mixed model for repeated measures (MMRM) with treatment, country, visit, and treatment-by-visit interaction as fixed effects; baseline as covariate; and patient as random effect. The secondary sensitivity analysis for the primary endpoint was ANCOVA with country and treatment as fixed effects and baseline as a covariate with the last (postbaseline HbA1c) observation carried forward (LOCF). MMRM and ANCOVA were used for change in bodyweight. Analyses for other measures used MMRM. Hypoglycaemia rates were analysed with a generalised linear model with negative binomial distribution. The percentage of patients with adverse

	events was analysed with use of a χ^2 test, unless insufficient data were available to meet analysis assumptions, then Fisher's exact test was used. Least-squares means (LSM) for HbA1c, fasting serum glucose, and bodyweight were calculated.

57.2. Study arms

57.2.1. Dulaglutide (N = 299)

Patients were given a prefilled syringe to be self-administered. Dulaglutide was started at the full 1·5 mg once-weekly dose. Patients unable to tolerate the full dose of study drug were required to discontinue the study drug but encouraged to remain in the study to collect safety data for the full intention-to-treat population. Patients continued metformin therapy (≥1500 mg/day and up to the highest dose allowed per local label) throughout the study. Patients with severe, persistent hyperglycaemia during the study could initiate additional glycaemic rescue therapy according to prespecified criteria. The antihyperglycaemic intervention was determined by the investigator; use of other non-study GLP-1 receptor agonists or inhibitors of dipeptidyl peptidase-4 was not permitted. Patients given dulaglutide were tested for the development of dulaglutide antidrug antibodies and serum calcitonin was measured throughout the study

57.2.2. Liraglutide (N = 300)

Patients were given a prefilled pen to be self-administered. Liraglutide was up-titrated from 0·6 mg/day in week 1, to 1·2 mg/day in week 2, and then to 1·8 mg/day in week 3. Patients unable to tolerate the full dose of study drug were required to discontinue the study drug but encouraged to remain in the study to collect safety data for the full intention-to-treat population. Patients continued metformin therapy (≥1500 mg/day and up to the highest dose allowed per local label) throughout the study. Patients with severe, persistent hyperglycaemia during the study could initiate additional glycaemic rescue therapy according to prespecified criteria. The antihyperglycaemic intervention was determined by the investigator; use of other non-study GLP-1 receptor agonists or inhibitors of dipeptidyl peptidase-4 was not permitted. Serum calcitonin was measured throughout the study

57.3. Characteristics

57.3.1. Arm-level characteristics

Characteristic	Dulaglutide (N = 299)	Liraglutide (N = 300)
% Male Sample size	n = 138 ; % = 46	n = 149 ; % = 50

Characteristic	Dulaglutide (N = 299)	Liraglutide (N = 300)
Mean age (SD) Mean (SD)	56.5 (9.3)	56.8 (9.9)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA
American-Indian/Alaska Native Sample size	n = 20 ; % = 7	n = 23 ; % = 8
Asian Sample size	n = 1 ; % = 0.3	n = 2 ; % = 1
Black or African American Sample size	n = 21 ; % = 7	n = 16 ; % = 5
Multiple Sample size	n = 1 ; % = 0.3	n = 2 ; % = 1
White Sample size	n = 256 ; % = 86	n = 259 ; % = 86
Hispanic or Latino (n=295, dulaglutide arm, n=295 for liraglutide arm) Sample size	n = 75 ; % = 25	n = 72 ; % = 24
Not Hispanic or Latino (n=295, dulaglutide arm, n=295 for liraglutide arm) Sample size	n = 221 ; % = 75	n = 223 ; % = 76
Presence of frailty Sample size	n = NR ; % = NR	n = NR ; % = NR
Time since type 2 diabetes diagnosed (Years (mean, SD)) Mean (SD)	7.1 (5.4)	7.3 (5.4)
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	n = NR ; % = NR	n = NR ; % = NR

Characteristic	Dulaglutide (N = 299)	Liraglutide (N = 300)
Sample size		
People with significant cognitive impairment Sample size	n = NR ; % = NR	n = NR ; % = NR
People with a learning disability Sample size	n = NR ; % = NR	n = NR ; % = NR
Number of people with obesity Sample size	n = NR ; % = NR	n = NR ; % = NR
Other antidiabetic medication used Sample size	n = NA ; % = NA	n = NA ; % = NA
Metformin use Sample size	n = 299 ; % = 100	n = 300 ; % = 100

58. Ferdinand, 2019

Bibliographic Reference	Ferdinand, K. C.; Izzo, J. L.; Lee, J.; Meng, L.; George, J.; Salsali, A.; Seman, L.; Antihyperglycemic and Blood Pressure Effects of Empagliflozin in Black Patients With Type 2 Diabetes Mellitus and Hypertension; Circulation; 2019; vol. 139 (no. 18); 2098-2109

58.1. 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	URL: https://www.clinicaltrials.gov. Unique identifier: NCT02182830
Study type	Randomised controlled trial (RCT)
Study location	92 centres in the United States
Study setting	Unspecified clinical setting
Study dates	2014-07-03 to 2018-07-31
Sources of funding	Boehringer Ingelheim
Inclusion criteria	• Diagnosis of Type 2 Diabetes Mellitus (T2DM) prior to informed consent. Male and female black/African American patients on diet and exercise regimen who are EITHER drug-naïve (defined as absence of any oral antidiabetic therapy, glucagon like peptide-1 (GLP-1) analogue or insulin for 12 weeks, 16 weeks for pioglitazone prior to randomisation) OR pre-treated with stable dose of • Metformin only, or • Sulfonylurea only, or

	• Dipeptidyl peptidase-4 (DPP-4) inhibitor only, or • metformin plus sulfonylurea, or • metformin plus DPP-4 inhibitor. Treatment has to be unchanged for a minimum of 12 weeks prior to randomization. Dose for metformin: maximum tolerated dose The maximum daily dose of Sulfonylurea (SU) or DPP-4 inhibitor should not exceed that stated in the local label. • HbA1c of >= 7.0% (53 mmol/mol) and ≤ 11.0% (97 mmol/mol) at Visit 1 (screening). • Mean seated Systolic Blood Pressure (SBP) 140-180 mmHg at Visit 1 (screening). • Successful completion of baseline Ambulatory Blood Pressure Monitor (ABPM) testing with a mean SBP 135-175 mmHg prior to randomisation. • Treatment with stable doses of at least one but not more than 4 antihypertensive medication >= 4 weeks prior to randomisation. • Age >= 18 years at Visit 1 (screening) • Signed and dated written informed consent by date of Visit 1 in accordance with Good Clinical Practice (GCP) and local legislation
Exclusion criteria	• Uncontrolled hyperglycemia with a glucose level >270 mg/dl (>15.0 mmol/L) after an overnight fast during placebo run-in (includes Visit 2.1) and confirmed by a second measurement (not on the same day). • Exposure to any other antidiabetic medication within 12 weeks prior to randomisation other than metformin, sulfonylurea, Dipeptidyl peptidase-4 (DPP-4) inhibitor, metformin plus sulfonylurea or metformin plus DPP-4 inhibitor. • Current hypertension treatment with oral Minoxidil (topical minoxidil for hair growth is allowed). • Mean seated Systolic Blood Pressure (SBP) ≥181 mmHg during placebo run-in visit and confirmed by a second measurement (not on the same day) preferably within one day. • Upper arm circumference that exceeds the upper circumference level of the cuff size of either Ambulatory Blood Pressure Monitor (ABPM) and/or (BP) measurement device used in the study. • Night shift workers who routinely sleep during the daytime and/or whose work hours include midnight. • Diagnosis of autoimmune diabetes/Type I diabetes mellitus, monogenic (neonatal or maturity onset diabetes of the young (MODY)) diabetes or Type I diabetes in adults/latent autoimmune diabetes of adults (LADA) per investigator or patient medical history at the time of Visit 1 (screening). • Known or suspected secondary hypertension (e.g. renal artery stenosis, phaeochromocytoma, Cushing's disease). • History or evidence of hypertensive retinopathy (Keith-Wagener grade III or IV) and/or hypertensive encephalopathy. • Clinically significant valvular heart disease or severe aortic stenosis in the opinion of the investigator. • Acute coronary syndrome (non- ST wave elevated myocardial infarction (STEMI), STEMI and unstable angina pectoris), stroke or transient ischemic attack within 3 months prior to informed consent. • Indication of liver disease, defined by serum levels of either Alanine Aminotransferase (ALT) (Serum Glutamic Pyruvate

	Transaminase(SGPT)), Aspartate Aminotransferase (AST) (Serum Glutamic Oxaloacetic Transaminase (SGOT)), or alkaline phosphatase above 3 x upper limit of normal (ULN) as determined during screening and/or run-in phase. • Impaired renal function, defined as Estimated Glomerular Filtration Rate (eGFR)< 45 ml/min/1.73m2 (moderate renal impairment, chronic kidney disease epidemiology collaboration Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula) as determined during screening and/or run-in phase. • Bariatric surgery within the past two years and other gastrointestinal surgeries that induce chronic malabsorption. • Medical history of cancer (except for basal cell carcinoma) and/or treatment for cancer within the last 5 years. • Blood dyscrasias or any disorders causing hemolysis or unstable Red Blood Cells (e.g. malaria, babesiosis, haemolytic anaemia, thalassemia, sickle cell anaemia (sickle cell trait is allowed)). • Medical history and signs and symptoms of diabetic autonomic neuropathy. • Treatment with anti-obesity drugs 3 months prior to randomisation (i.e. surgery, aggressive diet regimen, etc.) leading to unstable body weight. • Current treatment with systemic steroids at time of informed consent or change in dosage of thyroid hormones within 6 weeks prior to informed consent or any other uncontrolled endocrine disorder except Type 2 Diabetes Mellitus (T2DM) in the opinion of the investigator. Pre-menopausal women (last menstruation <=1 year prior to informed consent) who: • are nursing or pregnant or • are of child-bearing potential and are not practicing an acceptable method of birth control, or do not plan to continue using this method throughout the study and do not agree to submit to periodic pregnancy testing during participation in the trial. Acceptable methods of birth control include tubal ligation, transdermal patch, intra uterine devices/systems (IUDs/IUSs), oral, implantable or injectable contraceptives, complete sexual abstinence (if acceptable by local authorities), double barrier method and vasectomised partner. • Alcohol, drug or confectionary liquorice abuse within the 3 months prior to informed consent that would interfere with trial participation or any ongoing condition leading to a decreased compliance to study procedures or study drug intake in the investigator's opinion. • Intake of an investigational drug in another trial within 30 days prior to intake of study medication in this trial; or participating in another trial (involving an investigational drug and/or follow-up) after discontinuing medication in that trial. • Any other clinical condition that would jeopardize patient's safety while participating in this clinical trial in the opinion of the investigator.

Recruitment / selection of participants	Details not provided
Intervention(s)	Empagliflozin starting dose 10mg; forced titration after 4 weeks 25mg dose
Cointervention	Patients were either drug-naive or pretreated with a stable dose (≥12 weeks) of oral antihyperglycemic treatment, which was continued during the trial. All patients were on at least 1 antihypertensive medication that was similarly held stable. Patients received both glucose- and antihypertensive-rescue medication based on predefined criteria.
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear Not an inclusion/exclusion criteria. No information in baseline characteristics
Strata 2: People with atherosclerotic cardiovascular disease	People without atherosclerotic cardiovascular diseases Not an inclusion/exclusion criteria. Baseline characteristics only give breakdown of CAD, cerebrovascular disease and PAD separately with overlap unclear, however these proportions still only add up to <20% so likely to fit into this stratum.
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear Not an inclusion/exclusion criteria. Baseline characteristics give eGFR categories but not CKD diagnosis.
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	Data unavailable
Comparator	Comparator: Placebo starting dose 10mg; forced titration after 4 weeks 25mg dose
Number of participants	Of 166 patients randomly assigned, 150 received study medication and had at least 1 on-treatment HbA1c measurement and, thus, were included in the full analysis set (FAS; placebo, n=72; empagliflozin 10–25 mg, n=78).
Duration of follow-up	24 weeks treatment followed by 2 weeks follow up.
Indirectness	None identified
Method of analysis	Per protocol

58.2. Study arms

58.2.1. Empagliflozin (N = 78)

starting dose 10mg; forced titration after 4 weeks 25mg dose

58.2.2. Placebo (N = 72)

Matched dose placebo

58.3. Characteristics

58.3.1. Arm-level characteristics

Characteristic	Empagliflozin (N = 78)	Placebo (N = 72)
% Male Nominal	55.1	50
Mean age (SD) Mean (SD)	56.5 (9.3)	57.2 (9.3)
Black % Nominal	100	100
Diabetic neuropathy Nominal	14.1	18.1
Urinary tract infection Nominal	14.1	5.6
Coronary artery disease Nominal	7.7	6.9
Diabetic retinopathy Nominal	6.4	4.2
Genital infection Nominal	1.3	6.9
peripheral atery occlusive disease Nominal	1.3	2.8
Diabetic nephropathy Nominal	1.3	1.4
Cerebrovascular disease Nominal	1.3	0
Time since type 2 diabetes diagnosed Mean (SD)	9.3 (6.2)	9.3 (7.9)
Heart rate Mean (SD)	78.8 (9.5)	74.8 (10.3)
BMI	36.04 (12.83)	35.12 (8.29)

Characteristic	Empagliflozin (N = 78)	Placebo (N = 72)
Mean (SD)		
eGFR mL/min/1.73m2 Mean (SD)	91.15 (18.95)	91.49 (20.79)

59. Fernandez, 2008

Bibliographic Reference	Fernandez, M.; Triplitt, C.; Wajcberg, E.; Sriwijilkamol, A. A.; Musi, N.; Cusi, K.; DeFronzo, R.; Cersosimo, E.; Addition of pioglitazone and ramipril to intensive insulin therapy in type 2 diabetic patients improves vascular dysfunction by different mechanisms; Diabetes Care; 2008; vol. 31 (no. 1); 121-7

59.1. 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	NR
Study type	Randomised controlled trial (RCT)
Study location	Texas, the US
Study setting	Patients were recruited from the outpatient clinic at the Texas Diabetes Institute
Study dates	NR
Sources of funding	• American Diabetes Association • Takeda Pharmaceuticals
Inclusion criteria	• Patients with type 2 diabetes who required insulin therapy (A1C>8.0% despite optimized oral agent therapy) • Patients on insulin combination therapy with metformin, sulfonylureas, and/or meglitinide • Patients taking ACE inhibitors or angiotensin II receptor blockade (ARB) agents were switched to alpha-methyl dopa, and the dose was adjusted to re-establish blood pressure (<130/80 mmHg) control before they were enrolled in the study.

	• The ACE inhibitor/ARB therapy was discontinued for at least 2 months before the study, and other medications were allowed only if the subject was stable for at least 3 months.
Exclusion criteria	• Patients taking TZDs
Recruitment / selection of participants	Patients were recruited from the outpatient clinic at the Texas Diabetes Institute
Intervention(s)	• Pioglitazone 45 mg/day for 36 weeks • Pioglitazone was started at the dose of 15 mg daily and then increased to 30 mg daily at week 2 and to 45 mg daily at week 4
Cointervention	• 3-day comprehensive diabetes education and nutritional program conducted at the Texas Diabetes Institute. • Patients were allowed to select between insulin therapy using multiple daily insulin injection (MDII) or continuous subcutaneous insulin infusion (CSII). • MDII consisted of a basal-bolus program with four daily insulin injections using a combination of insulin glargine (sanofi-aventis) at bedtime plus premeal insulin aspart (Novo Nordisk). • CSII was implemented using the Medtronic/Minimed (n=6) or the Animas (n=6) pump using basal infusion and premeal boluses of insulin aspart (Novo Nordisk). • Participants were contacted by phone at least weekly during the first two months. Insulin dose was adjusted according to the University of Texas Hospital protocol to achieve the following pre-established glycemic goals: fasting and premeal capillary blood glucose values between 80 and 120 mg/dl, 2-h post meal glucose values <160 mg/dl, and bedtime glucose levels <140 mg/dl. If the premeal glycaemic goal range was not attained, patients were instructed to supplement their usual insulin dose with an additional 1, 2, or 3 units if the capillary blood glucose measurement was >120, >150, or >180 mg/dl, respectively. If the capillary blood glucose measurement was <80 mg/dl, the calculated premeal insulin dose was reduced by 1–2 units. If the fasting blood glucose concentration was >80 and <120 mg/dl for a minimum of 3 consecutive days, the insulin basal dose and the basal infusion rate were adjusted accordingly by ~10% daily.
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	Not stated/unclear

atherosclerotic cardiovascular disease	Not an inclusion/exclusion criteria. No information in baseline characteristics
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear Not an inclusion/exclusion criteria. No information in baseline characteristics
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	Not stated/unclear
Subgroup 1: People with moderate or severe frailty	Not stated/unclear
Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear
Subgroup 3: People with non-alcoholic fatty liver disease	Not stated/unclear
Subgroup 4: People with obesity	Not stated/unclear
Subgroup 5: eGFR category at baseline	Not stated/unclear
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Population subgroups	N/A

Comparator	Placebo tablets were added to match the other treatment regimen.
Number of participants	30 participants in total in the study, however only the pioglitazone (n=10) and placebo (n=10) arms are relevant to this review. The report does not mention any attrition, so it is assumed that data were available for all participants.
Duration of follow-up	36 weeks - All patients were asked to return for visits at 2- to 4-week intervals during the first 3 months and every 2 months there after for the remainder of the 9-month study period.
Indirectness	people are also on insulin and switch insulin at the start of the study
Method of analysis	ITT
Additional comments	A total of 10 subjects per group was derived from a two-sided test with significance levels alpha = 0.05 and a power of 1-beta = 0.90, using a mean SD of ±30%.

59.2. Study arms

59.2.1. Pioglitazone (N = 10)

45 mg/day. Pioglitazone was started at the dose of 15 mg daily and then increased to 30 mg daily at week 2 and to 45 mg daily at week 4.

59.2.2. Placebo (N = 10)

59.3. Characteristics

59.3.1. Study-level characteristics

Characteristic	Study (N = 20)
% Male Nominal	40
Time since type 2 diabetes diagnosed (years) Range	6.2 to 8.4
Systolic blood pressure Nominal	130
Diastolic blood pressure	70

Characteristic	Study (N = 20)
Nominal	
BMI Range	31 to 33

60. Ferrannini, 2009

Bibliographic Reference	Ferrannini, E; Fonseca, V; Zinman, B; Matthews, D; Ahren, B; Byiers, S; Shao, Q; Dejager, S; Fifty-two-week efficacy and safety of vildagliptin vs. glimepiride in patients with type 2 diabetes mellitus inadequately controlled on metformin monotherapy.; Diabetes, obesity & metabolism; 2009; vol. 11 (no. 2); 157-66

60.1. Study details

Secondary publication of another included study- see primary study for details	Parent study
Other publications associated with this study included in review	Also a 2 year extension study with meal test (Ahren 2010)
Trial name / registration number	ClinicalTrials.gov Identifier: NCT00106340
Study type	Randomised controlled trial (RCT)
Study location	Germany, United States
Study setting	Unspecified clinical setting
Study dates	March 2005 to May 2008
Sources of funding	Novartis Pharmaceuticals
Inclusion criteria	• On a stable dose of metformin as defined by the protocol • Body mass index (BMI) in the range 22-45 • Blood glucose criteria must be met

	• 18 Years to 73 Years
Exclusion criteria	• Pregnancy or lactation • Type 1 diabetes • Evidence of significant diabetic complications • Evidence of serious cardiovascular complications • Laboratory value abnormalities as defined by the protocol • Other protocol-defined exclusion criteria may apply
Recruitment / selection of participants	Patients attended one screening visit (week -4, visit 1)where inclusion and exclusion criteria were assessed
Intervention(s)	Eligible patients were randomized 1:1 at baseline (day 0) to receive vildagliptin(50 mg twice daily) or glimepiride (starting dose 2mg/day) in addition to metformin (dose remained unchanged). Further visits were scheduled at weeks 4,8, 12, 16, 20, 24, 32, 40, 46 and 52. Glimepiride/matched control could be up-titrated (to a maximum of 6 mg/day)
Cointervention	a stable dose of metformin (mean dose 1898 mg/day; mean duration of use 36 months)
Strata 1: People with type 2 diabetes mellitus and heart failure	People without heart failure Excluded "serious cardiac conditions (congestive heart failure requiring pharmacological treatment)".
Strata 2: People with atherosclerotic cardiovascular disease	People without atherosclerotic cardiovascular diseases Excluded "serious cardiac conditions (history of torsades de pointes or ventricular tachycardia; percutaneous coronary intervention in the past 3 months; myocardial infarction, coronary artery bypass surgery, unstable angina or stroke in the past 6 months; second- or third-degree atrioventricular block or prolonged QTc)". Unclear number of people who had CVD >6 months previously. Baseline characteristics show overall incidence of previous cardiac disorders was <20%
Strata 3: People with type 2 diabetes mellitus	People without chronic kidney disease Excluded clinically significant renal disease. However, baseline characteristics also show some people had renal insufficiency (43% mild and 4.8% moderate).

and chronic kidney disease	As mild renal deficiency does not always mean CKD, gone with the exclusion criteria to classify for this stratum.
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	People without non-alcoholic fatty liver disease Covered by exclusion of people with clinically significant liver or renal disease
Subgroup 4: People with obesity	People with obesity
Subgroup 5: eGFR category at baseline	eGFR ≥30mL/min/1.73m2
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Population subgroups	None

Comparator	This was a multicentre, randomized, double-blind, active-controlled study. Eligible patients were randomized 1:1 at baseline (day 0) to receive vildagliptin (50 mg twice daily) or glimepiride (starting dose 2mg/day) in addition to metformin (dose remained unchanged)
Number of participants	From a total of 2789 randomized patients (vildagliptin 1396 and glimepiride 1393), 1174 (84.1%) and 1118 (80.3%) completed 52 weeks of treatment respectively. Of the patients who completed the 52-week study period, 1118 (vildagliptin) and 1072 (glimepiride) patients were included in the PP analysis
Duration of follow-up	52 weeks
Indirectness	None
Method of analysis	Per protocol
Additional comments	

60.2. Study arms

60.2.1. Vildagliptin (N = 1396)

Drug: vildagliptin (50 mg twice daily) Drug: Metformin (dose remained unchanged) Drug: Glimepiride matching placebo

60.2.2. Glimepiride (N = 1393)

Drug: glimepiride (starting dose 2mg/day; could be up-titrated to a maximum of 6 mg/day) Drug: Metformin (dose remained unchanged) Drug: Vildagliptin matching placebo

60.3. Characteristics

60.3.1. Arm-level characteristics

Characteristic	Vildagliptin (N = 1396)	Glimepiride (N = 1393)
% Male Nominal	52.8	54.1
Mean age (SD) Mean (SD)	57.5 (9.06)	57.46 (9.28)

Characteristic	Vildagliptin (N = 1396)	Glimepiride (N = 1393)
Caucasian Nominal	86.3	85.2
Black Nominal	1.3	1.4
Asian Nominal	3.2	3.2
Hispanic or Latino Nominal	8.9	9.3
Other Nominal	0.4	1
Time since type 2 diabetes diagnosed Mean (SD)	5.71 (5.18)	5.75 (5.03)
HbA1c Mean (SD)	7.31 (0.64)	7.3 (0.65)
Hypertension Nominal	64.6	68.5
Dislipidaemia Nominal	49.3	50
Previous cardiac disorder Nominal	19.2	19.6
Smoking status (%) Nominal	16.8	15.7
BMI Mean (SD)	31.8 (5.27)	31.69 (5.25)
Obese (BMI>30) Nominal	58.9	57.3
Morbidly obese (BMI>35) Nominal	27.3	25.3
GFR: 60-90 Nominal	44.7	43.1

Characteristic	Vildagliptin (N = 1396)	Glimepiride (N = 1393)
GFR: 30-60 Nominal	4.7	5
Duration of metformin use (months) Mean (SD)	35.83 (34.66)	36.04 (35.35)
Total daily metformin dose (mg) Mean (SD)	1903.9 (413.47)	1892.64 (408)

61. Ferrannini, 2020

Bibliographic Reference	Ferrannini, Ele; Baldi, Simona; Frias, Juan P; Guja, Cristian; Hardy, Elise; Repetto, Enrico; Jabbour, Serge A; DeFronzo, Ralph A; Hormone-substrate changes with exenatide plus dapagliflozin versus each drug alone: The randomized, active-controlled DURATION-8 study.; Diabetes, obesity & metabolism; 2020; vol. 22 (no. 1); 99-106

61.1. Study details

Secondary publication of another included study- see primary study for details	Parent study Frias 2016

62. Filozof, 2010

Bibliographic Reference	Filozof, C.; Gautier, J. F.; A comparison of efficacy and safety of vildagliptin and gliclazide in combination with metformin in patients with Type 2 diabetes inadequately controlled with metformin alone: a 52-week, randomized study; Diabetic Med; 2010; vol. 27 (no. 3); 318-26

62.1. Study details

Secondary publication of another included study- see primary study for details	NA
Other publications associated with this study included in review	NA
Trial name / registration number	NR
Study type	Randomised controlled trial (RCT)
Study location	Unclear, but appears to be Switzerland and France
Study setting	Unspecified clinical setting
Study dates	Not provided
Sources of funding	Novartis Pharmaceuticals
Inclusion criteria	Male and female patients (non-fertile or using a medically approved birth control method) of 18 to 78 years with Type 2 diabetes and HbA1c 7.5–11.0%, who had received metformin for at least 3 months and were on a stable dose of ‡ 1500 mg daily for ‡ 4 weeks prior to visit 1 were eligible to participate in the study.
Exclusion criteria	Patients with a history of Type 1 diabetes, diabetes as a result of pancreatic injury or secondary forms of diabetes (Cushing’s syndrome and acromegaly) and patients experiencing acute metabolic diabetic complications (ketoacidosis or hyperosmolar state) within the past 6 months were excluded from the study. Patients with serious cardiac conditions [torsades de pointes, sustained and clinically relevant

	ventricular tachycardia or ventricular fibrillation, percutaneous coronary intervention within the past 3 months, myocardial infarction (MI), coronary artery bypass surgery, unstable angina; or stroke within the last 6 months and congestive heart failure requiring pharmacological treatment, second- or third-degree atrioventricular block or prolonged QTC) or clinically significant renal or liver disease were also excluded. Other exclusion criteria included alanine amino transferase (ALT) or aspartate aminotransferase (AST) > 2 times the upper limit of the normal range, total bilirubin > 2 times the upper limit of the normal range, positive hepatitis B surface antigen and／or hepatitis C antibody, serum creatinine ‡ 132 lmol／l in male patients and ‡ 123 lmol／l in female patients, or a history of abnormal creatinine clearance, clinically significant thyroid-stimulating hormone (TSH) values outside of normal range at screening, or fasting triglycerides > 7.9 mmol／l at screening
Recruitment / selection of participants	NR
Intervention(s)	Vildagliptin Gliclazide
Cointervention	Metformin ≥1500 mg daily at stable dose
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear Excluded "congestive heart failure requiring pharmacological treatment", other HF unclear. No information in baseline characteristics.
Strata 2: People with atherosclerotic cardiovascular disease	Not stated/unclear Excluded "percutaneous coronary intervention within the past 3 months, myocardial infarction (MI), coronary artery bypass surgery, unstable angina; or stroke within the last 6 months", prior unclear. No information in baseline characteristics.
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear Excluded "clinically significant renal or liver disease", CKD diagnosis unclear. Baseline characteristics give eGFR categories but not CKD diagnosis.
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	People without non-alcoholic fatty liver disease clinically significant renal or liver disease were excluded
Subgroup 4: People with obesity	Mixed population Approximately half of the patient population in both the treatment groups was obese
Subgroup 5: eGFR category at baseline	eGFR ≥30mL/min/1.73m2
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Population subgroups	None
Comparator	Active control study
Number of participants	One thousand and seven patients were randomly assigned to either vildagliptin 50 mg twice daily (n = 513) or gliclazide up to 320 mg (n = 494) as an add-on to metformin. Of these, 819 (81.3%) patients completed the study (vildagliptin: n = 407, 79.3%; gliclazide: n = 412, 83.4%)
Duration of follow-up	52 weeks
Indirectness	None
Method of analysis	Per protocol Modified ITT

Additional comments	Randomized (RAN) population: consisted of all randomized patients. • Intent-to-treat (ITT) population: randomized patients who had received at least one dose of study drug and had a baseline and at least one post-baseline assessment. • Per protocol (PP) population: included patients in the ITT population with more than 24 weeks of treatment, with no major protocol violations, and who underwent the final valid assessment of the primary efficacy variable HbA1c within 7 days after the last dose of study drug and either (i) completed more than 48 weeks of treatment or (ii) had < 48 weeks of treatment but discontinued from study drug because of unsatisfactory therapeutic response. • Safety (SAF) population: patients who received at least one dose of study drug and had at least one post-baseline safety assessment.

62.2. Study arms

62.2.1. Vildagliptin (N = 513)

vildagliptin (50 mg twice daily) in addition to a stable dose of metformin (1500 mg daily)

62.2.2. Gliclazide (N = 494)

gliclazide (80 mg／day) in addition to a stable dose of metformin (1500 mg daily). Gliclazide had to be up-titrated from a starting dose of 80 mg／day to a maximum of 320 mg／day if FPG was > 7.0 mmol／l or fasting blood glucose was > 6.3 mmol／l based on the fasting finger-stick capillary glucose measurement performed at the study centre. Patients were up-titrated to the next dose level at week 4 (160 mg), week 8 (240 mg) and week 12 (320 mg).

62.3. Characteristics

62.3.1. Arm-level characteristics

Characteristic	Vildagliptin (N = 513)	Gliclazide (N = 494)
% Male Nominal	52.2	51.8
Mean age (SD) Mean (SD)	59.2 (9.9)	59.7 (10.2)
Asian Nominal	8.4	8.3
Black	0.6	1.2

Characteristic	Vildagliptin (N = 513)	Gliclazide (N = 494)
Nominal		
Caucasian Nominal	78.9	77.5
Hispanic or Latino Nominal	11.3	11.9
Other Nominal	0.8	1
Time since type 2 diabetes diagnosed Mean (SD)	6.4 (5.1)	6.8 (5.3)
HbA1c Mean (SD)	8.5 (1)	8.5 (1)
Weight (kg) Mean (SD)	85.7 (16.6)	84.2 (17.9)
BMI Mean (SD)	31.2 (5)	30.8 (5)
Normal >80 Nominal	67.8	67.8
Mild 50-80 Nominal	30.4	30.8
Moderate 30-50 Nominal	1.8	1.4

63. Filozof, 2010

Bibliographic Reference	Filozof, Claudia; Schwartz, Sherwyn; Foley, James E; Effect of vildagliptin as add-on therapy to a low-dose metformin.; World journal of diabetes; 2010; vol. 1 (no. 1); 19-26

63.1. Study details

Secondary publication of another included study- see primary study for details	
Other publications associated with this study included in review	Filozof 2010
Trial name / registration number	ClinicalTrials.gov Identifier: NCT00396357
Study type	Randomised controlled trial (RCT)
Study location	Germany, United States
Study setting	Unspecified clinical setting
Study dates	October 2006 to June 2008
Sources of funding	Novartis Pharmaceuticals
Inclusion criteria	• 18-78 years inclusive • Type 2 diabetes diagnosis at least 2 months prior to study entry • Body mass index in the range of 22-45 kg/m2 • HbA1c in the range of 6.5 to 9% inclusive • Fasting plasma glucose <270 mg/dL (15 mmol/L)
Exclusion criteria	• A history of type 1 diabetes • Evidence of significant diabetic complications • Treatment with insulin or any other oral antidiabetic agents • Congestive heart failure requiring pharmacologic treatment

	• Clinically significant renal dysfunction defined by metformin labelling criteria (serum creatinine levels >/= 1.5 mg/dl (males) and >/= 1.4 mg/dl (females) • Other protocol-defined inclusion/exclusion criteria may apply
Recruitment / selection of participants	Male and female (non-fertile or using a medically approved birth control method) patients aged 18-78 years with HbA1c 6.5%-9.0%, FPG < 270 mg/dL (15 mmol/ L) and a body mass index (BMI) of 22-45 kg/m2 who received metformin 850-1000 mg daily for at least 2 months prior to screening were eligible to participate in the study
Intervention(s)	All patients received open-label metformin 500 mg bid at visit 1 for a period of 4 wk. Eligible patients were then randomized to receive either vildagliptin 100 mg qd or metformin 500 mg qd (double-dummy design) for 2 week and then metformin 500 mg bid. All patients continued with the open-label metformin 500 mg bid for the 24 wk. Dose adjustments of vildagliptin or open-label metformin were not allowed at any time after randomization. Analysed in review as Vildagliptin v Metformin (as the open-label metformin is the concomitant / background therapy) - so considering it as the addition of metformin to background treatment for the metformin arm.
Cointervention	open-label metformin 500 mg bid
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear Excluded "Congestive heart failure requiring pharmacological treatment" but unclear if there would be other HF. No information in baseline characteristics.
Strata 2: People with atherosclerotic cardiovascular disease	Not stated/unclear Excluded "acute infections, myocardial infarction, unstable angina or coronary artery bypass surgery within the previous 6 months", otherwise unclear. No information in baseline characteristics.
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear Excluded "clinically significant renal dysfunction as indicated by serum creatinine levels ≥ 1.5 mg/dL (132 µmol/L) in males, ≥ 1.4 mg/dL (123 µmol/L) in females, or a history of abnormal creatinine clearance", but unclear based on CKD diagnosis. No information in baseline characteristics.
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	People without non-alcoholic fatty liver disease Liver disease in general is excluded
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	None
Comparator	metformin 500 mg qd for 2 wk and then metformin 500 mg bid.
Number of participants	A total of 914 patients (Figure 2) were randomized to receive either vildagliptin 100 mg qd/metformin 500 mg bid (n = 456) or metformin monotherapy (n = 458 patients) up to 1000 mg bid (final mean metformin dose after uptitration at visit 4 was 1984 mg). Of these patients, 798 (87.3%) completed the study.
Duration of follow-up	24 weeks
Indirectness	None
Method of analysis	Per protocol ITT

63.2. Study arms

63.2.1. Vildagliptin (N = 456)

vildagliptin in combination with open label metformin 500 mg bid

63.2.2. metformin (N = 458)

metformin 500 mg bid in combination with open label metformin 500mg bid

63.3. Characteristics

63.3.1. Arm-level characteristics

Characteristic	Vildagliptin (N = 456)	metformin (N = 458)
% Male (%) Nominal	50.4	45
Mean age (SD) (%) Mean (SD)	56.9 (9.76)	57 (10.02)
Caucasian Nominal	53.1	51.7
Asian non-Indian Nominal	9.6	9.6
Hispanic or Latino Nominal	32.2	31.7
Black Nominal	2	2.6
Asian (Indian subcontinent) Nominal	0.7	1.1
Native American Nominal	0.2	0.4
Other Nominal	2.2	2.8

Characteristic	Vildagliptin (N = 456)	metformin (N = 458)
Time since type 2 diabetes diagnosed (years) Mean (SD)	4.6 (4.91)	4.7 (4.94)
HbA1c (%) Mean (SD)	7.4 (0.78)	7.3 (0.79)
Weight (%) Mean (SD)	84.6 (17.01)	84.4 (18.94)
BMI (%) Mean (SD)	31.1 (5.11)	31.2 (5.47)

64. Fioretto, 2018

Bibliographic Reference	Fioretto, P.; Del Prato, S.; Buse, J. B.; Goldenberg, R.; Giorgino, F.; Reyner, D.; Langkilde, A. M.; Sjöström, C. D.; Sartipy, P.; Efficacy and safety of dapagliflozin in patients with type 2 diabetes and moderate renal impairment (chronic kidney disease stage 3A): the DERIVE Study; Diab Obes Metab; 2018; vol. 20 (no. 11); 2532-2540

64.1. Study details

Secondary publication of another included study- see primary study for details	None
Other publications associated with this study included in review	No
Trial name / registration number	DERIVE/NCT02413398
Study type	Randomised controlled trial (RCT) Double-blind parallel group RCT
Study location	International (88 sites in Bulgaria, Canada, Czech Republic, Italy, Poland, Spain, Sweden, USA).
Study setting	Outpatient
Study dates	06/2015 to 11/2017
Sources of funding	Funded by AstraZeneca and supported by grant from National Institutes of Health, Grant/Award Number: UL1TR001111.
Inclusion criteria	• Provision of informed consent prior to any study specific procedures • Female or male aged ≥18 years and <75 years • History of T2DM>12 months • Inadequate glycaemic control (HbA1c ≥7.0% and ≤11.0%) measured at screening (value from blood sample obtained at Visit 1) for patient to be randomized

	• Stable anti-diabetic treatment regimen, defined as stable diet and exercise therapy alone or in combination with any or both of the two following alternatives:
	  ○ A regimen of any approved oral anti-diabetic medication (except SGLT2-inhibitors) where no dose-changes have occurred during 12 weeks before randomization
	  ○ Long acting or intermediate acting insulin and mixed insulin permitted as long as the dose is stable during last 12 weeks before randomization, changes ± 10% are allowed (in relation to number of units at randomization). For example, if the patient is taking 50 units/day of insulin at randomization, the total daily doses in the past 12 weeks should not have exceeded 55 units or been less than 45 units. However, occasional exceptions (≤ one day/week) during this time period are permitted
	• Renal impairment: CKD 3A
	  ○ eGFR 40–65 mL/minute/1.73 m2 at Visit 2 (value from blood sample obtained at Visit 1) to enter the lead-in period
	  ○ GFR 45–59 mL/minute/1.73 m2 at Visit 1, or Visit 2, or Visit 3 for randomization
	• BMI 18-45 kg/m2 (inclusive) at Visit 1

Exclusion criteria	• History of
	  ○ Severe uncontrolled hypertension
	  ○ CV/vascular diseases within 3 months prior to enrolment (myocardial infarction, cardiac surgery or revascularization, unstable angina, unstable heart failure, heart failure Class IV according to the New York Heart Association [NYHA], transient ischaemic attack or significant cerebrovascular disease, unstable or previously undiagnosed arrhythmia)
	  ○ Renal disease worsening of renal function from Visit 1 to Visit 3, intercurrent kidney disease other than diabetic nephropathy, renal transplant, dialysis or ultrafiltration)
	• Use of metformin was restricted to doses for moderate renal impairment (eGFR, 30–59 mL/min/1.73 m2) according to local guidelines or investigator's judgement.
	• Received treatment with an SGLT2 inhibitor, a glucagon-like peptide 1 (GLP-1) receptor agonist or a rapid/short-acting insulin at screening
	• Serum potassium level of >5.5 mmol/L, a serum calcium level of <1.99 mmol/L or > ULN, or a haemoglobin level of ≤90 g/L

Recruitment / selection of participants	Participants recruited from 88 sites in 8 countries and randomised 1:1, using interactive voice response system or interactive web response system, stratified by pre-enrolment glucose-lowering therapy (long-/intermediate- acting, mixed insulins; metformin, sulphonylurea; thiazolidinedione or other regimen). Investigator provided with unique Kit ID number by voice/web system matching treatment arm for each randomized participant. Initial 2-wk screening period, 4-wk single blind placebo lead-in period, 24 weeks treatment and 3 weeks post-treatment FU period. Study visits after randomisation at weeks 1, 4, 12, 24 (end of treatment), and 27. Participants with loss of glycaemia control (FPG>13.3

	mmol/L during weeks 4-12 or FPG>11.1 during weeks 12-24) eligible for open-label rescue medication (any glucose-lowering drug except SGLT2 inhibitors) in addition to trial treatment.
Intervention(s)	• Dapagliflozin 10 mg once daily Oral dapagliflozin 10 mg once daily in morning for 24 weeks. in addition to their usual stable glucose-lowering treatment regimen (diet, exercise + oral glucose lowering medication + long-/intermediate-acting or mixed insulin). Antihypertensive drugs, lipid-lowering drugs and anti-platelet drugs permitted if dose remained constant during 24-wk treatment phase.
Cointervention	Stable glucose-lowering treatment regimen (diet, exercise, oral glucose lowering medication (excluding SGLT2 inhibitors) + long-/intermediate-acting or mixed insulin)
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear Excluded "unstable heart failure, heart failure Class IV according to the New York Heart Association [NYHA]", otherwise unclear. No information in baseline characteristics.
Strata 2: People with atherosclerotic cardiovascular disease	Not stated/unclear Excluded "certain CV/vascular diseases within 3 months prior to enrolment", unclear prior to this. No information in baseline characteristics.
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	People with chronic kidney disease Recruited people with CKD stage 3A. This was only based on eGFR and not a prior clinical diagnosis, however was classified by the study itself as CKD based on the eGFR at more than one timepoint during the screening and run-in period. Inclusion criteria states "CKD 3A (eGFR, 40–65 mL/min/1.73 m2 at Visit 1 to enter the 4-week single-blind placebo lead-in period and eGFR, 45–59 mL/min/1.73 m2 at Visits 1, 2 or 3 to be randomized".
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 Inclusion criteria: eGFR 45-59
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Comparator	• Placebo Oral placebo once daily in morning for 24 weeks in addition to their usual stable glucose-lowering treatment regimen (diet, exercise + oral glucose lowering medication + long-/intermediate-acting or mixed insulin). Antihypertensive drugs, lipid-lowering drugs and anti-platelet drugs permitted if dose remained constant during 24-wk treatment phase.
Number of participants	N=321
Duration of follow-up	24 weeks + 3 weeks post-treatment follow up
Indirectness	None
Method of analysis	Modified ITT mITT analysis (all randomised participants who received at least 1 dose of double-blinded study medication and had baseline HbA1c and at least one post-baseline HbA1c assessment) for efficacy analysis (HbA1c, body weight, seated systolic blood pressure) with missing data assumed to be missing at random. Data from before rescue or discontinuation included. mITT analysis (all randomised participants who received at least 1 dose of double-blinded study medication) for safety outcomes (adverse events).

64.2. Study arms

64.2.1. Dapagliflozin 10 mg once daily (N = 160)

Oral dapagliflozin 10 mg once daily in morning for 24 weeks.

64.2.2. Placebo (N = 161)

Oral placebo in morning for 24 weeks in addition to usual care.

64.3. Characteristics

64.3.1. Arm-level characteristics

Characteristic	Dapagliflozin 10 mg once daily (N = 160)	Placebo (N = 161)
% Male Sample size	n = 91 ; % = 56.9	n = 91 ; % = 56.5
Mean age (SD) (years) Median (IQR)	66 (NR to NR)	68 (NR to NR)
Mean age (SD) (years) Mean (SD)	65.3 (NR)	66.2 (NR)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA
American Indian/Alaska Native Sample size	n = 2 ; % = 1.3	n = 0 ; % = 0
Asian Sample size	n = 5 ; % = 3.1	n = 8 ; % = 5
Black/African American Sample size	n = 11 ; % = 6.9	n = 12 ; % = 7.5
Hispanic or Latino Sample size	n = 33 ; % = 20.6	n = 44 ; % = 27.3
Not hispanic or latino Sample size	n = 127 ; % = 79.4	n = 117 ; % = 72.7
White Sample size	n = 141 ; % = 88.1	n = 140 ; % = 87
Other	n = 1 ; % = 0.6	n = 1 ; % = 0.6

Characteristic	Dapagliflozin 10 mg once daily (N = 160)	Placebo (N = 161)
Sample size		
Comorbidities Nominal	NR	NR
Presence of frailty Nominal	NR	NR
Time since type 2 diabetes diagnosed (years) Mean (SD)	14.3 (8.1)	14.5 (8.3)
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 Sample size	n = NA ; % = NA	n = NA ; % = NA
Insulin Sample size	n = 80 ; % = 50	n = 80 ; % = 49.7
Metformin Sample size	n = 111 ; % = 69.4	n = 103 ; % = 64

Characteristic	Dapagliflozin 10 mg once daily (N = 160)	Placebo (N = 161)
Sulphonylurea Sample size	n = 64 ; % = 40	n = 67 ; % = 41.6
Blood pressure-lowering medication used Sample size	n = NA ; % = NA	n = NA ; % = NA
ACE inhibitor/angiotensin II receptor blocker Sample size	n = 137 ; % = 85.6	n = 132 ; % = 82
Beta blockers Sample size	n = 59 ; % = 36.9	n = 77 ; % = 47.8
Diuretics Sample size	n = 67 ; % = 41.9	n = 68 ; % = 42.2
Other Sample size	n = 21 ; % = 13.1	n = 20 ; % = 12.4
Statins/lipid-lowering medication used Nominal	NR	NR
Other treatment being received Nominal	NR	NR

65. Fonseca, 2007

Bibliographic Reference	Fonseca, V.; Schweizer, A.; Albrecht, D.; Baron, M. A.; Chang, I.; Dejager, S.; Addition of vildagliptin to insulin improves glycaemic control in type 2 diabetes; Diabetologia; 2007; vol. 50 (no. 6); 1148-55

65.1. 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	NCT00099931
Study type	Randomised controlled trial (RCT)
Study location	Germany (ten), Finland (five), Spain (four) and the USA (49)
Study setting	Unspecified clinical setting
Study dates	May 2004 to June 2005
Sources of funding	Novartis Pharmaceuticals
Inclusion criteria	• Blood glucose criteria must be met • On a stable dose of insulin as defined by the protocol • Body mass index (BMI) in the range 22-45 • 18 Years to 80 Years
Exclusion criteria	• Type 1 diabetes • Pregnancy or lactation • Evidence of serious diabetic complications • Evidence of serious cardiovascular complications • Laboratory value abnormalities as defined by the protocol • Other protocol defined exclusion criteria may apply

Recruitment / selection of participants	Potential participants attended a screening visit (Week −4), during which inclusion/exclusion criteria were assessed.
Intervention(s)	vildagliptin (50 mg twice daily)
Cointervention	injectable insulin for at least 3 months, at a dose of at least 30 U/day for a minimum of 4 weeks prior to enrolment
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	People without non-alcoholic fatty liver disease clinically significant liver disease excluded

fatty liver disease	
Subgroup 4: People with obesity	People with obesity Participants were predominantly white and obese (one in three being severely obese, with a BMI >35 kg/m2)
Subgroup 5: eGFR category at baseline	Not stated/unclear
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Population subgroups	Subgroups based on age: Subgroup aged <65 years (n=203) Subgroup aged ≥65 years (n=93)
Comparator	Placebo
Number of participants	In total, 296 patients were randomised and 290 patients were included in the intent-to-treat population comprising all patients who received at least one dose of study medication and for whom at least one post-baseline HbA1c result was obtained. vildagliptin (n=144) or placebo (n=152)
Duration of follow-up	24 weeks
Indirectness	None
Method of analysis	ITT

65.2. Study arms

65.2.1. vildagliptin (N = 144)

vildagliptin 50 mg twice per day added to insulin

65.2.2. placebo (N = 152)

placebo added to insulin

65.3. Characteristics

65.3.1. Arm-level characteristics

Characteristic	vildagliptin (N = 144)	placebo (N = 152)
% Male Nominal	47.9	54.6
Mean age (SD) Mean (SD)	59.6 (10.3)	58.9 (10.8)
Black Nominal	15.3	11.2
White Nominal	70.1	72.4
Hispanic or Latino Nominal	11.8	14.5
Other Nominal	2.8	2
Time since type 2 diabetes diagnosed Mean (SD)	14.4 (8.6)	14.9 (8.4)
HbA1c Mean (SD)	8.4 (1)	8.4 (1.1)
BMI Mean (SD)	33.3 (5.2)	32.9 (5.9)
Duration of insulin use (months) Mean (SD)	82.5 (79.3)	67.9 (65.2)
Mean daily insulin dose (U) Mean (SD)	81.2 (44.8)	81.9 (49.4)

66. Fonseca, 2013

Bibliographic Reference	Fonseca, V.; Staels, B.; Morgan, J. D.; Shentu, Y.; Golm, G. T.; Johnson-Levonas, A. O.; Kaufman, K. D.; Goldstein, B. J.; Steinberg, H.; Efficacy and safety of sitagliptin added to ongoing metformin and pioglitazone combination therapy in a randomized, placebo-controlled, 26-week trial in patients with type 2 diabetes; J Diabetes Complications; 2013; vol. 27 (no. 2); 177-83

66.1. 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	NCT00885352
Study type	Randomised controlled trial (RCT)
Study location	The trial included 58 sites in 12 countries, including 20 sites in the United States, 4 in Europe, 8 in Latin America, and 26 in 7 other countries
Study setting	Unspecified clinical setting
Study dates	April 15, 2009 to November 10, 2010
Sources of funding	Merck Sharp & Dohme LLC
Inclusion criteria	• has type 2 diabetes and is at least 18 years of age and no older than 78 years of age • is male or is a female who is unlikely to conceive children • is on stable doses of a peroxisome proliferator-activated receptor gamma agonist and metformin OR metformin and a sulfonylurea agent

Exclusion criteria	• has type 1 diabetes • has taken a dipeptidyl peptidase (DPP-4) inhibitor or a glucagon-like peptide-1 (GLP-1) analogue • is on a weight loss program that is not in the maintenance phase or has started a weight loss medication within 8 weeks of screening • has had surgery within 30 days of screening or has major surgery planned during the study • is on or is likely to require treatment with corticosteroids for more than 2 weeks • has a history of active liver disease, including hepatitis B or C, cirrhosis, or gallbladder disease • is human immunodeficiency virus (HIV) positive • has congestive heart failure, or has had new or worsening symptoms of coronary heart disease within 3 months prior to screening • has had acute coronary syndrome, coronary artery intervention, or stroke within 3 months of screening • has severe active peripheral vascular disease • has a history of cancer or blood disorder • is pregnant or breast feeding
Recruitment / selection of participants	Randomization was contingent on an HbA1c ≥7.5% and ≤11.0% at the beginning of the placebo run-in period, treatment compliance with single-blind placebo ≥75% (based on tablet counts), fingerstick fasting blood glucose ≥7.2 and ≤13.9 mmol/L and meeting all other criteria prior to randomization.
Intervention(s)	Sitagliptin 100 mg tablet orally once daily for 26 weeks Participants not meeting specific glycemic controls during the 26-week treatment period will use glipizide oral tablets as rescue therapy. In countries where glipizide is not available, participants will receive a sulfonylurea marketed in that country.
Cointervention	Pioglitazone and Metformin Participants taking 30 mg or more pioglitazone oral tablet(s) daily at screening in combination with metformin will enter a 4-week dose-stable period followed by a 2-week single-blind run-in and a 26-week treatment period. Participants taking 4 mg or more rosiglitazone oral tablet(s) daily at screening in combination with metformin were to be switched to a corresponding dose of pioglitazone prior to starting a 4-week dose-stable period. Participants who are taking less than 30 mg/day or no pioglitazone at screening will be titrated to a stable dose of at least 30 mg pioglitazone once daily over a maximum of 4 weeks followed by a dose-stable period of 10 weeks, a 2-week single-blind placebo run-in, and a 26-week treatment period. Total treatment with pioglitazone will be up to 42 weeks. Other Name: Actos Participants taking 1500 mg or more metformin oral tablet(s) and at least 30 mg pioglitazone or 4 mg rosiglitazone daily at screening will enter a 4-week dose-stable period followed by a 2-week single-blind placebo run-in, and a 26-week treatment period. Participants who are taking less than

	1500 mg/day metformin at screening will be titrated to a stable dose of at least 1500 mg metformin once daily over a maximum of 4 weeks followed by a dose-stable period of 10 weeks, a 2-week single-blind placebo run-in, and a 26-week treatment period. Total treatment with metformin will be up to 42 weeks.
Strata 1: People with type 2 diabetes mellitus and heart failure	People without heart failure Excluded "congestive heart failure (NYHA Class I–IV)"
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	People without non-alcoholic fatty liver disease Patients were excluded if they had active 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	patients with baseline HbA1c ≥9.0%
Comparator	Placebo
Number of participants	Screened = 855 Randomised = 313 Sitagliptin: initial = 157; completed=149 Placebo: initial=156; completed=136
Duration of follow-up	26 weeks
Indirectness	None
Method of analysis	Not stated/unclear

66.2. Study arms

66.2.1. Sitagliptin (N = 157)

Sitagliptin 100 mg tablet orally once daily for 26 weeks.

66.2.2. Placebo (N = 156)

Placebo to sitagliptin orally once daily for 26 weeks

66.3. Characteristics

66.3.1. Arm-level characteristics

Characteristic	Sitagliptin (N = 157)	Placebo (N = 156)
% Male Nominal	61.8	62.8
Mean age (SD) Mean (SD)	55.7 (8.7)	56.4 (9.4)
Caucasian Nominal	47.8	53.2
Black Nominal	5.7	1.9
Asian Nominal	21	22.4
Native American/Alaskan Nominal	14	11.5
Other Nominal	11.5	10.9
Hispanic or Latino Nominal	38.2	35.9
HbA1c Mean (SD)	8.8 (1)	8.7 (1)
Weight Mean (SD)	82.1 (19.1)	83.8 (19.1)
BMI Mean (SD)	29.9 (5.2)	30 (5.2)

67. Forst, 2014

Bibliographic Reference	Forst, T.; Guthrie, R.; Goldenberg, R.; Yee, J.; Vijapurkar, U.; Meininger, G.; Stein, P.; Efficacy and safety of canagliflozin over 52 weeks in patients with type 2 diabetes on background metformin and pioglitazone; Diabetes Obes Metab; 2014; vol. 16 (no. 5); 467-477

67.1. 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	NCT01106690
Study type	Randomised controlled trial (RCT)
Study location	Canada, Finland, France, Germany, Greece, India, Mexico, Spain, Thailand, United Kingdom, United States
Study setting	Unspecified clinical setting
Study dates	June 2010 to November 2011
Sources of funding	Janssen Research & Development, LLC
Inclusion criteria	• All patients must have a diagnosis of T2DM and be currently treated with PPAR gamma agent ((pioglitazone or rosiglitazone) and another anti-diabetes agent (metformin) • Patients in the study must have a HbA1c between >=7 and <=10.5% and a fasting plasma glucose (FPG) <270 mg/dL (15 mmol/L)

Exclusion criteria	• History of diabetic ketoacidosis, type 1 diabetes mellitus (T1DM), pancreas or beta cell transplantation, or diabetes secondary to pancreatitis or pancreatectomy • or a severe hypoglycemic episode within 6 months before screening
Recruitment / selection of participants	Patients on protocol-specified doses of metformin [≥2000 mg/day (or 1500 mg/day if unable to tolerate higher dose)] and pioglitazone (30 or 45 mg/day) with haemoglobin A1c (HbA1c) ≥7.0% to 10.5% at screening directly entered the placebo run-in period. Patients on other background therapies entered a metformin/pioglitazone dose titration/dose-stable period of up to 12 weeks; patients with HbA1c ≥7.0% to ≤10.5% on metformin and pioglitazone (at the doses described above) after the dose-titration/dose-stable period then entered the placebo run-in period
Intervention (s)	Canagliflozin 100 mg and Canagliflozin 300 mg
Cointervention	Metformin and Pioglitazone. Metformin: The patient's stable dose of metformin background therapy should be continued throughout the study. Pioglitazone: The patient's stable dose of pioglitazone background therapy should be continued throughout the study.
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 "cardiovascular disease (including myocardial infarction, unstable angina, revascularization procedure or cerebrovascular accident) within 3 months prior to screening", prior 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) <55 ml/min/1.73 m2 (or <60 ml/min/1.73 m2 if based upon restriction of metformin use in local label) ", otherwise unclear. No information in baseline characteristics.
Strata 4: People with type 2 diabetes mellitus and high	Not stated/unclear Excluded: cardiovascular disease (including myocardial infarction, unstable angina, revascularization procedure or cerebrovascular accident) within 3 months prior to screening. Other risk factors not addressed.

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 Excluded: estimated glomerular filtration rate (eGFR) <55 ml/min/1.73 m2
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Population subgroups	None
Comparator	Placebo/Sitagliptin: Each patient will receive matching placebo once daily for 26 weeks with stable doses of metformin and pioglitazone. At Week 26, patients will be switched from placebo to 100 mg of sitagliptin once daily with stable doses of metformin and pioglitazone until Week 52.
Number of participants	A total of 342 patients were randomized into the core treatment period and received ≥1 dose of study drug, comprising the mITT analysis set (Figure 1). Of the 342 patients, 296 (86.5%) completed the core period; of these, 289 entered the extension period and 263 completed 52 weeks of treatment
Duration of follow-up	52 weeks
Indirectness	Variable cointerventions

Method of analysis	Modified ITT

67.2. Study arms

67.2.1. Canagliflozin 100 mg (N = 113)

Each patient will receive 100 mg of canagliflozin once daily for 52 weeks with stable doses of metformin and pioglitazone.

67.2.2. Canagliflozin 300 mg (N = 114)

Each patient will receive 300 mg of canagliflozin once daily for 52 weeks with stable doses of metformin and pioglitazone

67.2.3. Placebo/Sitagliptin (N = 115)

Each patient will receive matching placebo once daily for 26 weeks with stable doses of metformin and pioglitazone. At Week 26, patients will be switched from placebo to 100 mg of sitagliptin once daily with stable doses of metformin and pioglitazone until Week 52.

67.3. Characteristics

67.3.1. Arm-level characteristics

Characteristic	Canagliflozin 100 mg (N = 113)	Canagliflozin 300 mg (N = 114)	Placebo/Sitagliptin (N = 115)
% Male Nominal	68.1	55.3	66.1
Mean age (SD) Mean (SD)	56.7 (10.4)	57 (10.2)	58.3 (9.6)
White Nominal	73.5	78.9	68.7
Black Nominal	3.5	8.8	5.2
Asian	20.4	9.6	18.3

Characteristic	Canagliflozin 100 mg (N = 113)	Canagliflozin 300 mg (N = 114)	Placebo/Sitagliptin (N = 115)
Nominal			
Other Nominal	2.7	2.6	7.8
Time since type 2 diabetes diagnosed (years) Mean (SD)	10.5 (6.6)	11 (7.6)	10.1 (6.6)
HbA1c Mean (SD)	8 (0.9)	7.9 (0.9)	8 (1)
Weight Mean (SD)	94.2 (22.2)	94.4 (25.9)	93.8 (22.4)
BMI Mean (SD)	32.3 (6.2)	32.8 (7.7)	32.5 (6.4)
eGFR mL/min/1.73m2 Mean (SD)	94.6 (17.5)	87.4 (19.5)	87.2 (18.8)

68. Forst, 2005

Bibliographic Reference	Forst, T.; Hohberg, C.; Fuellert, S. D.; Lübben, G.; Konrad, T.; Löbig, M.; Weber, M. M.; Sachara, C.; Gottschall, V.; Pfützner, A.; Pharmacological PPARgamma stimulation in contrast to beta cell stimulation results in an improvement in adiponectin and proinsulin intact levels and reduces intima media thickness in patients with type 2 diabetes; Horm Metab Res; 2005; vol. 37 (no. 8); 521-7

68.1. Study details

Trial name / registration number	None
Study type	Randomised controlled trial (RCT)
Study location	Unclear: appears to be Germany
Study setting	Unspecified clinical setting
Study dates	Not provided
Sources of funding	TAKEDA Germany
Inclusion criteria	Patients eligible for the study were aged 40 to 75 years and had glycosylated hemoglobin values (HbA1c) between 6.6% and 9.9%
Exclusion criteria	Exclusion criteria included type 1 diabetes, smoking, and substantial cardiovascular, renal, or hepatic disease
Recruitment / selection of participants	One hundred and ninety two orally treated patients with type 2 diabetes mellitus according to the American Diabetes Association criteria without previous PPARg agonist treatment were consecutively randomized
Intervention(s)	either a fixed dose of pioglitazone at 45 mg/day in the morning or glimepiride 1± 6 mg/day titrated for optimal glycemic control for 24 +/- 2 weeks
Cointervention	To achieve the best possible metabolic control, patients randomized to the pioglitazone group were permitted to receive additional antidiabetic medication with the exception of metformin, while patients randomized to the glimepiride group were allowed to add additional antidiabetic medication with the exception of b−cell stimulatory drugs and PPARg agonists.
Strata 1: People with type 2 diabetes	Not stated/unclear Excluded "substantial cardiovascular, renal, or hepatic disease", otherwise unclear.

mellitus and heart failure	
Strata 2: People with atherosclerotic cardiovascular disease	Not stated/unclear Excluded "substantial cardiovascular, renal, or hepatic disease", otherwise unclear
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear Excluded "substantial cardiovascular, renal, or hepatic disease", otherwise unclear
Strata 4: People with type 2 diabetes mellitus and high cardiovascular risk	Not stated/unclear Exclusion criteria included type 1 diabetes, smoking, and substantial cardiovascular, renal, or hepatic disease. Unclear what risk constitutes substantial.
Subgroup 1: People with moderate or severe frailty	Not stated/unclear
Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear
Subgroup 3: People with non-alcoholic fatty liver disease	People without non-alcoholic fatty liver disease Exclusion criteria included type 1 diabetes, smoking, and substantial cardiovascular, renal, or hepatic disease
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	Active control, no placebo
Number of participants	Out of 192 patients enrolled,179 were treated (92 in the pioglitazone group, 87 in the glimepiride group) and 173 were included in the intention−to−treat population (89 in the pioglitazone group, 84 in the glimepiride group).
Duration of follow-up	24 +/- 2 weeks
Indirectness	None
Method of analysis	ITT
Additional comments	NB: When I change units in the baseline table, it applies the changes to all rows. I've left in on months for duration as the rest can be inferred from context.

68.2. Study arms

68.2.1. Pioglitazone (N = 89)

pioglitazone at 45 mg/day in the morning

68.2.2. glimepiride (N = 84)

glimepiride 1-6 mg/day titrated for optimal glycemic control

68.3. Characteristics

68.3.1. Arm-level characteristics

Characteristic	Pioglitazone (N = 89)	glimepiride (N = 84)
% Male Nominal	61.79	61.9
Mean age (SD) (Months) Mean (SD)	62.2 (8.4)	63 (7.4)

Characteristic	Pioglitazone (N = 89)	glimepiride (N = 84)
Time since type 2 diabetes diagnosed (Months) Mean (SD)	89 (94.8)	82.5 (77.5)
HbA1c (Months) Mean (SD)	7.52 (0.85)	7.44 (0.89)
BMI (Months) Mean (SD)	31.7 (5)	31.8 (4.3)

69. Forst, 2015

Bibliographic Reference	Forst, T.; Koch, C.; Dworak, M.; Vildagliptin versus insulin in patients with type 2 diabetes mellitus inadequately controlled with sulfonylurea: Results from a randomized, 24 week study; Curr Med Res Opin; 2015; vol. 31 (no. 6); 1079-1084

69.1. 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	NCT01649466
Study type	Randomised controlled trial (RCT)
Study location	Germany
Study setting	47 centres
Study dates	NR
Sources of funding	Novartis Pharma GmbH Nűrnberg
Inclusion criteria	• aged 18–85 years • patients with T2DM not achieving adequate glycaemic control using sulfonylurea monotherapy • participant could not receive metformin either due to a contraindication or intolerance • had HbA1c ≥7.0% to ≤8.5% • BMI 21–45 kg/m2 • inadequate glycaemic control as judged by the investigator

Exclusion criteria	• had been treated with oral anti-diabetes drugs other than SU within the past 12 weeks • had an acute metabolic complication in the past 6 months • had a clinically significant medical condition (serious cardiac conditions or liver disease) • had been receiving any SU for more than 5 years before screening [During the study, patients were discontinued if they did not achieve glycaemic control after 12 weeks of treatment]
Recruitment / selection of participants	The study included an initial screening period of up to 1 week. Patients receiving SU monotherapy for at least 12 weeks and on a stable dose of glimepiride 4mg or maximum tolerated dose for at least 4 weeks before screening proceeded to randomization.
Intervention(s)	50 mg vildagliptin once daily
Cointervention	Glimepiride dose was kept stable throughout the study.
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	Not stated/unclear

moderate or severe frailty	
Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear
Subgroup 3: People with non-alcoholic fatty liver disease	Not stated/unclear
Subgroup 4: People with obesity	Not stated/unclear
Subgroup 5: eGFR category at baseline	Not stated/unclear
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Population subgroups	NA
Comparator	The initial insulin dose was 0.3–0.4 U/kg based on glimepiride dosing and body mass index (BMI; 0.3 U/kg if glimepiride ≤4mg and BMI <25 kg/m2 and 0.4 U/kg if glimepiride ≤4mg and BMI ≥25 kg/m2). The insulin dose was titrated individually over the initial 4 week treatment period to maintain the target fasting plasma glucose concentration of <5.5 mmol/L without significant hypoglycemia. After 4 weeks of treatment, the frequency of titration was left to the investigators' discretion. NPH insulin was injected subcutaneously daily as bedtime dose.
Number of participants	Vildagliptin: 83 participants were randomised and 82 participants received treatment (1 patient died before treatment began). 58 participants (69.9%) completed. Insulin: 79 participants were randomised and 70 participants (88.6%) completed.
Duration of follow-up	24 weeks
Indirectness	Directly applicable
Method of analysis	ITT The efficacy analyses were performed on the full analysis set (FAS) consisting of all randomized patients who received at least one dose of the

	study drug. The last observation carried forward method was used for missing data.
Additional comments	N

69.2. Study arms

69.2.1. Vildagliptin (N = 82)

69.2.2. NPH insulin (N = 79)

69.3. Characteristics

69.3.1. Arm-level characteristics

Characteristic	Vildagliptin (N = 82)	NPH insulin (N = 79)
% Male Sample size	n = 46 ; % = 56.1	n = 48 ; % = 60.8
Mean age (SD) Mean (SD)	65.9 (9.8)	67.6 (11.9)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA
Caucasian Sample size	n = 79 ; % = 96.3	n = 79 ; % = 100
Asian Sample size	n = 3 ; % = 3.7	n = 0 ; % = 0
Comorbidities Nominal	NR	NR
Presence of frailty Nominal	NR	NR
Time since type 2 diabetes diagnosed	7.3 (4.4)	8.6 (5.8)

Characteristic	Vildagliptin (N = 82)	NPH insulin (N = 79)
Mean (SD)		
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
Other treatment being received Nominal	NR	NR

70. Forst, 2010

Bibliographic Reference	Forst, Thomas; Weber, Matthias M; Lobig, Mirjam; Lehmann, Ute; Muller, Jurgen; Hohberg, Cloth; Friedrich, Christiane; Fuchs, Winfried; Pfutzner, Andreas; Pioglitazone in addition to metformin improves erythrocyte deformability in patients with Type 2 diabetes mellitus.; Clinical science (London, England : 1979); 2010; vol. 119 (no. 8); 345-51

70.1. Study details

Secondary publication of another included study- see primary study for details	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 Jun;13(6):637-43. doi: 10.1089/dia.2010.0233. Epub 2011 Apr 2. PMID: 21457065.
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.

71. Frias, 2021

Bibliographic Reference	Frias, J. P.; Davies, M. J.; Rosenstock, J.; Perez Manghi, F. C.; Fernandez Lando, L.; Bergman, B. K.; Liu, B.; Cui, X.; Brown, K.; Investigators, Surpass-; Tirzepatide versus Semaglutide Once Weekly in Patients with Type 2 Diabetes; New England Journal of Medicine; 2021; vol. 385 (no. 6); 503-515

71.1. 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-2 [NCT03987919]
Study type	Randomised controlled trial (RCT)
Study location	128 sites in the United States, Argentina, Australia, Brazil, Canada, Israel, Mexico, and the United Kingdom
Study setting	Multicentre trial
Study dates	Between July 30, 2019 and February 15, 2021
Sources of funding	Eili Lilly
Inclusion criteria	• Aged 18 years or older with type 2 diabetes that was inadequately controlled with metformin at a dose of at least 1500 mg per day. • A glycated hemoglobin level of 7.0 to 10.5% • Body-mass index of at least 25, and stable weight (±5%) during the previous 3 months
Exclusion criteria	• Type 1 diabetes • An estimated glomerular filtration rate below 45 ml per minute per 1.73 m2

	• A history of pancreatitis • A history of any of the following: non-proliferative diabetic retinopathy that warranted urgent treatment, proliferative diabetic retinopathy, or diabetic maculopathy • History of ketoacidosis or hyperosmolar state/coma • History of severe hypoglycaemia and/or hypoglycaemia unawareness within 6 months • Known clinically significant gastric emptying abnormality, have undergone or plan to have during the course of the study: gastric bypass (bariatric) surgery or restrictive bariatric surgery (for example, Lap-Band®), or chronically take drugs that directly affect GI motility • Have any of the following cardiovascular (CV) conditions within 2 months prior: acute myocardial infarction, cerebrovascular accident (stroke), or hospitalization due to congestive heart failure (CHF) • Have a history of New York Heart Association Functional Classification IV CHF • Have acute or chronic hepatitis, signs and symptoms of any liver disease other than non-alcoholic fatty liver disease (NAFLD), or alanine aminotransferase (ALT) level >3.0 times the upper limit of normal (ULN) for the reference range, as determined by the central laboratory at study entry. Patients with NAFLD are eligible to participate in this trial if their ALT level is ≤3.0 times the ULN for the reference range • Have an estimated glomerular filtration rate <45 mL/min/1.73 m2, (or lower than the country-specific threshold for discontinuing metformin therapy per local label) • Have evidence of a significant, uncontrolled endocrine abnormality • Have family or personal history of medullary thyroid carcinoma (MTC) or Multiple Endocrine Neoplasia type 2 (MEN2) • Have a serum calcitonin level of ≥35 ng/L • Known or suspected hypersensitivity to trial product(s) or related products • Have evidence of a significant, active autoimmune abnormality that is likely to require concurrent treatment with systemic glucocorticoids in the next 12 months • Have had a transplanted organ (corneal transplants [keratoplasty] allowed) or awaiting an organ transplant • Have a history of an active or untreated malignancy or are in remission from a clinically significant malignancy (other than basal or squamous cell skin cancer, in situ carcinomas of the cervix, or in situ prostate cancer) for less than 5 years • Have a history of any other condition (such as known drug, alcohol abuse, or psychiatric disorder) that may preclude the patient from following and completing the protocol • Have any hematological condition that may interfere with HbA1c measurement • Have been treated with any antihyperglycemic medication (other than metformin) within the 3 months. An exception is for the use of insulin for gestational diabetes or short-term use (<14 days) for acute conditions such as acute illness, hospitalization, or elective surgery • Have been treated with prescription drugs that promote weight loss (for example, liraglutide 3.0 mg, orlistat, sibutramine,

	phenylpropanolamine, mazindol, phentermine, lorcaserin, phentermine/topiramate combination, naltrexone/bupropion or similar other body weight loss medications including over-the-counter [OTC] medications) within 3 months • Are receiving chronic (>2 weeks or 14 days) systemic glucocorticoid therapy (excluding topical, intraocular, intranasal, or inhaled preparations) or have received such therapy within 1 month
Recruitment / selection of participants	2526 patients were assessed for trial eligibility; 1879 patients underwent randomization, and 1878 patients received at least one dose of tirzepatide or semaglutide
Intervention(s)	Tirzepatide was initiated at a dose of 2.5 mg once weekly, and the doses were increased by 2.5 mg every 4 weeks until the randomly assigned dose was reached. The final dose was then maintained for the duration of the trial.
Cointervention	• Metformin at a dose of at least 1500 mg per day. • Initiation of new antihyperglycemic medications was allowed according to specific criteria: o As an antihyperglycemic intervention for severe, persistent hyperglycaemia (“rescue therapy”) o In patients who require permanent discontinuation of study drug, but remain in the study o During the safety follow-up period
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear Excluded "history of New York Heart Association Functional Classification IV CHF", otherwise unclear. No information in baseline characteristics.
Strata 2: People with atherosclerotic cardiovascular disease	Not stated/unclear Excluded "cardiovascular (CV) conditions within 2 months prior to Visit 1", otherwise unclear. No information in baseline characteristics.
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear Excluded "an estimated glomerular filtration rate below 45 ml per minute per 1.73 m2", otherwise unclear. No information in baseline characteristics.
Strata 4: People with type 2 diabetes	Not stated/unclear

mellitus and high cardiovascular risk	
Subgroup 1: People with moderate or severe frailty	Not stated/unclear
Subgroup 2: Onset of type 2 diabetes mellitus	Not stated/unclear
Subgroup 3: People with non-alcoholic fatty liver disease	Not stated/unclear
Subgroup 4: People with obesity	Mixed population Table S4 shows that the baseline BMI was mixed
Subgroup 5: eGFR category at baseline	eGFR ≥30mL/min/1.73m2 96.6% of participants had eGFR of >=60 ml/min/1.73m2 at baseline and 3.4% of participants had eGFR <60 ml/min/1.73m2 at baseline
Subgroup 6: Albuminuria category at baseline	Mixed population At baseline: 75.3% participants had ACR of <30, 19.9% participants had ACR 30 to <=300, 4.7% participants had ACR >300
Population subgroups	NA
Comparator	Semaglutide was initiated at a dose of 0.25 mg once weekly, and the dose was doubled every 4 weeks until 1 mg was reached. The final dose was then maintained for the duration of the trial.20
Number of participants	• Tirzepatide 5 mg - 471 participants allocated, 431 participants (91.5%) completed the study drug, 452 participants (96%) completed study • Tirzepatide 10 mg - 469 participants allocated, 411 (87.6%) participants completed study drug, 442 participants (94.2%) completed study • Tirzepatide 15 mg - 470 participants allocated, 408 (86.8%) participants completed study drug, 446 (94.9%) completed study • Semaglutide 1 mg - 469 participants allocated, 428 (91.3%) participants completed study drug, 443 (94.5%) completed study

Duration of follow-up	40 weeks
Indirectness	Directly applicable
Method of analysis	Modified ITT Data from the following analysis were extracted for HbA1c and weight change- Treatment policy estimand - The primary analysis was from full analysis set (FAS, defined as all available data obtained during Study Period II from mITT, excluding patients discontinued study drug due to inadvertent enrolment, regardless of adherence to study drug or initiation of rescue antihyperglycemic medication.) using analysis of covariance (ANCOVA). Efficacy estimand - defined as data obtained during Study Period II from mITT, excluding patients discontinued study drug due to inadvertent enrolment and data after initiating rescue antihyperglycemic medication or prematurely stopping study drug). Analysis conducted using a mixed model for repeated measures (MMRM) for HbA1c data from baseline through to 40 weeks with country, treatment, visit, treatment-by-visit interaction as fixed effects, baseline HbA1c as a covariate, and patient as a random effect. [Extracted for extended outcomes as treatment policy estimand was not available]
Additional comments	NA

71.2. Study arms

71.2.1. Tirzepatide 5 mg (N = 470)

71.2.2. Tirzepatide 10 mg (N = 469)

71.2.3. Tirzepatide 15 mg (N = 470)

71.2.4. Semaglutide 1 mg (N = 469)

71.3. Characteristics

71.3.1. Arm-level characteristics

Characteristic	Tirzepatide 5 mg (N = 470)	Tirzepatide 10 mg (N = 469)	Tirzepatide 15 mg (N = 470)	Semaglutide 1 mg (N = 469)
Mean age (SD) Mean (SD)	56.3 (10)	57.2 (10.5)	55.9 (10.4)	56.9 (10.8)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
American Indian or Alaska Native Sample size	n = 53 ; % = 11.3	n = 53 ; % = 11.3	n = 57 ; % = 12.1	n = 45 ; % = 9.6
Asian Sample size	n = 6 ; % = 1.3	n = 11 ; % = 2.3	n = 5 ; % = 1.1	n = 3 ; % = 0.6
Black Sample size	n = 28 ; % = 6	n = 21 ; % = 4.5	n = 15 ; % = 3.2	n = 15 ; % = 3.2
White Sample size	n = 382 ; % = 81.3	n = 376 ; % = 80.2	n = 392 ; % = 83.4	n = 401 ; % = 85.5
Hispanic Sample size	n = 325 ; % = 69.1	n = 322 ; % = 68.7	n = 334 ; % = 71.1	n = 336 ; % = 71.6
Non-Hispanic Sample size	n = 145 ; % = 30.9	n = 147 ; % = 31.3	n = 136 ; % = 28.9	n = 133 ; % = 28.4
Comorbidities Nominal	NR	NR	NR	NR
Presence of frailty Nominal	NR	NR	NR	NR
Time since type 2 diabetes diagnosed Mean (SD)	9.1 (7.16)	8.4 (5.9)	8.7 (6.85)	8.3 (5.8)
Cardiovascular risk factors Nominal	NR	*empty data*	NR	NR
Smoking status	NR	NR	NR	NR

Characteristic	Tirzepatide 5 mg (N = 470)	Tirzepatide 10 mg (N = 469)	Tirzepatide 15 mg (N = 470)	Semaglutide 1 mg (N = 469)
Nominal				
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
Number of people with obesity Calculated by analyst based on the number of participants with BMI >=30 Sample size	n = 330 ; % = 70.2	n = 336 ; % = 71.6	n = 335 ; % = 71.3	n = 325 ; % = 69.3
Albumin creatinine ratio Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
≤30 Sample size	n = 340 ; % = 72.3	n = 353 ; % = 75.3	n = 357 ; % = 76	n = 364 ; % = 77.6
30 to <=300 Sample size	n = 111 ; % = 23.6	n = 87 ; % = 18.6	n = 85 ; % = 18.1	n = 90 ; % = 19.2
>300 Sample size	n = 18 ; % = 3.8	n = 29 ; % = 6.2	n = 27 ; % = 5.7	n = 15 ; % = 3.2
Other antidiabetic medication used Metformin Sample size	n = 470 ; % = 100	n = 469 ; % = 100	n = 470 ; % = 100	n = 469 ; % = 100
Blood pressure-lowering medication used Nominal	NR	NR	NR	NR

Characteristic	Tirzepatide 5 mg (N = 470)	Tirzepatide 10 mg (N = 469)	Tirzepatide 15 mg (N = 470)	Semaglutide 1 mg (N = 469)
Statins/lipid-lowering medication used Nominal	NR	NR	NR	NR
Other treatment being received Nominal	NR	NR	NR	NR
% Female Sample size	n = 265 ; % = 56.4	n = 231 ; % = 49.3	n = 256 ; % = 54.5	n = 244 ; % = 52

72. Frias, 2018

Bibliographic Reference	Frias, J. P.; Nauck, M. A.; Van, J.; Kutner, M. E.; Cui, X.; Benson, C.; Urva, S.; Gimeno, R. E.; Milicevic, Z.; Robins, D.; et, al.; Efficacy and safety of LY3298176, a novel dual GIP and GLP-1 receptor agonist, in patients with type 2 diabetes: a randomised, placebo-controlled and active comparator-controlled phase 2 trial; Lancet; 2018; vol. 392 (no. 10160); 2180-2193

72.1. 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	NCT03131687
Study type	Randomised controlled trial (RCT)
Study location	47 sites in Poland, Puerto Rico, Slovakia, and USA
Study setting	Medical and clinical research centres
Study dates	Participants were assessed for eligibility between May 24, 2017, and March 28, 2018.
Sources of funding	Eli Lilly and Company
Inclusion criteria	• Aged 18–75 • Had type 2 diabetes for at least 6 months (glycated haemoglobin A1c [HbA1c] 7.0–10.5%) that was inadequately controlled with diet and exercise alone or with stable metformin therapy for at least 3 months before screening • A body-mass index (BMI) of 23–50 kg/m²

Exclusion criteria	• Type 1 diabetes • Uncontrolled diabetes defined as more than two episodes of ketoacidosis or hyperosmolar state requiring hospitalization in the 6 months prior to Visit 1 • More than one episode of severe hypoglycaemia within 6 months prior to Visit 1, or a history of hypoglycaemia unawareness or poor recognition of hypoglycaemic symptoms. • A history of acute or chronic pancreatitis or elevation in serum lipase/amylase (>2x upper limit of normal [ULN]) or fasting serum triglyceride level of >500 mg/dL at screening • Active proliferative diabetic retinopathy • Known liver disease, obvious clinical signs or symptoms of liver disease, acute or chronic hepatitis, or alanine aminotransferase levels >2·5x ULN at Visit 1, as determined by the central laboratory at screening • Any of the following within the last six months prior to screening: myocardial infarction, unstable angina, coronary artery bypass graft, percutaneous coronary intervention (diagnostic angiograms are permitted), transient ischaemic attack, cerebrovascular accident or decompensated congestive heart failure, or currently have New York Health Association Class III or IV heart failure. Have an electrocardiogram (ECG) considered by the investigator indicative of active cardiac disease or with abnormalities that may interfere with the interpretation of changes in ECG intervals at screening. A QTc (Fridericia) interval >450 ms in men and >470 ms in women was specifically excluded. • Poorly controlled hypertension (i.e., mean seated systolic BP =160 mm Hg or mean seated diastolic BP =95 mm Hg) at screening, or a change in antihypertensive medications within 30 days of screening, renal artery stenosis, or evidence of labile blood pressure including symptomatic postural hypotension. Random triglycerides >500 mg/dL (5·7 mmol/L). If the patient is on lipid-lowering therapies, doses must be stable for 30 days prior to screening. • An estimated glomerular filtration rate (eGFR) of <45 mL/min/1·73 m2, as determined by the central laboratory at Visit 1, or a level of eGFR that would contraindicate the use of metformin per the label in the respective country. Patients on metformin must meet local label requirements. • With the exception of stable doses of metformin, patients on another oral antihyperglycaemic medication (OAM) (including, but not limited to, sulfonylureas, DPP-4i, sodium-glucose cotransport 2 inhibitors, alpha-glucosidase inhibitors, meglitinides) in addition to metformin therapy may be randomised if the additional OAM treatment was discontinued at least 3 months prior to screening. • Use of insulin for diabetic control within the prior year. However, short-term use of insulin for acute conditions is allowed (=14 days) in certain situations, such as during a hospitalisation or perioperatively. • Any exposure to dulaglutide, other GLP-1 analogues, or other related compounds within the prior three months or any history ever of allergies to these medications. Patients who previously took GLP-1 analogues or related compounds and who discontinued

	those medications >3 months prior to Visit 1 for intolerability or lack of efficacy were not to be randomised. • An average weekly alcohol intake that exceeds 21 units/week (males) and 14 units/week (females) [1 unit = 12 oz or 360 mL of beer; 5 oz or 150 mL of wine; 1.5 oz or 45 mL of distilled spirits].
Recruitment / selection of participants	NR
Intervention(s)	• Tirzepatide 1 mg - administered subcutaneously once a week - no dose escalation • Tirzepatide 5 mg - administered subcutaneously once a week - no dose escalation • Tirzepatide 10 mg - administered subcutaneously - received 5 mg for the first 2 weeks, and then 10 mg for the rest of the study • Tirzepatide 15 mg - administered subcutaneously - received 5 mg for the first 2 weeks, 10 mg for the next 4 weeks and 15 mg for the rest of the study • Dulaglutide 1.5 mg - administered subcutaneously once a week - no dose escalation
Cointervention	Participants receiving metformin should continue the baseline dose of metformin, unless they experience documented hypoglycemia, in which case the dose may be reduced
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	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	Placebo subcutaneous once weekly
Number of participants	555 participants were assessed for eligibility and 318 were randomised. 51 participants were assigned to placebo, 51 were included in analysis, 42 completed treatment and 45 completed the study. 53 participants were assigned to 1 mg tirzepatide. 52 were included in analyses, 44 completed treatment and 44 completed the study. 55 participants were assigned to 5 mg tirzepatide, 55 were included in the analysis, 47 completed treatment and 52 completed the study. 52 participants were assigned to 10 mg tirzepatide, 51 were included in the analysis, 44 completed treatment and 48 completed the study. 53 participants were assigned to 15 mg tirzepatide, 53 were included in the analysis, 35 completed treatment and 45 completed the study. 54 participants were assigned to 1.5 mg dulaglutide, 54 were included in the analysis, 46 completed treatment and 49 completed the study.
Duration of follow-up	26 weeks

Indirectness	Directly applicable
Method of analysis	Modified ITT All participants who took at least one dose of study drug and had at least one postbaseline measurement of any outcome. To address the concerns around adherence and rescue therapy, data were presented with and without rescue treatment. For participants who discontinued the study early or with missing week 26 data the last observation was carried forward. Data from a mixed-effect model were extracted. Analysis from a Bayesian hierarchical logistic dose-response model were also presented.
Additional comments	NA

72.2. Study arms

72.2.1. Tirzepatide 1 mg (N = 53)

72.2.2. Tirzepatide 5 mg (N = 55)

72.2.3. Tirzepatide 10 mg (N = 52)

72.2.4. Tirzepatide 15 mg (N = 53)

72.2.5. Dulaglutide 1.5 mg (N = 54)

72.2.6. Placebo (N = 51)

72.3. Characteristics

72.3.1. Study-level characteristics

Characteristic	Study (N = 318)
Time since type 2 diabetes diagnosed Nominal	NR
Cardiovascular risk factors Nominal	NR
Smoking status Nominal	NR
Alcohol consumption Nominal	NR
Presence of severe mental illness Nominal	NR
People with significant cognitive impairment Nominal	NR
People with a learning disability Nominal	NR
Number of people with obesity Nominal	NR
Blood pressure-lowering medication used Nominal	NR
Statins/lipid-lowering medication used Nominal	NR
Other treatment being received Nominal	NR

72.3.2. Arm-level characteristics

Characteristic	Tirzepatide 1 mg (N = 53)	Tirzepatide 5 mg (N = 55)	Tirzepatide 10 mg (N = 52)	Tirzepatide 15 mg (N = 53)	Dulaglutide 1.5 mg (N = 54)	Placebo (N = 51)
% Male Sample size	n = 29 ; % = 56	n = 34 ; % = 62	n = 30 ; % = 59	n = 22 ; % = 42	n = 24 ; % = 44	n = 29 ; % = 57
Mean age (SD) (years) Mean (SD)	57.4 (8.9)	57.9 (8.2)	56.5 (9.9)	56 (7.6)	58.7 (7.8)	56.6 (8.9)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
White Sample size	n = 42 ; % = 81	n = 46 ; % = 84	n = 37 ; % = 74	n = 43 ; % = 81	n = 44 ; % = 83	n = 41 ; % = 80
Asian Sample size	n = 0 ; % = 0	n = 0 ; % = 0	n = 1	n = 1 ; % = 2	n = 2 ; % = 4	n = 1 ; % = 2
Black or African American Sample size	n = 5 ; % = 10	n = 6 ; % = 11	n = 7 ; % = 14	n = 6 ; % = 11	n = 4 ; % = 8	n = 2 ; % = 4
Hispanic or Latino Sample size	n = 25 ; % = 52	n = 22 ; % = 49	n = 26 ; % = 57	n = 23 ; % = 46	n = 19 ; % = 41	n = 27 ; % = 59
Not hispanic or latino Sample size	n = 23 ; % = 48	n = 23 ; % = 51	n = 20 ; % = 44	n = 27 ; % = 54	n = 27 ; % = 59	n = 19 ; % = 41
Comorbidities Nominal	NR	NR	NR	NR	NR	NR
Presence of frailty Nominal	NR	NR	NR	NR	NR	NR
Other antidiabetic medication used Metformin Sample size	n = 46 ; % = 88.5	n = 49 ; % = 89.1	n = 44 ; % = 86.3	n = 51 ; % = 96.2	n = 48 ; % = 88.9	n = 47 ; % = 92.2

73. Frias, 2020

Bibliographic Reference	Frias, Juan P; Gonzalez-Galvez, Guillermo; Johnsson, Eva; Maaske, Jill; Testa, Marcia A; Simonson, Donald C; Dronamraju, Nalina; Garcia-Sanchez, Ricardo; Peters, Anne L; Efficacy and safety of dual add-on therapy with dapagliflozin plus saxagliptin versus glimepiride in patients with poorly controlled type 2 diabetes on a stable dose of metformin: Results from a 52-week, randomized, active-controlled trial.; Diabetes, obesity & metabolism; 2020; vol. 22 (no. 7); 1083-1093

73.1. Study details

Secondary publication of another included study- see primary study for details	NA
Other publications associated with this study included in review	Frias 2022
Trial name / registration number	NCT02419612
Study type	Randomised controlled trial (RCT)
Study location	87 centres in Germany, the Czech Republic, Hungary, Mexico, Poland, Romania, Russia, Sweden, the UK and the United States.
Study setting	NR
Study dates	The first patient was enrolled on August 14, 2015 and the last patient was enrolled on August 3, 2016
Sources of funding	AstraZeneca
Inclusion criteria	• 18 years and older • diagnosis of type 2 diabetes currently treated with metformin, and on a stable dose (≥1500 mg/day) for at least 8 weeks before enrolment • BMI 20 to 45 kg/m2 • fasting plasma glucose ≤ 270 mg/dL (≤15 mmol/L) at the time of randomization

	• HbA1c 7.5%–10.5% (58–91 mmol/mol)
Exclusion criteria	• A cardiovascular event in the 3 months before enrolment • eGFR <60 mL/min • Presence or history of unstable, acute or severe congestive heart failure (New York Heart Association Functional Classification III and IV) and/or left ventricular ejection fraction ≤40%, obtained from medical records
Recruitment / selection of participants	There was a 2-week screening period and a 2-week lead-in period prior to randomisation
Intervention(s)	Dapagliflozin 10mg plus saxagliptin 5 mg plus glimepiride placebo. Saxagliptin and dapagliflozin were taken orally once daily at fixed doses throughout the treatment period.
Cointervention	• Metformin • Patients were eligible for initiation of open-label rescue with insulin from week 9 of the study if their FPG levels met the following criteria: week 9, FPG >270 mg/dL (15.0 mmol/L); weeks 10–16, FPG >240 mg/dL (13.3 mmol/L); weeks 17–28, FPG >220 mg/dL (12.2 mmol/L); and weeks 29–52, FPG >200 mg/dL (11.1 mmol/L).
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear Excluded "the presence or history of unstable, acute or severe congestive heart failure (New York Heart Association Functional Classification III and IV)", otherwise unclear. No information in baseline characteristics.
Strata 2: People with atherosclerotic cardiovascular disease	Not stated/unclear Excluded "a cardiovascular event in the 3 months before enrolment", prior unclear. Baseline characteristics give vascular history, but unclear if this included CHF and hypertension.
Strata 3: People with type 2 diabetes mellitus and chronic kidney disease	Not stated/unclear Excluded "an estimated glomerular filtration rate (GFR) <60 mL/min", otherwise unclear. No information in baseline characteristics.
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
Population subgroups	NA
Comparator	Glimepiride titrated at 1, 2, 3, 4 or 6 mg plus saxagliptin and dapagliflozin matching placebos. Glimepiride treatment was initiated at 1 mg/day and could be up-titrated in increments of 1–2 mg at 3-week intervals during the first 12 weeks of the study to a maximum of 6 mg/day. Up-titration, permitted only during the first 12 weeks, was performed based on FPG levels [target of ≤110 mg/dL (6.1 mmol/L)] or to the highest tolerable dose; down-titration, permitted throughout the study, was allowed in patients who experienced hypoglycaemic episodes.
Number of participants	823 participants were
Duration of follow-up	823 participants were enrolled, 466 participants entered the lead-in period and 444 participants were randomised. Out of the 227 participants allocated to the dapagliflozin + saxagliptin arm, 227 received treatment, 197 participants completed treatment at 52 weeks, 196 participants entered the extension period, and 174 completed the 104-week extension period. Out of the 217 participants allocated to the glimepiride arm, 216 received treatment, 188 completed treatment at 52 weeks, 186 participants

	entered the extension period, and 164 participants completed the 104-week extension period.
Indirectness	Directly applicable
Method of analysis	Not stated/unclear Exploratory change-from-baseline endpoints used a mixed model of repeated measures, which assumes that data are missing at random. Efficacy results were summarized prior to rescue and treatment discontinuation (plus a tolerance window after the last dose). HbA1c and body weight, assessments collected after initiation of rescue medication or collected >8 days after the last dose in the 156-week treatment period were excluded from the analysis.
Additional comments	NA

73.2. Study arms

73.2.1. Saxagliptin + Dapagliflozin (N = 227)

73.2.2. Glimepiride (N = 217)

73.3. Characteristics

73.3.1. Arm-level characteristics

Characteristic	Saxagliptin + Dapagliflozin (N = 227)	Glimepiride (N = 217)
% Male Sample size	n = 117 ; % = 51.5	n = 101 ; % = 46.8
Mean age (SD) Mean (SD)	56.1 (10.1)	56.1 (9.2)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA
White Sample size	n = 204 ; % = 89.9	n = 195 ; % = 90.3

Characteristic	Saxagliptin + Dapagliflozin (N = 227)	Glimepiride (N = 217)
Black/African America Sample size	n = 4 ; % = 1.8	n = 5 ; % = 2.3
American-Indian/Alaska Native Sample size	n = 11 ; % = 4.8	n = 10 ; % = 4.6
Other Sample size	n = 8 ; % = 3.5	n = 6 ; % = 2.8
Hispanic or Latino Sample size	n = 36 ; % = 15.9	n = 35 ; % = 16.2
Comorbidities Sample size	n = NA ; % = NA	n = NA ; % = NA
Vascular history Sample size	n = 163 ; % = 71.8	n = 160 ; % = 74.1
Hypertension Sample size	n = 160 ; % = 70.5	n = 158 ; % = 73.1
Carotid artery disease Sample size	n = 1 ; % = 0.4	n = 0 ; % = 0
Coronary artery disease Sample size	n = 21 ; % = 9.3	n = 16 ; % = 7.4
Peripheral vascular disease Sample size	n = 13 ; % = 5.7	n = 5 ; % = 2.3
Stable angina Sample size	n = 17 ; % = 7.5	n = 11 ; % = 5.1
Other Sample size	n = 22 ; % = 9.7	n = 16 ; % = 7.4
Presence of frailty Nominal	NA	NA
Time since type 2 diabetes diagnosed Mean (SD)	7.7 (6.4)	7.9 (6.5)

Characteristic	Saxagliptin + Dapagliflozin (N = 227)	Glimepiride (N = 217)
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
Other treatment being received Nominal	NR	NR

74. Frias, 2016

Bibliographic Reference	Frias, Juan P; Guja, Cristian; Hardy, Elise; Ahmed, Azazuddin; Dong, Fang; Ohman, Peter; Jabbour, Serge A; Exenatide once weekly plus dapagliflozin once daily versus exenatide or dapagliflozin alone in patients with type 2 diabetes inadequately controlled with metformin monotherapy (DURATION-8): a 28 week, multicentre, double-blind, phase 3, randomised controlled trial.; The lancet. Diabetes & endocrinology; 2016; vol. 4 (no. 12); 1004-1016

74.1. Study details

Secondary publication of another included study- see primary study for details	NA
Other publications associated with this study included in review	Jabbour, Serge A, Frias, Juan P, Hardy, Elise et al. (2018) Safety and Efficacy of Exenatide Once Weekly Plus Dapagliflozin Once Daily Versus Exenatide or Dapagliflozin Alone in Patients With Type 2 Diabetes Inadequately Controlled With Metformin Monotherapy: 52-Week Results of the DURATION-8 Randomized Controlled Trial. Diabetes care 41(10): 2136-2146 Ferrannini, Ele, Baldi, Simona, Frias, Juan P et al. (2020) Hormone-substrate changes with exenatide plus dapagliflozin versus each drug alone: The randomized, active-controlled DURATION-8 study. Diabetes, obesity & metabolism 22(1): 99-106 Jabbour, S. A., Frias, J. P., Ahmed, A. et al. (2020) Efficacy and Safety Over 2 Years of Exenatide Plus Dapagliflozin in the DURATION-8 Study: A Multicenter, Double-Blind, Phase 3, Randomized Controlled Trial. Diabetes Care 43(10): 2528-2536
Trial name / registration number	DURATION-8 NCT02229396
Study type	Randomised controlled trial (RCT)
Study location	118 sites in six countries: Hungary, Poland, Romania, Slovakia, South Africa, United States
Study setting	NR

Study dates	Between Sept 4, 2014, and Oct 15, 2015, participants were randomised to treatment arms.
Sources of funding	AstraZeneca
Inclusion criteria	• At least 18 years old at screening; the upper age limit should be based on local metformin label restrictions • Has a diagnosis of type 2 diabetes • Has HbA1c of 8.0% to 12.0%, inclusive • Treated with a stable dose of metformin ≥1500 mg/day for at least 2 months prior to screening • Not breastfeeding, pregnant, or if of childbearing potential is practicing/will be continuing to practice appropriate birth control • Patients who are receiving antihypertensive agents, thyroid replacement therapy, or antidepressant agents must be on a stable treatment regimen for a minimum of 2 months prior to screening
Exclusion criteria	• Fasting plasma glucose ≥15·6 mmol/L (≥280 mg/dL) • Serum calcitonin concentration ≥40 ng/L (≥40 pg/mL) at screening • Clinically significant abnormal free T4 values or patients needing initiation or adjustment of thyroid treatment • Known active proliferative retinopathy • History of, or currently have, acute or chronic pancreatitis, or have triglyceride concentrations ≥5·65 mmol/L (≥500 mg/dL) at screening • History or presence of inflammatory bowel disease or other severe gastrointestinal diseases, particularly those that may impact gastric emptying, such as gastroparesis or pyloric stenosis • History of gastric bypass surgery or gastric banding surgery, or either procedure is planned during the time period of the study; current use of gastric balloons is also excluded • Significant hepatic disease including, but not limited to, acute hepatitis, chronic active hepatitis, or severe hepatic insufficiency, including patients with alanine aminotransferase and/or aspartate aminotransferase >3 × upper limit of normal and/or total bilirubin >34.2 µmol/L (>2 mg/dL). Patients with total bilirubin >34·2 µmol/L (>2 mg/dL) and documented Gilbert syndrome will be allowed to participate • Known history of hepatotoxicity with any medication • Known history of severe hepatobiliary disease • Positive serological test for hepatitis B or hepatitis C • Clinically significant cardiovascular disease or procedure within 3 months of screening including, but not limited to, myocardial infarction, clinically significant arrhythmia, unstable angina, coronary artery bypass surgery, or angioplasty; or are expected to require coronary artery bypass surgery or angioplasty during the course of the study • Presence or history of severe congestive heart failure (New York Heart Association Class IV) • Severe uncontrolled hypertension defined as systolic blood pressure ≥180 mmHg and/or diastolic blood pressure ≥110 mmHg • Creatinine clearance <60 mL/min (<1 mL/s) (calculated by Cockcroft-Gault formula) or a measured serum creatinine value of

	≥133 µmol/L (≥1·5 mg/dL) for male patients and ≥124 µmol/L (≥1·4 mg/dL) for female patients • Congenital renal glucosuria • History of unstable or rapidly progressing renal disease • History of unexplained microscopic or gross haematuria, or microscopic haematuria at screening, confirmed by a follow-up sample at next scheduled visit, where according to the investigator a satisfactory evaluation of haematuria has not been conducted • Known or suspected human immunodeficiency virus infection • History of organ transplantation • Presence or history of medullary thyroid carcinoma or MEN 2 or a family history of medullary thyroid carcinoma or MEN 2 • Malignancy (with the exception of basal and squamous cell carcinoma of the skin) within 5 years of screening • Haemoglobinopathy, haemolytic anaemia, or chronic anaemia (haemoglobin concentration <115 g/L for males and <105 g/L for females) or any other condition known to interfere with the HbA1c methodology • Has donated blood or had a significant blood loss within 2 months of first dose of study medication or is planning to donate blood during the study • Has donated plasma within 7 days prior to first dose of study medication • Any exposure to exenatide or any glucagon-like peptide-1 analog • Any exposure to dapagliflozin or any sodium glucose cotransporter-2 inhibitor • Administration of any antihyperglycemic therapy, other than metformin, for more than 14 days (consecutive or not) during the 12 weeks prior to screening. • Administration of any anti-hyperglycaemic therapy, other than metformin, at any dose, at 3 any time during the 4 weeks prior to screening • Has a clinically significant medical condition that could potentially affect study participation and/or personal well-being, as judged by the investigator • Has clinically significant abnormal laboratory test values (clinical chemistry, haematology, urinalysis) as judged by the investigator at screening • Has known contraindication, allergies, or hypersensitivity to any component of exenatide once weekly or to dapagliflozin • Has a contraindication to metformin use, including known metabolic or lactic acidosis, or any condition associated with hypoperfusion, hypoxemia, dehydration, or sepsis • Patients who, in the judgment of the investigator, may be at risk for dehydration or volume depletion that may affect the patient's safety and/or the interpretation of efficacy or safety data • Has evidence of current abuse of drugs or alcohol or a history of abuse that, in the investigator's opinion, would cause the individual to be noncompliance • Has been treated, is currently being treated, or is expected to require or undergo treatment with any of the following treatment excluded medications: ○ Any dipeptidyl peptidase--4 inhibitor within 3 months prior to screening

	○ Systemic corticosteroids within 3 months prior to screening by oral, intravenous, intra-articular, or intramuscular route; or potent, inhaled, or intrapulmonary steroids known to have a high rate of systemic absorption ○ Prescription or over-the-counter weight loss medications within 3 months prior to screening
Recruitment / selection of participants	NR
Intervention(s)	• Exenatide plus Dapagliflozin: Exenatide 2 mg (extended-release form) once weekly with dapagliflozin 10 mg once daily • Exenatide: Exenatide 2 mg (extended-release form) once weekly with once-daily oral placebo tablets • Dapagliflozin: Dapagliflozin 10 mg once daily with once-weekly injections with placebo microspheres [Placebo was supplied as oral tablets matching those of dapagliflozin or as powder along with prefilled syringes of diluent as a suspension for injection matching that provided for exenatide. Participants used a single-dose syringe to self-administer exenatide or matching placebo by subcutaneous injection in the abdomen, thigh, or upper arm at any time of day immediately after dose preparation. Injections were administered once weekly at home or at a study visit. Dapagliflozin or matching placebo tablets were self-administered]
Cointervention	• Existing metformin regimen • Diet and exercise instructions were provided as per usual. • Patients requiring rescue therapy received open-label titrated basal insulin based on fasting plasma glucose (FPG) criteria: FPG more than 15 mmol/L (270 mg/dL) between weeks 8 and 12; more than 13.2 mmol/L (240 mg/dL) between weeks 12 and 20; and more than 11.1 mmol/L (200 mg/dL) between week 20 and study end. • Use of background antihypertensive or anti-hyperlipidaemic drugs was not restricted.
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	Mixed population
Subgroup 5: eGFR category at baseline	eGFR ≥30mL/min/1.73m2 Over 95% of participants have eGFR >=60 mL/min/1.73 m2
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Population subgroups	NA
Comparator	NA

Number of participants	1375 participants were screened and 695 participants were randomly assigned. • Exenatide + dapagliflozin: 231 participants were allocated, 202 completed to week 28, 193 completed to week 52, 104 completed to week 104 • Exenatide: 231 participants were allocated, 177 completed to week 52, 136 completed to week 104 • Dapagliflozin: 233 participants allocated, 194 completed to week 52, 155 completed to week 104
Duration of follow-up	28, 52 and 104 weeks
Indirectness	Directly applicable
Method of analysis	Per protocol At week 28, change in Hb1Ac was underwent per-protocol analysis, defined as the subset of the intention-to-treat population with exclusion of participants with one or more important protocol violations (inadequate compliance, use of restricted medications during the trial conduct, study medication dosing error, deviations from the key inclusion and exclusion criteria, clinically important abnormalities noted before the first day of assigned study treatment, and previous exposure to exenatide treatment). ITT All randomly assigned patients who received at least one dose of study drug with at least one post-baseline HbA1c assessment. The primary endpoint was assessed with a mixed-effects model for repeated measures (MMRM), with change in HbA1c as the dependent variable; treatment, region, baseline HbA1c stratum (<9·0% vs =9·0% [<75 vs >=75 mmol/mol]), week, and treatment-by-week interaction as fixed factors; and baseline HbA1c as a continuous covariate. Changes in other continuous endpoints were tested with MMRM analyses or an analysis-of-covariance model. Data collected after the initiation of glycemic rescue therapy or at the posttreatment follow-up visits after premature treatment discontinuation were excluded from the efficacy analyses, except for SBP, which included data after rescue and excluded data after treatment discontinuation. All safety variables were analysed in the safety analysis set, defined as all randomly assigned patients who received at least one dose of the study drug, and were summarized descriptively.

Additional comments	N

74.2. Study arms

74.2.1. Exenatide 2 mg weekly + Dapagliflozin 10 mg daily (N = 231)

74.2.2. Exenatide 2 mg weekly + Placebo (N = 231)

Subcutaneous exenatide + matched placebo for oral dapagliflozin.

74.2.3. Dapagliflozin 10 mg daily + Placebo (N = 233)

Oral dapagliflozin + matched-placebo for subcutaneous exenatide.

74.3. Characteristics

74.3.1. Arm-level characteristics

Characteristic	Exenatide 2 mg weekly + Dapagliflozin 10 mg daily (N = 231)	Exenatide 2 mg weekly + Placebo (N = 231)	Dapagliflozin 10 mg daily + Placebo (N = 233)
% Male Sample size	n = 102 ; % = 45	n = 116 ; % = 51	n = 26 ; % = 11
Mean age (SD) Mean (SD)	54 (10)	54 (10)	55 (9)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
White Sample size	n = 190 ; % = 83	n = 194 ; % = 85	n = 189 ; % = 82
Black Sample size	n = 34 ; % = 15	n = 27 ; % = 12	n = 33 ; % = 14
Asian	n = 3 ; % = 1	n = 1 ; % = 0.4	n = 1 ; % = 0.4

Characteristic	Exenatide 2 mg weekly + Dapagliflozin 10 mg daily (N = 231)	Exenatide 2 mg weekly + Placebo (N = 231)	Dapagliflozin 10 mg daily + Placebo (N = 233)
Sample size			
Other Sample size	n = 1 ; % = 0.4	n = 5 ; % = 2	n = 7 ; % = 3
Comorbidities Nominal	NR	NR	NR
Presence of frailty Nominal	NR	NR	NR
Time since type 2 diabetes diagnosed Mean (SD)	7.6 (6)	7.4 (5.5)	7.1 (5.5)
Cardiovascular risk factors Nominal	NR	NR	NR
Smoking status Nominal	NR	NR	NR
Alcohol consumption Nominal	NR	NR	NR
Presence of severe mental illness Nominal	NR	NR	NR
People with significant cognitive impairment Nominal	NR	NR	NR
People with a learning disability Nominal	NR	NR	NR
Number of people with obesity >=30 kg/m2 Sample size	n = 140 ; % = 61	n = 132 ; % = 58	n = 158 ; % = 69

Characteristic	Exenatide 2 mg weekly + Dapagliflozin 10 mg daily (N = 231)	Exenatide 2 mg weekly + Placebo (N = 231)	Dapagliflozin 10 mg daily + Placebo (N = 233)
eGFR mL/min/1.73m2 Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
>=30 to <60 mL/min per 1.73 m2 Sample size	n = 6 ; % = 3	n = 7 ; % = 3	n = 12 ; % = 5
>=60 mL/min per 1.73 m2 Sample size	n = 222 ; % = 97	n = 220 ; % = 97	n = 128 ; % = 95
Other antidiabetic medication used Metformin use was required for eligibility Sample size	n = 231 ; % = 100	n = 230 ; % = 100	n = 223 ; % = 100
Blood pressure-lowering medication used Nominal	NR	NR	NR
Statins/lipid-lowering medication used Nominal	NR	NR	NR

75. Frias, 2023

Bibliographic Reference	Frias, Juan P; Hsia, Stanley; Eyde, Sarah; Liu, Rong; Ma, Xiaosu; Konig, Manige; Kazda, Christof; Mather, Kieren J; Haupt, Axel; Pratt, Edward; Robins, Deborah; Efficacy and safety of oral orforglipron in patients with type 2 diabetes: a multicentre, randomised, dose-response, phase 2 study.; Lancet (London, England); 2023; vol. 402 (no. 10400); 472-483

75.1. 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	NCT05048719
Study type	Randomised controlled trial (RCT)
Study location	The US, Hungary, Poland, and Slovakia
Study setting	45 study sites (private clinics, hospitals, or research centres)
Study dates	Between Sept 15, 2021, and Sept 30, 2022
Sources of funding	Eli Lilly and Company
Inclusion criteria	Participants aged 18 years or older with type 2 diabetes and a HbA1c of 7.0–10.5%, treated with diet and exercise, with or without a stable dose of metformin for at least 3 months, a BMI of 23 kg/m² or more, and a stable bodyweight (≤5% bodyweight gain or loss) for 3 months before random assignment were included.
Exclusion criteria	Proliferative diabetic retinopathy, diabetic maculopathy, or severe non-proliferative diabetic retinopathy; an estimated glomerular filtration rate of less than 30 mL per min per 1·73 m²; poorly controlled hypertension; and New York Health Association Class 3 or 4 heart failure.

Recruitment / selection of participants	There was a screening and study lead-in period of approximately 2 weeks.
Intervention(s)	Dulaglutide 1.5 mg weekly injection plus daily placebo tablet
Cointervention	Healthy eating and physical activity education periodically by study personnel, along with education regarding the signs, symptoms, and management of hypoglycaemia. ~94% participants at baseline were on metformin.
Strata 1: People with type 2 diabetes mellitus and heart failure	Not stated/unclear Exclusion criteria: NYHA Class 3 or 4 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	Not stated/unclear Exclusion criteria: eGFR less than 30 mL per 1.73 m2
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	People with obesity ~80% of participants in trial were living with obesity, whilst ~85% participants in dulaglutide and placebo groups were living with obesity.
Subgroup 5: eGFR category at baseline	eGFR ≥30mL/min/1.73m2
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Comparator	Placebo tablet daily plus placebo injection once per week
Number of participants	569 people were assessed for eligibility and 383 were randomly assigned to treatment. Of 50 participants allocated to dulaglutide, 45 (90%) completed treatment and 49 (98%) completed the study. Of 55 participants allocated to placebo, 44 (80%) completed treatment and 51 (93%) completed the study.
Duration of follow-up	26 weeks plus a 2-week safety follow-up
Indirectness	Directly applicable
Method of analysis	Other Efficacy analysis - included data from all randomly assigned participants who were exposed to at least one dose of the study drug excluding data after the permanent discontinuation of the study drug or initiation of rescue medication. A restricted maximum likelihood-based, mixed-effect model for repeated measures analysis was used. Not stated/unclear Safety analysis - data from safety population were obtained during the treatment period plus safety follow-up from all randomly assigned participants exposed to at least one dose of the study drug, regardless of adherence.
Additional comments	This was a 9-arm trial with 7 orfoglipron arms at various doses. Data for these 7 arms was not extracted because orfoglipron is not a relevant intervention for this review.

75.2. Study arms

75.2.1. Dulaglutide (N = 50)

75.2.2. Placebo (N = 53)

75.3. Characteristics

75.3.1. Arm-level characteristics

Characteristic	Dulaglutide (N = 50)	Placebo (N = 53)
% Male Sample size	n = 30 ; % = 60	n = 28 ; % = 51
Mean age (SD) (years) Mean (SD)	58.8 (10.2)	58.3 (9.5)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA
White Sample size	n = 44 ; % = 88	n = 50 ; % = 91
Black or African American Sample size	n = 4 ; % = 8	n = 4 ; % = 7
Asian Sample size	n = 1 ; % = 2	n = 1 ; % = 2
American Indian or Alaska Native Sample size	n = 0 ; % = 0	n = 1 ; % = 2
Other Sample size	n = 1 ; % = 2	n = 0 ; % = 0
Hispanic or Latino Sample size	n = 7 ; % = 14	n = 14 ; % = 25
Not hispanic or latino Sample size	n = 43 ; % = 86	n = 41 ; % = 75
Comorbidities Nominal	NA	NA
Presence of frailty	NA	NA

Characteristic	Dulaglutide (N = 50)	Placebo (N = 53)
Nominal		
Time since type 2 diabetes diagnosed (years) Median (IQR)	7.9 (4.1 to 12.5)	7.8 (4 to 12.5)
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 (Metformin use at baseline) Metformin Sample size	n = 47 ; % = 94	n = 51 ; % = 93
Blood pressure-lowering medication used Nominal	NR	NR
Statins/lipid-lowering medication used Nominal	NR	NR
Other treatment being received Nominal	NR	NR

76. Frias, 2022

Bibliographic Reference	Frias, Juan P; Maaske, Jill; Suchower, Lisa; Johansson, Lars; Hockings, Paul D; Iqbal, Nayyar; Wilding, John P H; Long-term effects of dapagliflozin plus saxagliptin versus glimepiride on a background of metformin in patients with type 2 diabetes: Results of a 104-week extension to a 52-week randomized, phase 3 study and liver fat MRI substudy.; Diabetes, obesity & metabolism; 2022; vol. 24 (no. 1); 61-71

76.1. Study details

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

77. Fujioka, 2003

Bibliographic Reference	Fujioka, Ken; Pans, Miranda; Joyal, Steven; Glycemic control in patients with type 2 diabetes mellitus switched from twice-daily immediate-release metformin to a once-daily extended-release formulation.; Clinical therapeutics; 2003; vol. 25 (no. 2); 515-29

77.1. Study details

Trial name / registration number	No additional information
Study type	Randomised controlled trial (RCT)
Study location	42 centres in the United States
Study setting	No additional information
Study dates	July 1998 and June 1999
Sources of funding	NR
Inclusion criteria	Eligible patients had been receiving MIR 500 mg BID for the treatment of type 2 diabetes for at least 8 weeks. They were required to have a HbA1c value <8.5% and mean fasting plasma glucose (FPG) concentrations <200 mg/dL.
Exclusion criteria	Patients symptomatic of type 2 diabetes, diabetic ketoacidosis, hyperosmolar nonketotic coma, significant renal disease/dysfunction (serum creatinine level >1.5 mg/dL for men, >1.4 mg/dL for women), hepatic dysfunction (serum aspartate aminotransferase or alanine aminotransferase >2 times the upper limit of normal or total bilirubin >2 times the upper limit of normal), congestive heart failure, major psychiatric disorders, alcohol and/or substance abuse, seizure disorders, or a history of malignancy. Additionally, patients could not be receiving long-term insulin therapy or any other antihyperglycemic therapy apart from MIR, anticoagulants, antiepileptic drugs, or oral steroids. Pregnant or breast-feeding women were excluded from the study.
Recruitment / selection of participants	No additional information
Intervention(s)	Extended-release formation of metformin (MXR) 1000 mg (n=75) administered once a day with the evening meal for 1 week for 24 weeks

	MXR 1500 mg (n=71) 1000 mg administered once daily with the evening meal for 1 week, followed by an increase to 1500 mg once a day for 24 weeks
Cointervention	None
Strata 1: People with type 2 diabetes mellitus and heart failure	People without heart failure Excluded "congestive heart failure".
Strata 2: People with atherosclerotic cardiovascular disease	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 "significant renal disease/dysfunction (serum creatinine level >1.5 mg/dL for men, >1.4 mg/dL for women)", 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	Mixed population
Subgroup 5: eGFR category at baseline	Not stated/unclear
Subgroup 6: Albuminuria category at baseline	Not stated/unclear
Population subgroups	No additional information
Comparator	Immediate release formulation of metformin (n=71) MIR 500 mg twice daily with the morning and evening meals. After 12 weeks, the daily dose could be increased by 500 mg in any group if HbA1c was >8% at that time.
Number of participants	217
Duration of follow-up	24 weeks
Method of analysis	Other
Additional comments	For the primary efficacy variable, mean change in HbA1c from baseline to week 12, 95% CIs were constructed within each randomly assigned treatment group. Similarly, secondary efficacy parameters at weeks 12 and 24 were summarized for each treatment group with the use of 95% CIs. Whenever data were not available for secondary end points at week 12 or 24, a last-observation-carried-forward analysis of change was performed using the last measurement obtained before these time points.

77.2. Study arms

77.2.1. Extended release metformin (1000 mg) (N = 75)

Patients received 1000 mg to be administered orally with the evening meal for 24 weeks

77.2.2. Extended release metformin (1500 mg) (N = 71)

Patients initially received 1000 mg administered with the evening meal for 1 week followed by an increase to 1500 mg for the remaining 23 weeks

77.2.3. Immediate release formulin (1000mg) (N = 71)

Patients received 500 mg administered twice daily with morning and evening meals

77.3. Characteristics

77.3.1. Arm-level characteristics

Characteristic	Extended release metformin (1000 mg) (N = 75)	Extended release metformin (1500 mg) (N = 71)	Immediate release formulin (1000mg) (N = 71)
% Male Sample size	n = 34 ; % = 45.3	n = 28 ; % = 39.4	n = 31 ; % = 43.7
Mean age (SD) (years) Mean (SD)	54 (NR)	55 (NR)	54 (NR)
Ethnicity Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Time since type 2 diabetes diagnosed (years) Mean (SD)	3 (NR)	3 (NR)	3 (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

Characteristic	Extended release metformin (1000 mg) (N = 75)	Extended release metformin (1500 mg) (N = 71)	Immediate release formulin (1000mg) (N = 71)
Other antidiabetic medication used Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Blood pressure-lowering medication used Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
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

78. Gadde, 2017

Bibliographic Reference	Gadde, K. M.; Vetter, M. L.; Iqbal, N.; Hardy, E.; Ohman, P.; Efficacy and safety of autoinjected exenatide once-weekly suspension versus sitagliptin or placebo with metformin in patients with type 2 diabetes: The DURATION-NEO-2 randomized clinical study; Diabetes Obes Metab; 2017; vol. 19 (no. 7); 979-988

78.1. Study details

Trial name / registration number	DURATION-NEO-2 / NCT01652729
Study type	Randomised controlled trial (RCT)
Study location	81 centres in the USA
Study setting	No additional information
Study dates	February 2013 and April 2014
Sources of funding	AstraZeneca. Primary author declares funding from Bristol-Myers Squibb, Eisai and the NIDDK. A second author was an employee of Bristol-Myers Squibb during the conduct of the study and two further authors are employees of AstraZeneca
Inclusion criteria	Eligible patients were aged ≥18 years with T2D on a stable regimen of metformin ≥1500 mg/d for ≥2 months before screening. Additional inclusion criteria were HbA1c of 7.1% to 11.0% at screening, FPG <280 mg/ dL at screening and at visit 2, BMI ≤45 kg/m2 and stable body weight (≤3% variation for ≥3 months before screening).
Exclusion criteria	Exclusion criteria included any clinically significant medical condition that could affect study participation; an EGFR <30 mL/min/1.73 m2 ; exposure to exenatide or any GLP-1RA; use of any DPP-4i, sulfonylurea or thiazolidinedione, or weight-loss medications within 3 months before screening; or ≥2 episodes of severe hypoglycaemia within 6 months of screening.
Recruitment / selection of participants	No additional information
Intervention(s)	Exenatide QWS-AI 2.0mg (n=181) Administered QW by subcutaneous injection in the abdomen, thigh or upper arm via prefilled, single-dose autoinjector with an integrated needle on the same day of the week at any time of day

	Sitagliptin 100mg (n=122) Administered orally once daily in the morning for 28 weeks
Cointervention	Metformin Stable doses of metformin (≥ 1500 mg/d) were continued throughout the study.
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 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=61) Administered orally once daily in the morning for 28 weeks. Stable doses of metformin (≥ 1500 mg/d) were continued throughout the study as cointervention
Number of participants	364
Duration of follow-up	28 weeks
Indirectness	No additional information
Method of analysis	Modified ITT
Additional comments	Efficacy and pharmacodynamic variables were analysed using the modified intent-to-treat (mITT) population, defined as all randomized patients who received ≥1 dose of study drug. The primary endpoint was assessed using a mixed-effects model repeated measures (MMRM) with change in HbA1c as the dependent variable; treatment, week of visit, treatment-by-week interaction, baseline HbA1c stratum and baseline HbA1c stratum-by-week interaction as fixed factors; and patient as random effect. Covariates included baseline HbA1c and baseline HbA1c-by-week interaction. Changes in continuous endpoints were tested using MMRM analyses. A general linear model evaluated change from baseline for parameters assessed only at baseline and 1 post-baseline visit.

78.2. Study arms

78.2.1. Exenatide QWS-AI (N = 181)

Exenatide delivered as a single 2.0 mg once weekly dose via auto-injector (AI) in a premeasured volume (0.85 ml) for 28 weeks

78.2.2. Sitagliptin (100 mg) (N = 122)

Administered orally once daily in the morning for 28 weeks

78.2.3. Placebo (N = 61)

Administered once daily in the morning for 28 weeks

78.3. Characteristics

78.3.1. Arm-level characteristics

Characteristic	Exenatide QWS-AI (N = 181)	Sitagliptin (100 mg) (N = 122)	Placebo (N = 61)
% Male Sample size	n = 89 ; % = 49.2	n = 66 ; % = 54.1	n = 37 ; % = 60.7
Mean age (SD) (Years (mean, SD)) Mean (SD)	53.4 (9.8)	54.3 (9)	53.4 (9.5)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
White Sample size	n = 148 ; % = 81.8	n = 98 ; % = 80.3	n = 50 ; % = 82
Black Sample size	n = 24 ; % = 13.3	n = 18 ; % = 14.8	n = 7 ; % = 11.5
Asian Sample size	n = 9 ; % = 5	n = 2 ; % = 1.6	n = 3 ; % = 4.9
Other Sample size	n = 0 ; % = 0	n = 4 ; % = 3.3	n = 1 ; % = 1.6
Hispanic ethnicity Sample size	n = 111 ; % = 61.3	n = 77 ; % = 63.1	n = 32 ; % = 52.5
Time since type 2 diabetes diagnosed (Years (mean, SD)) Mean (SD)	8.5 (6.3)	7.9 (4.6)	8.7 (5.8)
Smoking status Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR

Characteristic	Exenatide QWS-AI (N = 181)	Sitagliptin (100 mg) (N = 122)	Placebo (N = 61)
Alcohol consumption Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Presence of severe mental illness Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
People with significant cognitive impairment Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
People with a learning disability Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Number of people with obesity Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Other antidiabetic medication used Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Blood pressure-lowering medication used Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
Agents acting on the renin-angiotensin system Sample size	n = 81 ; % = 44.8	n = 55 ; % = 45.1	n = 29 ; % = 47.5
Calcium-channel blockers Sample size	n = 10 ; % = 5.5	n = 4 ; % = 3.3	n = 8 ; % = 13.1
Other antihypertensive Sample size	n = 2 ; % = 1.1	n = 3 ; % = 2.5	n = 0 ; % = 0
Statins/lipid-lowering medication used Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
Lipid modifying agents Sample size	n = 52 ; % = 28.7	n = 40 ; % = 32.8	n = 19 ; % = 31.1
Other treatment being received Sample size	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA

Characteristic	Exenatide QWS-AI (N = 181)	Sitagliptin (100 mg) (N = 122)	Placebo (N = 61)
Beta blocking agents Sample size	n = 15 ; % = 8.3	n = 9 ; % = 7.4	n = 6 ; % = 9.8